KCE REPORT 204

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

SEASONAL INFLUENZA VACCINATION: PRIORITIZING CHILDREN OR OTHER TARGET GROUPS?

PART II: COST-EFFECTIVENESS ANALYSIS

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HEALTH TECHNOLOGY ASSESSMENT

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COLOPHON

Title: Seasonal influenza vaccination: prioritizing children or other target groups?

Part II: cost-effectiveness analysis.

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Acknowledgements: Yannick Vandendijck acknowledges support from a doctoral grant of the Universiteit Hasselt (BOF11D04FAEC). Lander Willem acknowledges support from an interdisciplinary doctoral grant of the Universiteit Antwerpen (ID-BOF25759), Nele Goeyvaerts is beneficiary of a postdoctoral grant from the AXA Research Fund, Adriaan Blommaert acknowledges support from the Universiteit Antwerpen concerted research action number 23405 (BOF-GOA), Joke Bilcke is supported by a postdoctoral grant from the Fund for Scientific Research Flanders (FWO), Niel Hens acknowledges support from the Universiteit Antwerpen scientific chair in Evidence-Based Vaccinology, financed in 2009–2013 by a gift from Pfizer. Support from the IAP Research Network P7/06 of the Belgian State (Belgian Science Policy) is gratefully acknowledged.

For the simulations we used the infrastructure of the VSC - Flemish Supercomputer Center, funded by the Hercules foundation and the Flemish Government - department EWI. We thank Geert Jan Bex (Universiteit Hasselt and KULeuven) for support with using the VSC cluster, as well as Frank Van Reeth (Expertise Centre for Digital Media, Universiteit Hasselt).

We are indebted to the following persons for their help mainly through general advice, data delivery, data interpretation or review.

We thank Anthony Newall (University of New South Wales, Sydney, Australia) and Mark Jit (Health Protection Agency, The UK) for support in conducting systematic reviews of economic evaluations.

We are grateful to Samuel Coenen and Niels Adriaenssens (Centre for General Practice & Laboratory of Medical Microbiology, Vaccine & Infectious Disease Institute, University of Antwerp), Curt Brugman (Julius Center for Health Science and Primary Care, UMC Utrecht, the Netherlands), Pierre Van Damme (Centre for the Evaluation

of Vaccination, Vaccine & Infectious Disease Institute, University of Antwerp) and Herman Goossens (Laboratory of Medical Microbiology, Vaccine & Infectious Disease Institute, University of Antwerp, and coordinator of Genomics to combat Resistance against Antibiotics in Community-acquired LRTI in Europe – GRACE, DG Research, 2005) for helping with interpreting reviews and the medication data we collected through our survey on influenza like illness, and sharing antibiotics data of GRACE.

We also thank marketing research company "DayOne" (in particular Koen Van Bulck) for conducting the 2011-2012 influenza season survey on influenza like illness in the general population.

This study was made possible thanks to the collaboration of the Institut Scientifique de Santé Publique/Wetenschappelijk Instituut Volksgezondheid (ISP – WIV) that provided the sentinel laboratory and influenza data, the Reference Laboratory for *Streptococcus pneumoniae* at the UZ Leuven, the Technical Cell for the Minimal Clinical Data, the Federation Wallonia-Brussels, the Vlaams Agentschap Zorg en Gezondheid and the Observatorium voor Gezondheid en Welzijn van Brussel-Hoofdstad – Observatoire de la Santé et du Social de Bruxelles-Capitale for the data on the causes of death. We particularly thank Jan Verhaegen and Jozef Vandeven (UZ Leuven), Françoise Wuillaume, Viviane van Casteren, Geneviève Ducoffre and Isabelle Thomas (ISP – WIV), Déogratias Mazina and Murielle Deguerry (Observatoire de la Santé et du Social de Bruxelles-Capitale – Observatorium voor Gezondheid en Welzijn van Brussel-Hoofdstad), Erik Hendrickx, Anne Kongs and Heidi Cloots (Vlaams Agentschap Zorg en Gezondheid), Virginie Charlier (Fédération Wallonie-Bruxelles), Yves Parmentier (INAMI – RIZIV), France Vrijens, Jo Robays, Carl Devos, Stephan Devriese and Frank Hulstaert (KCE). We also thank Esther Kissling (EpiConcept) and Bianca Cox (University Hasselt) for advices on STATA programming. We also thank Kristel De Gauquier (KCE) for continuous support and management throughout the study.

External validators: Daniel Brasseur (AFMPS – FAGG, European Medicines Agency and Hôpital Universitaire des Enfants Reine Fabiola), Marc Van Ranst (KULeuven, Hoge Gezondheidsraad – Conseil Supérieur de la Santé), Emilia Vynnycky (London School of Tropical Medicine and Hygiene).

Conflict of interest: Marc Van Ranst (MVR) has acted as principal investigator or consultant for projects for which the University of Leuven received grants and funds for research. These grants and funds were directly paid to the University and MVR received no personal remuneration for this work. Yves Van Laethem received funds for research and consultancy fees and fees to speak at conferences from companies involved in influenza vaccines but these activities were not related to influenza, and these fees were paid directly to the Research Unit of his hospital. Anne Vergison received consultancy fees from companies involved in pneumococcal vaccines to participate to scientific advisory boards and to speak at conferences on pneumococcal vaccination. These fees were paid directly to her hospital. Beatrice Swennen received a travel grant to participate at a scientific conference. Patrick Tréfois collaborates to the Vax Info journal which received unrestricted educational grant from GSK.

Layout: Sophie Vaes

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- **The external experts were consulted about a (preliminary) version of the scientific report. Their comments were discussed during meetings. They did not co-author the scientific report and did not necessarily agree with its content.**
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- **Finally, this report has been approved by common assent by the Executive Board.**
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Publication date:	12 juli 2013
Domain:	Health Technology Assessment (HTA)
MeSH:	Influenza Vaccines; Influenza, Human; Pregnancy; Comorbidity; Health Personnel; Infant; Child, Preschool; Child; Adolescent; Young Adult; Middle Aged; Aged; Cost-Benefit Analysis; Costs and Cost Analysis.
NLM Classification:	WC 515
Language:	English
Format:	Adobe® PDF™ (A4)
Legal depot:	D/2013/10.273/43

How to refer to this document?

Beutels P, Vandendijck Y, Willem L, Goeyvaerts N, Blommaert A, Van Kerckhove K, Bilcke J, Hanquet G, Neels P, Thiry N, Liesenborgs J, Hens N. Seasonal influenza vaccination: prioritizing children or other target groups? Part II: cost-effectiveness analysis. Health Technology Assessment (HTA) Brussels: Belgian Health Care Knowledge Centre (KCE). 2013. KCE Reports 204. D/2013/10.273/43.

This document is available on the website of the Belgian Health Care Knowledge Centre.

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AE	Adverse event
AICc	Corrected Aikake Information Criterion
BOI	Burden-of-illness
CAIV	Cold Adapted Influenza Vaccine
CB	Cost-benefit
CCII	Cultured-Confirmed Influenza Illness
CDC	Centers for Disease Control and Prevention
CE	Cost-effectiveness
CEAC	Cost-effectiveness acceptability curve
CHMP	Committee for Human Medicinal Products
CU	Cost-utility
DALY	Disability-adjusted life-year
Dev	Deviance
DF	Degree of freedom
DIC	Deviance information criterion
EC	European Commission
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EQ-5D	EuroQoL
EU	European Union
FDA	Food and Drug Administration
GBS	Guillain-barre syndrome
GP	General practitioner
HBD	Hospital billing data

HCW	Health care worker
HGR – CSS	Hoge GezondheidsRaad – Conseil Supérieur de la Santé (Superior Health Council)
HI	Hemagglutinination-inhibition
HIV	Human Immunodeficiency Virus
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
HUI-2	Health Utilities Index Mark 2
ICD9(-CM code)	International Classification of Diseases, 9th Revision (Clinical Modification code)
ICER	Incremental cost-effectiveness ratio
I	Influenza
ID	Intradermal
ILI	Influenza-like illness
IM	Intramuscular
IMS	Intercontinental Marketing Services
ITT	Intention to treat
IVE	Influenza vaccine efficacy
LAIV	Live Attenuated Influenza Vaccine
LOS	Length of stay
MCD	Minimal Clinical Data
MFD	Minimal Financial Data
N(A)CSF	National (Alliance of) Christian Sickness Fund(s)
NHS	National Health Service
P	Pneumonia
PSA	Probabilistic sensitivity analysis

QALY	Quality-adjusted life-year
QoL	Quality of life
RCT	Randomized Controlled Trial
RIZIV – INAMI	Rijksinstituut voor ziekte- en invaliditeitsverzekering – Institut national de l'assurance maladie-invalidité
RR	Risk ratio
SEIR	Susceptible Exposed Infectious Recovered
SIR	Susceptible Infectious Recovered
SPC	Summary of Product characteristics
SRTI	Secondary respiratory tract infections
SVIRS	Susceptible Vaccinated Infectious Recovered Susceptible
TIV	Trivalent inactivated Influenza Vaccine
US	United States
VAS	Visual Analogue Scale
VE	Vaccine efficacy
VE_I	Vaccine efficacy for infectiousness
VE_S	Vaccine efficacy for susceptibility
VE_{SP}	Vaccine efficacy for susceptibility to disease
WIV – ISP (IPH)	Wetenschappelijk Instituut Volksgezondheid – Institut national de la Santé Publique (Scientific Institute of Public Health)
WHO	World Health Organization
WLS	Weighted Least Squares

SCIENTIFIC REPORT

1 BACKGROUND

The strategy of annual vaccination of children against seasonal influenza is receiving increasing attention in recent years. In the US, annual vaccination of children is recommended since 2004. The rationale for this recommendation was that the risk of influenza-associated hospitalization in healthy children <24 months of age has been shown to be equal to or greater than the risk in previously recognized high-risk groups.[1] This recommendation has then expanded from 6-23 months (2004), to over 6-59 months (2006), all children aged 6 months to 18 years (2009) and all persons aged ≥6 months in 2010,[2, 3] due to the increased risk for influenza-associated outpatient and emergency department visits observed in the older age groups as well.[4, 5] Nonetheless, influenza vaccine uptake in US children has remained relatively low, not exceeding 50%.[6]

Most other countries did not expand childhood influenza vaccination to children who are not at increased risk of influenza complications. In Europe as of April 2013, only seven countries (Austria, Estonia, Finland, Latvia, Poland, Slovakia and Slovenia) recommend universal seasonal influenza vaccination for different age groups <18 years of age but Finland is the only country that has introduced it into the routine childhood vaccination programme, in children aged from 6 months to 3 years.[7-9] The United Kingdom (UK) has announced in 2012 its plan to introduce vaccination of all children aged 5-17 years from 2014 onwards, on the basis that the additional herd immunity conferred by this strategy makes it a highly cost effective public health intervention.[10, 11] The World health Organization (WHO) also advised in 2012 to consider all children aged <5 years as a risk group to be considered for influenza vaccination because of a high burden of severe disease in this group.[12]

As for many childhood infections, children experience the greatest incidence and force of influenza infection.[13] Since children shed relatively more virus, and have intensive contacts with other children, and across generations in their families, they are also the key group that drives transmission in the entire population. Childhood influenza vaccination has thus the potential to prevent a substantial number of influenza cases by direct protection of those at highest risk of infection (direct effects), and through indirect protection of other age groups through reducing the virus transmission (indirect effect).[14] The inter-year variability of influenza makes

however generalisation difficult. In the US, the report of >150 pediatric influenza-associated deaths during the high 2003–04 season (most with no known high-risk conditions) played a role in the decision to introduce universal influenza vaccination of children.[5, 15] However, recent empirical evidence of herd protection may prove to be a turning point for the consideration of childhood influenza vaccination in other countries as well as an efficient option to reduce the disease burden of influenza. A number of trials and observational studies have shown a significant reduction in the rates of influenza-related illness and hospitalizations among contacts of vaccinated subjects. The highest evidence comes from a cluster clinical trial conducted in Hutterite communities in Canada. Children 36 months – 15 years of age in intervention clusters were vaccinated, reaching 83% coverage.[16] Among non-vaccinated individuals living in vaccinated clusters, laboratory-confirmed influenza was reduced by 61% compared to placebo communities. Other studies were mostly open community trials achieving moderate coverage; incidence of clinical influenza among unvaccinated persons from vaccinated communities reduced significantly by 8-18%.[17, 18] An Italian study compared incidence of clinical influenza between households where children were vaccinated and households of placebo children; household contacts of the children had 30% significantly fewer illness compared to those of unvaccinated children.[19] This reduction was also observed in seasons with very poor match between circulating and vaccine viruses.

Two main types of influenza vaccines are currently registered in Europe: (1) the trivalent inactivated influenza vaccine (TIV), which is injectable (predominantly intramuscular or intradermal), and (2) the live attenuated influenza vaccine (LAIV), which is given as a nasal spray. Both TIV and LAIV currently contain three influenza virus strains, which are reconsidered and recommended by the World Health Organization (WHO) on an annual basis.[20] A first LAIV vaccine (Fluenz, from MedImmune LLC) has been authorized in the US in 2003 but was only authorized in the European Union in 2011 and is not yet on the Belgian market.[21] The company has announced it could be available around the 2014-15 season.

In Belgium, up till the season 2012-2013 thus only TIV has been used. It is reimbursed by the National Health Insurance (INAMI–RIZIV) for the high risk groups defined by the Superior Health Council (CSS–HGR).

During the winter season 2011-2012, the following TIVs were available:

Vaccines with dosage of 1 x 0.5ml:[22]

- α-Rix (GSK): €12.16 per dose
- Agrippal (Novartis Pharma): €10.80 per dose
- Inflexal V (Janssen-Cilag): €11.80 per dose
- Influvac S (Abbott Products): €11.48 per dose
- Vaxigrip (Sanofi Pasteur MSD): €11.82 per dose

Vaccine with alternative dosage and administration route (intradermal):

- Intanza (Sanofi Pasteur MSD) – 1 x 9µg / 0.1ml: €12.47 per dose
- Intanza (Sanofi Pasteur MSD) – 1 x 15µg / 0.1ml: €12.16 per dose

The overall goal of this study is to offer guidance for prioritising influenza vaccine target groups, and thus to recommend optimal usage of scarce seasonal influenza vaccines.

A first part of this project (KCE report 162, entitled “Seasonal influenza vaccination: priority target groups – Part I”)[23] estimated the morbidity and mortality impact (without any cost estimates) of different adult vaccination scenarios (health care workers, elderly aged 65+ years, persons with chronic disease and pregnant women).

In this second part, we estimate the costs and benefits of a wider range of influenza vaccination options through economic evaluation, including the universal vaccination of children. In order to do this to the best of our ability we make model projections of the potential impact of targeted and widespread vaccination on both vaccine recipients and – where relevant – on the transmission dynamics of influenza in the entire population.

2 OBJECTIVES

There are 2 main research questions addressed in the current report:

1. What is the population impact of vaccinating children for seasonal influenza vaccination, in terms of prevented cases of influenza and influenza like illness (ILI), of prevented hospital admissions and prevented deaths?
2. What is the cost-effectiveness of seasonal influenza vaccination for various options of vaccination (including but not limited to current target groups)?

The first phase of this project considered adult vaccination options (see changes in uptake in Table 1), and presented estimates for each target group of the number of people to be targeted, as well as of the number of cases, hospital admissions and deaths occurring currently and with a limited set of changes in vaccine uptake of adult target groups.

Table 1 – Target groups and vaccine uptake change as proposed in part I of this project (KCE report 162)[23]

Target groups	Change in vaccine uptake to consider
Persons 1-64 years with co-morbidities	+10% and +20%
Pregnant women	+ 50%
Healthy 18-49 years	-10% (reach 0%)
Healthy 50-64 years	+10% and +20%
Elderly 65-74 years	+25% (reach 75%, WHO target)
Elderly 75+ years	+4% (reach 75%)
Health care workers	+15%
Children (by major age groups)	To determine

3 EVIDENCE REVIEWS

In the part I report, a focused literature review was undertaken on the efficacy of adult seasonal influenza vaccination, up to the year 2011.

In the current report we undertake numerous literature reviews and discuss these in this section. In a nutshell, we summarise and review the evidence on both efficacy/effectiveness and safety of seasonal influenza vaccines for both children and adults, on economic evaluations of seasonal influenza vaccination in both children and adults, on quality of life studies for influenza illness and on dynamic transmission models of seasonal influenza vaccination. We distinguish the various target groups for seasonal influenza vaccination listed in Table 1, where relevant.

The full literature review is described in Supplement 1, and a summary of the results that are relevant to our models is described in the section below.

3.1 Vaccine efficacy and effectiveness

In the current report we undertake a review on the efficacy of vaccinating children with seasonal influenza vaccine. Furthermore we update the part I report literature review for adults as well with a new search. We gather information from the European Public Assessment Reports (EPAR) and perform standard searches in international databases to identify relevant previous reviews on the subject, as well as relevant new publications.

3.1.1 Methods

For the literature review on children efficacy, we first selected the most recent systematic reviews, retrieved all the included primary studies that fitted with our selection criteria, as well as the studies publishing the data described in the EPAR on LAIV. We also updated them with primary studies after the last search date of these reviews. For the literature review on adults, we updated the Part I review by searching for systematic reviews and primary studies published after the last search date (December 2010). We thus searched for full text articles using the broad text string “vaccin*” AND “influenza” AND “trial*” for the publication years 2011 and 2012 (up to April 2012) in Pubmed (which includes Medline) and Web of Science (SCI and SSCI expanded). From our search results we identified the latest published reviews, and verified that the search period

in those reviews covered at least part of 2011 (which was the case, see results). Our selection of the search results is depicted in Figure 1. Studies were selected irrespective of outcomes, and subsequently further categorized (see below and results). We did not include vaccine efficacy studies involving the pandemic H1N1 2009 strain.

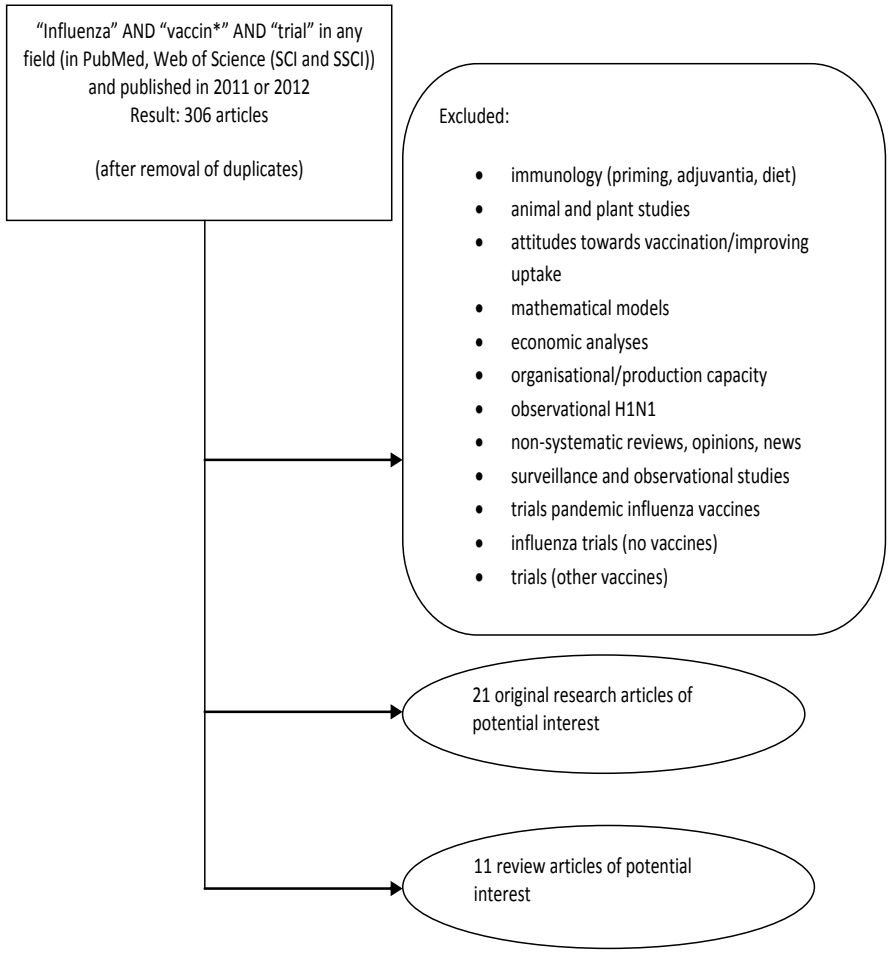
For children and healthy adults ≤65 years of age (including pregnant women), only double blind randomised controlled trials (RCT) were selected. For the elderly and persons with co-morbidities, in which the influenza vaccine is already widely recommended and RCTs are rarely conducted, observational prospective studies were also retrieved.

For adults and persons with co-morbidities, we included only studies involving non adjuvanted trivalent inactivated vaccines (TIV), conducted in European and North American (US and Canada) settings, as the prevalence of other seasonal pathogens may differ across regions. Outcomes were restricted to influenza cases and deaths that are laboratory confirmed by culture and/or PCR. For observational studies (in the elderly and persons with co-morbidities), we only included studies that adjusted for the most important confounding factors (including presence of underlying disease and its severity).

For the search in the elderly, defined as those ≥60 years, we only included studies that provided estimates for this subgroup.

When available, intention to treat (ITT) estimates were used for analysis. Vaccine efficacy estimates from RCTs were pooled as risk ratios (RR) and 95% confidence intervals were calculated, using Review Manager 5.2, when relevant. We used random-effects models to take into account the between-study variance in our findings, as there are unpredictable systematic differences between trials regarding the circulating strains and the levels of immunity presented by different populations in different settings. Influenza vaccine efficacy (IVE) was calculated as VE=1-RR and expressed as a percentage.

Figure 1 – Flow chart of literature selection for vaccine efficacy (children and adults)



3.1.2 *Influenza vaccine efficacy in children*

Following the European Summary of Product Characteristics (SPC) of the Trivalent Inactivated Influenza Vaccines (TIV), these vaccines can be used in children from 6 months onwards.[24-26] However, this assessment is given with a warning, because the data on the use of TIV in children remain sparse. On the other hand, one Live Attenuated Influenza Vaccine (LAIV) formulation ("FLUENZ") has been granted a license for children only, and in contrast to TIV, the use of this LAIV in children has been discussed explicitly in these public EC documents.[21, 27]

3.1.2.1 *Live Attenuated Influenza Vaccine (LAIV) studies in children*

The European Commission has granted MedImmune on 27/01/2011 a marketing authorisation for FLUENZ for children from 24 months onwards up to 18 years based on a positive opinion from the Committee for Human Medicinal Products (CHMP). [27, 24] The SPC warns for the use of this vaccine below the age of 12 months for safety reasons, pointing to a clinical trial in which a post-vaccination increase in all-cause hospitalisations was observed in infants and toddlers younger than 12 months (see also separate safety review below). Since an increased rate of wheezing after vaccination was observed in infants and toddlers 12-23 months of age, it is not recommended to administer FLUENZ to infants and toddlers 12-23 months of age. Most data from the EPAR[21, 27] have been published in peer-reviewed journals. Of the 31 studies that included paediatric subjects, 15 were designed to evaluate the efficacy of FLUENZ. However, of these trials only 6 were randomised, placebo controlled, double-blind and only one was randomised, active controlled (versus TIV) double-blind. Other trials were not double blind and were thus not included. Additional trials on LAIV efficacy have not been published.

An overview of the six included placebo-controlled trials, based on published studies and data from the EPAR, is provided below and in Table 2, together with the pooled estimates that are required for model parameters. These studies are also described in greater details in Supplement 1. Outcomes of all trials are laboratory confirmed influenza, by culture and/or PCR, unless specified.

Table 2 – Overview of LAIV efficacy in children from randomised placebo-controlled double blind clinical trials

Author of related publication, study number	Region[a]	Age[b] range	Number of subjects in primary analysis	Influenza season, degree of matching	PP or ITT	Efficacy (95%CI) against matched strains	Efficacy (95%CI) against all strains regardless of antigenic match
Tam 2007, D153-P501	Asia/Oceania	12 to <36M	2764	2000-2001, good	PP ITT	72.9% (62.8–80.5) Not available	70.1% (60.9–77.3) 67.8% (58.8–74.9)
				2001-2002, good	PP	84.3% (70.1–92.4)[c] for 2 doses year 1 and 1 dose year 2	64.2% (44.2–77.3)[c] for 2 doses year 1 and 1 dose year 2
				2001-2002, good	PP	59.9% (31.3–77.4) for 1 dose	56.7% (30.3–73.8) for 1 dose
Vesikari 2006, D153-P502	Europe	6 to <36M	1616	2000-2001, good	PP ITT	85.4% (74.3–92.2) Not available	85.9% (76.3–92.0) 83.8% (74.2–90.2)

Author of related publication, study number	Region[a]	Age[b] range	Number of subjects in primary analysis	Influenza season, degree of matching	PP or ITT	Efficacy (95%CI) against matched strains	Efficacy (95%CI) against all strains regardless of antigenic match
				2001-2002, good		For 2 doses year 1 and 1 dose year 2:	For 2 doses year 1 and 1 dose year 2:
					PP	88.7% (82.0–93.2)[c]	85.8% (78.6–90.9)[c]
					ITT	Non available	85.3% (78.3–90.4)
Bracco Neto 2009, D153-P504[28]	Africa Latin America	6 to <36M	1886	2001, good	PP	73.5% (63.6–81.0)	72.0% (61.9–79.8)
				2002, relative	PP	For 2 doses year 1 and 1 dose year 2: 73.6% (33.3–91.2)[c]	For 2 doses year 1 and 1 dose year 2: 46.6% (14.9–67.2)[c]
				2001, good	PP	For 1 dose only: 57.7% (44.7–67.9)	For 1 dose only: 56.3% (43.1–66.7)
				2002, relative	PP	For 1 dose only: 60.3% (10.9–83.8)	For 1 dose only: 59.4% (32.3–76.4)
Lum 2010, D153-P522	Asia/Oceania Latin America	11 to 24M	1150	2002-2003, relative	PP	78.4% (50.9–91.3)	63.8% (36.2–79.8)
					ITT	72.8% (46.1–86.9)	63.8% (39.6–78.5)
Belsche 1998, AV006Yr1[29]	USA	15 to 71M	1259	1996-1997, good	PP	Not applicable	93.4% (87.5–96.5)[d]
Belsche 2000, AV006Yr2[30]	USA	27 to 83M	1358[e]	1997-1998, poor	PP	100% (63.1–100)[c] for 2 doses year 1 and 1 dose year 2	87.1% (77.7–92.6)[c] for 2 doses year 1 and 1 dose year 2

Source: European Commission, EPAR LAIV, 2011.[27]
PP: per protocol analysis; ITT: intention-to-treat analysis; PP are taken from the EMA EPAR report while ITT are extracted from the related published studies.
a: For purposes of study grouping, Europe includes Western and Eastern Europe, Scandinavia, Israel and Lebanon, while Asia/Oceania includes East Asia, Southeast Asia, South Asia, and Australia.
b: Age range as described in the protocol for the study, M = months.
c: Rates shown are for second-season revaccination.
d: Results for subjects in the 2-dose group (primary endpoint).
e: All subjects in AV006 Year 2 were included in AV006 Year 1.

In the six selected trials, which involved more than 10 000 subjects aged between 6 and 71 months, LAIV efficacy for a 2 dose schedule ranged 49–93% in children aged 6–71 months (Table 2). Efficacy was generally higher in Europe and US settings compared to the other settings, with an efficacy for 2 doses against any influenza strain ranging 84–93% in Europe/US compared to 64–72% in other settings where influenza is usually not epidemic (i.e. Asia and Africa).

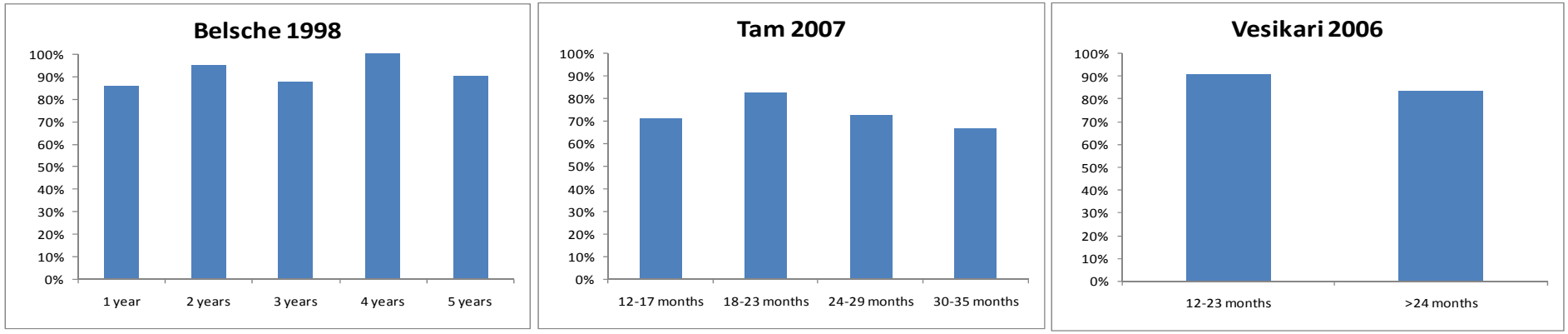
The efficacy of a single LAIV dose was estimated in three studies over four seasons and ranged 56–89%.[28, 29, 31] Comparing estimates from the same studies and the same season, a two dose schedule achieved a 5–16% higher efficacy compared to a single dose in two studies (94% and 72% for 2 doses vs. 89% and 56%, respectively).

LAIV efficacy in subjects receiving 2 primary doses followed by a single dose in the next year ranged 47-97%, with the same difference across regions as for the primary 2-dose schedule. In two studies, some degree of protection of a 2-dose schedule in the first season persisted in the second season without revaccination, but ranked lower due to waning immunity and was not significant against any strain (efficacy in the second season without re-vaccination: 35.3% (95%CI -0.3–58.7%);[28] 23% (95%CI -7–44%)).[31]

Unlike observed for TIV efficacy in adults, the degree of matching and viral intensity did not seem to affect LAIV efficacy estimates, and these remained high in seasons with poor match between vaccine and circulating strains (Table 2).[30, 32] LAIV efficacy was equally high for older and younger children, remaining stable across age throughout the studied age range (6-71 months) as illustrated in Figure 2. No clinical trial provided efficacy data in ages above 6 years. LAIV efficacy was equally high for older and younger children, remaining stable across age throughout the studied age range (6-71 months) as illustrated in Figure 2.

No clinical trial provided efficacy data in ages above 6 years but recent observational studies in the US did not indicate significant differences in effectiveness in older ages. An observational study conducted during the mismatched 2003-04 season revealed a LAIV effectiveness against culture-confirmed influenza at 60% (95%CI 25–84%) in the 5-9 years and 54% (95%CI 23–78%) in the 10-18 years of age.[33] Other studies mostly pooled LAIV and TIV but showed similar effectiveness across ages, including in children >6 years of age.[34-36]

Figure 2 – LAIV efficacy across age groups in clinical trials among children 6-71 months of age[29, 31, 37]



The only included trial that compared LAIV to TIV efficacy in children found a significantly higher efficacy of LAIV compared to TIV among subjects aged 6-59 months in the well matched 2004-05 season in sites across Europe, US and Asia.[38] The relative efficacy of LAIV vs. TIV was estimated at 44.5% (95%CI 22.4–60.6%) against culture-confirmed influenza caused by antigenically matched strains and at 54.9% (95%CI 45.4–62.9%) for any strains. Other published studies suggested a higher efficacy for TIV compared to LAIV, but these were not included in the review as they involve other endpoints or a substantially different population.[39, 40] The EMA concluded that LAIV consistently performed better than TIV.[27]

The adult data indicated some degree of efficacy over placebo but unexplained inconsistencies between and within studies. For this reason, the CHMP advised to reduce the upper age limit of the LAIV indication to 18 years as no conclusive data were provided on the benefit of this vaccine in the adult population.[27]

3.1.2.2 Pooled LAIV efficacy estimates

We calculated pooled estimates for the key vaccination schedules to provide LAIV efficacy parameters for the models, after excluding one study that targeted children outside the recommended age (Lum et al. in 11–23 months)[32] and another trial that did not provide numbers of cases.[28] Partial data from this latter study could however be obtained in a meta-analysis.[41]

Results are presented in Table 3 and Figure 3. As studies providing efficacy of 2 doses and 1 dose differed in setting, subjects and season, we calculated the relative efficacy of 2 doses vs. 1 dose among subjects from the same setting and in the same season, which was only available in the US large trial.[30]

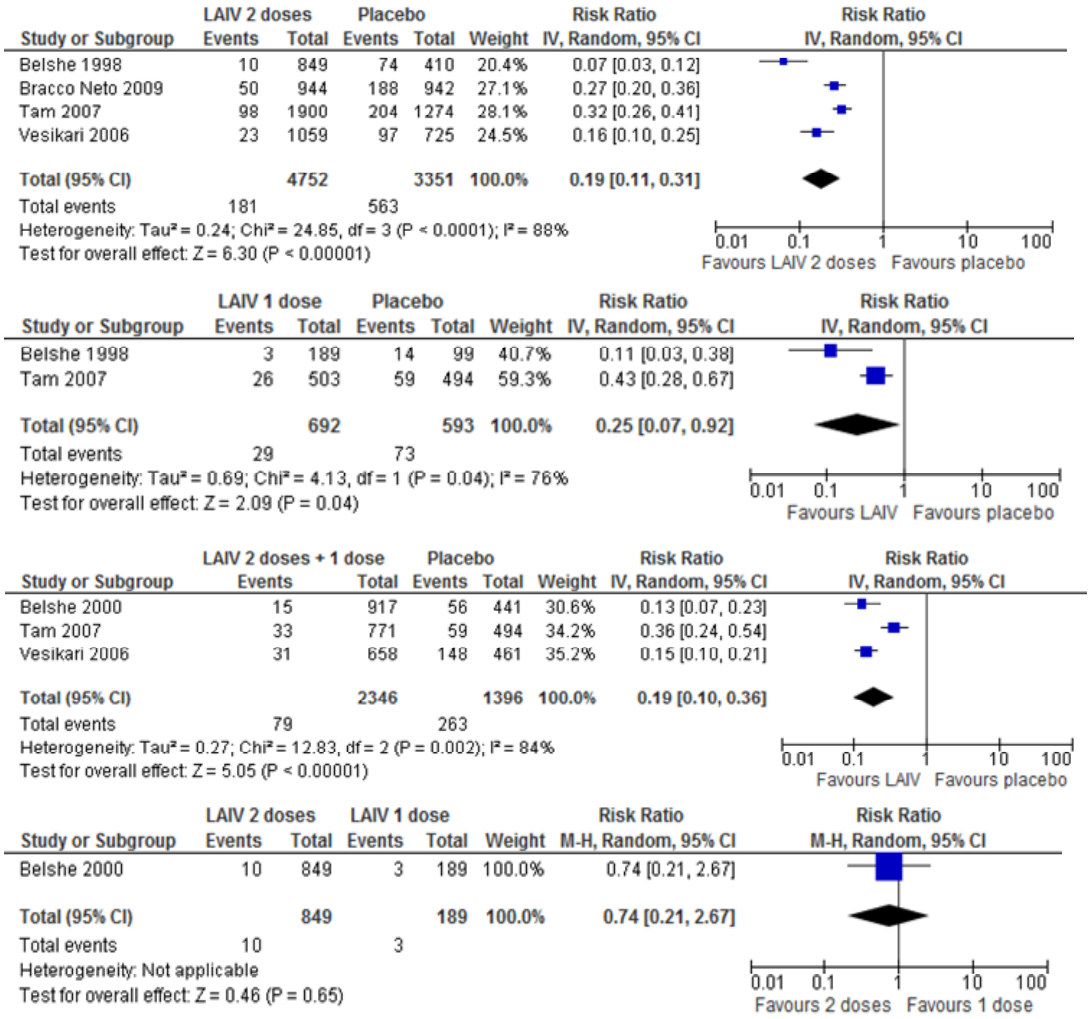
Given the stability of LAIV efficacy across age below 6 years and the stability of LAIV effectiveness in older age groups observed in recent observational studies, we assumed a constant LAIV efficacy between 2 and 17 years.

Table 3 – Pooled estimates of LAIV efficacy, per schedule, in children 6-71 months of age

LAIV schedule tested	Number studies	Number subjects	Efficacy (95%CI)
VE 2 doses	4	8103	81% (69–89%)
VE 1 dose	2	1285	75% (8–93%)
VE 2 doses year 1, 1 dose year 2	3	3742	81% (64–90%)
Relative efficacy 2 doses vs. 1 dose	1	1038	26% (-167–79%)

VE : Vaccine efficacy.

Figure 3 – Forest plot on LAIV efficacy for 2 doses, 1 dose, 2 doses + 1 dose (year 1, year 2) and relative efficacy for 2 vs. 1 dose



3.1.2.3 *Trivalent Inactivated Vaccine (TIV) studies in children*

Supplement 1 (Section 1) lists the primary research and review articles, respectively, found in the updated search identified for further scrutiny, along with the reasons for their exclusion (if applicable). The review published by Osterholm et al provided the most interesting insights on TIV efficacy in children.[42]

Only one placebo-controlled randomized study involving cases that are laboratory confirmed by culture and/or PCR was identified.[43] It ran over two consecutive respiratory seasons among children 6–24 months of age. During the first season the attack rate in the placebo group was 16% and thus the influenza activity was regarded as normal. A significant efficacy of 66% was reported, shown with point estimates for efficacy in children aged 6–12 months, 13–18 months, and 19–24 months at 63%, 66%, and 69%, respectively. These estimates can be considered high for TIV in children. A decrease of the incidence of influenza-associated acute otitis media by 62% in the vaccinated group was noted. In the second season, however, an exceptionally low influenza activity in the area (attack rate in the placebo group, 3%) was noted and no vaccine efficacy against influenza could be observed. It should be noted that a Cochrane review on influenza vaccine efficacy in children, published after our search period, included this low activity season. The Cochrane review thus concluded that TIV in children aged two years or younger is not significantly more efficacious than placebo, because the pooled vaccine efficacy estimate over the two seasons included in this trial was not significant.[44]

Table 4 – Randomised controlled trial of TIV in children meeting the inclusion criteria by Osterholm et al[42]

First author	Healthy children aged 6–24 months Number of participants (trial period)	Vaccine efficacy (95%CI)	Reported antigenic match	
Hoberman[43]	411 (in 1999–2000)	66% (34–82)	Type A: similar H3N2 and H1N1	Type B: not reported
Hoberman[43]	375 (in 2000–2001)	-7% (-247–67)	Type A: similar H3N2 and H1N1	Type B: lineage match

3.1.3 *Influenza vaccine efficacy in healthy adults*

The issues related to vaccine efficacy in adults were discussed at length in the Part I report. We therefore discuss this only briefly in this section, based on the most suitable recent reviews we identified, and the search update we made to the part I report.

Supplement 1 (Section 1) lists the search results from our updated search, which were selected for further scrutiny. The review published by Osterholm et al[42] provides the most interesting insights as it used the same inclusion criteria regarding study methods and restricted outcomes to cases confirmed by PCR/culture (see Supplement 1). Osterholm retrieved 8 RCTs in healthy adults aged 18–64 years, covering nine influenza seasons, with vaccine efficacy ranging 16–76% (median 62%), see Supplement 1. A random-effect pooled vaccine efficacy was estimated at 59% (95%CI 51–67).

Part I had already included all these studies, except Frey and Madhi. All of these trials are double blind trials with the exception of Frey et al, which is a single blinded observer RCT and thus not included.[45] The Madhi study was not conducted in healthy adults and is thus not considered in this section.[46] Michiels et al reported on an additional RCT conducted by Barrett et al.[47] This trial investigated the safety, immunogenicity and protective efficacy of a Vero-cell-culture-derived influenza vaccine against culture and/or PCR confirmed influenza infection.[48] They also assessed the correlation between vaccine efficacy and haemagglutination inhibition antibody titer. During the 2008–09 season, 7250 participants were double-blind randomly assigned to vaccine (n=3626) and placebo (n=3624). Overall protective efficacy for antigenically matched culture-confirmed influenza infection was 78.5% (95%CI 60.8–88.2); efficacy for all laboratory-confirmed infection (by culture and/or PCR) caused by any strain was 71.5% (95%CI 54.7–82.1%).

3.1.4 Influenza vaccine efficacy/effectiveness in the elderly

The review update identified five eligible systematic reviews out of the 81 retrieved by the literature search.[41, 42, 47, 49, 50] Osterholm included RCTs and observational studies in the elderly, using the same selection criteria and outcome as the review in Part I, and searched studies up to February 2011.[42] It retrieved no RCT and only one additional observational study,[51] which was excluded from our former review (Part I) because it involved a subset of cases analyzed in another included study.[52] Another study was retrieved but did not provide separate VE estimates for the elderly.[53] In a report published in 2012, Osterholm updated his search up to April 2012, and retrieved seven additional studies.[50] Out of these studies, none was eligible as two were from other settings,[54, 55] two involved pandemic influenza only,[56, 57] one was restricted to children,[58] and three did not provide separate estimates for the elderly because too few cases were identified in that age group.[34, 59, 60] Lang performed a review of reviews on efficacy in the elderly, including only RCTs.[49] The included reviews were already covered by Part I, with the exception of Osterholm described above. Michiels also included controlled trials but excluded observational studies.[47] She retrieved one recent RCT that was not included in part I but it only involved adults <65 years of age.[48] She did not include any more recent studies in the elderly. Manzoli performed an "umbrella review" and did not identify any more recent review.[41]

The search for primary studies published after April 2012 (last search from Osterholm report) retrieved 378 additional papers (as of 19/11/2012). No RCT involving elderly was retrieved. Only four observational studies were eligible and provided separate estimates for the elderly.[35, 61-63] Search from references of key papers also retrieved one primary study missed by the Osterholm updated search.[42, 64] These five eligible studies are listed in Table 5 (together with the study retrieved in Part I) and the findings are described below, by outcome.

3.1.4.1 Laboratory confirmed influenza like illness

A pooled case-control analysis involved eight EU countries (I Move study) in the 2010-11 season and considered all potential confounders.[64] Adjusted VE in the ≥60 years was 60% (95%CI 17–81%). The 2010-11 season was characterized by a good match between vaccine and circulating strains and high to moderate intensity, depending on the country. The same pooled analysis was repeated in the 2011-12 season, which was characterized by a low intensity, delayed season and relative match between strains.[65] However, only early estimates were provided and did not allow for stratified results in the elderly. Final results were presented at a congress but not published at the date of last search. A German study conducted a similar study in the 2010-11 season based on outpatient cases from GP practices but did not adjust for severity of underlying disease.[61] The number of influenza cases in the elderly was limited (18 cases) and IVE was not significant in this group. However, the IVE point estimate was surprisingly high (92.4%, 95%CI -66.7–99.7%), even higher than in the other age groups, but all 95%CI were overlapping due to small numbers. Another similar study was conducted among GP practices of England, Wales, Northern Ireland and Scotland, and did not adjust for severity of underlying disease neither. The IVE estimates by age are only provided by strains and amount to around 65–75% (Table 5).[63]

A number of other studies involved elderly subjects but did not provide separate estimates for this group.

3.1.4.2 Influenza-related admissions

Only one study involved influenza-related hospitalizations and provided separate estimates in the elderly. This case-control Spanish study evaluated IVE in preventing influenza hospitalization in adults, by taking into consideration all major potential confounding factors.[62] It found an adjusted IVE at 58.5% (95%CI 16.1–79.4%) in the elderly ≥65 years of age during the 2010-11 season. A number of other studies also evaluated the IVE in preventing admissions, but did not provide estimates in the elderly,[59, 66] or did not involve laboratory confirmed cases.[67]

3.1.4.3 Mixed influenza-related outcomes

A US case control study evaluated IVE in the 2010-11 season, enrolling patients with acute respiratory illness and positive PCR from hospitals, emergency departments and outpatient clinics in four states.[35] Controls were influenza negative patients. The analysis did adjust for most potential confounding factors but not for severity of underlying disease. IVE was estimated at 38% and not statistically significant (95%CI -22%–66%) due to small sample size, and was lower than in the other age groups. The

2010-11 US influenza season showed a good match between vaccine and circulating strains, and the season was described as of moderate intensity.

A study conducted in Hong Kong, which was excluded because it concerned the pandemic H1N1 influenza, is described below due to interesting findings on TIV effect on all-cause mortality.[68] Chan et al describe a prospective 12-month cohort study for mortality on institutionalized elderly of nine nursing homes in Hong Kong during the 2009 pandemic. Elderly persons who were followed up and had been vaccinated by the Department of Health were included. On the 711 included elderly, 274 received both seasonal influenza vaccine and (H1N1) 2009 vaccine (H1N1-TIV), 368 received seasonal influenza vaccine only (TIV alone) and 69 received no vaccination (unvaccinated). Multivariate analysis demonstrated that H1N1-TIV vaccination in the institutionalized elderly significantly reduced all cause mortality by 54% (Hazard Ratio (HR) 0.46; 95%CI 0.29–0.72; p < 0.001) and 74% (HR 0.26; 95%CI 0.13–0.49; p < 0.001), compared with vaccination of seasonal vaccination alone and no vaccination, respectively. In univariate analysis, TIV alone did reduce mortality by 39% compared to unvaccinated, at the limit of significance (RR 0.62; 95%CI 0.38–1.01), but results of multivariate analysis are not provided. This observational study did adjust for possible confounding factors, including for functional status.

3.1.4.4 Summary of vaccine efficacy and effectiveness studies in the elderly

Only few IVE studies could provide significant IVE estimates for influenza confirmed cases in the elderly, in spite of seasons with good match between influenza strains, mostly due to difficulties in recruiting cases in that age group. The most robust estimates are from the European pooled analyses from case control studies across 5-8 EU countries, which involved around 300-500 patients (cases and controls) by season, are based on PCR/culture confirmation and adjust analyses for the major confounding factors.[64, 65] The IVE estimates ranged 59-60% in the two seasons with good match and medium/high intensity. A Spanish study found a similar IVE (58.5%) to prevent influenza confirmed hospitalisations in 2010-11.[62] Other studies involved too few cases or composite influenza outcomes, with non-significant IVE and large 95%CI around point estimates.

Table 5 – Vaccine effectiveness of TIV in studies in the elderly meeting the inclusion criteria; cases confirmed by culture and/or PCR

First author (year)	Population	Number of included influenza cases	Adjusted vaccine effectiveness (95%CI)	Season
Outpatient cases				
Kissling (2009)[1]	All patients ≥65 years with laboratory confirmed ILI in 5 EU countries	NA	59% (15–80)	2008-09, good match, medium/high intensity
Kissling (2011)	All patients ≥60 years with laboratory confirmed ILI in 8 EU countries	113	59.9% (17–81)	2010-11, good match, medium/high intensity
Englund (2012)	All outpatient ≥60 years from GP practices with PCR confirmed ILI from Bavaria, Germany	18	92.4% (-66.7–99.7)[2]	2010-11, good match, medium/high intensity
Pebody (2012)	Outpatient from GP practices with PCR confirmed ILI from England, Wales, Northern Ireland and Scotland	53	By strain: A/H1N1: ~73% B: ~65%	2010-11, good match, medium intensity
Hospitalisations				
Puig Barbera (2012)	Influenza-related hospitalised cases, ≥65 years, from Valencia region of Spain	58	58.5% (16.1–79.4)	2010-11, good match, medium intensity
Composite outcomes				
Treanor (2012)	All patients ≥65 years with laboratory confirmed ARI from hospitals, emergency departments and outpatient clinics in 4 US states	63	36% (-22–66)[2]	2010-11, good match, medium intensity

ILI: Influenza like illness; ARI: Acute respiratory infections; NA: Not available.
1: Included in part I.
2: Not adjusted for severity of underlying disease.

3.1.5 *Influenza vaccine efficacy/effectiveness in the persons ≤65 years with co-morbidities*

The Osterholm review only retrieved one RCT in adults with HIV, which was conducted in other settings (Africa),[46] and noted that no eligible observational studies provided separate estimates for persons with co-morbidities.[42] The search for primary studies after the Osterholm report search period retrieved no eligible primary studies in patients with co-morbidities exclusively. However, six effectiveness studies involving adults provided stratified IVE results for persons with co-morbidities and IVE estimates ranged 36-81% (Table 6).[35, 61, 62, 64, 69, 70] Four studies also provided IVE in persons without co-morbidities, and suggested no or minor differences in IVE between persons with or without co-morbidities and no clear trend.[35, 61, 69, 70] The two other studies showed that IVE in persons with co-morbidities was grossly similar to those estimated in the total population.[62, 64] However, most studies provided IVE estimates for all age groups confounded (not limited to those ≤65 years of age); an exception was the Kissling study but the estimate is for the target group for influenza vaccination aged 15-59 years, thus including some health care workers as well.[64]

In conclusion, these data do not suggest that IVE against laboratory confirmed influenza differs between persons with or without co-morbidities.

Table 6 – TIV effectiveness in persons with co-morbidities; cases confirmed by culture and/or PCR

First author (year)	Population	Adjusted vaccine effectiveness (95%CI) in adults with co-morbidities	Adjusted vaccine effectiveness (95%CI) in healthy adults	Season
Outpatient cases				
Janjua (2012)	Outpatient cases, all ages, with confirmed ILI from Canada	58% (42–69)	65% (49–76)	2007-08, relative match, medium intensity
Skowronski (2012)	Outpatient cases, all ages, with confirmed ILI from Canada	36% (16–51%)	38% (14–55%)	2010-11, good match, medium intensity
Englund (2012)	Outpatient cases from GP practices, all ages, with PCR confirmed ILI from Bavaria, Germany	80.6% (32.7–94.4)	75.7% (32.8–91.2)	2010-11, good match, medium/high intensity
Kissling (2011)	Patients 15-59 years with laboratory confirmed ILI in 5 EU countries. Co-morbidity = target group for TIV	54.0% (6.6–77.3)	NA (in all 41.3%; -2.6–66.4)	2010-11, good match, medium/high intensity
Hospitalisations				
Puig Barbera (2012)	Influenza-related hospitalised cases, all ages, from Valencia region of Spain	53.4% (4.1–77.3)	NA (in all 53.9%; 11.4–76.0)	2010-11, good match, medium intensity
Composite influenza outcomes				
Treanor (2012)	Patients from all ages with laboratory confirmed ARI from hospitals, emergency departments and outpatient clinics in 4 US states	54% (40–64%)	62% (53–69)	2010-11, good match, medium intensity

ILI: Influenza like illness; ARI: Acute respiratory infections; NA: Non available.

3.2 Vaccine safety

The sections below describe the safety issues related to children (TIV and LAIV), and adults (TIV). The more exceptional and more severe potential adverse events, such as Guillain-barre syndrome, which concern both adults and children, are described in a separate section.

3.2.1 *Influenza vaccines safety in children*

3.2.1.1 *TIV*

An overview of the safety of seasonal influenza vaccines for children is provided by Heikkinen & Heinonen.[71] They conclude that some local reactogenicity, such as swelling, redness and soreness at the site of injection are common but short-lived (as is the case for any vaccine). The article summarises published data from several clinical trials in children:

- France et al[72] published data from 251 600 children who had received a total of 438 167 influenza injections. The children served as their own control, the investigators compared the numbers of medically attended events during the 14 days after vaccination with two control periods (days 15–28 before vaccination and days 15–28 after vaccination). Only 9 cases of impetigo in children 6–23 months of age were significantly associated with influenza vaccination. This large study did not reveal any evidence for important safety concerns.
- Hambridge et al[73] reported on the safety of TIV in 45 356 children 6–23 months of age, amounting to 69 359 vaccinations in a retrospective study. This was also a self-control evaluation. They compared the rates of any medically attended events in various risk windows up to 42 days after vaccination with two controls periods, one before vaccination and the second after the risk window. During the 14 days after vaccination (primary analysis) 13 different medically attended events were less likely to occur, while only the diagnosis of gastritis/duodenitis was more frequent during this period. After chart review, this diagnosis was not any more significantly associated with influenza vaccination
- Englund et al[74] evaluated the use of influenza vaccines in the very young children: they tested 1375 infants at age 6–12 weeks. Within 3 days of vaccination, fever was reported in 11.2% of TIV recipients and in 11.7% of infants who received placebo. In a 28-day follow-up period serious adverse events were reported in 1.9% of TIV and 1.5% of placebo recipients.

Heikinnen & Heinonen[71] also cite Vesikari et al,[75] who reported on the use of the Novartis adjuvanted (MF59) seasonal vaccine in children. They concluded that solicited local or systemic reactions were reported more frequently in recipients of MF59-adjuvanted vaccine than among those who received a non-adjuvanted vaccine. There was no increase in the incidence of unsolicited or serious adverse events (AE) and most of the reactions were mild to moderate and transient. This study was heavily criticised by the European Registration authorities and the Company has withdrawn its application. Heikkinen also report on the association of narcolepsy and the pandemic vaccine that was published by the Finnish and Swedish authorities after the use of the H1N1 AS03 adjuvanted pandemic vaccine. This last issue is also discussed below.

3.2.1.2 *LAIV*

Heikkinen & Heinonen's[71] conclusions on LAIV safety concur with those of the LAIV EPAR, which gives in much more detail the safety profile of this vaccine. As said above under LAIV efficacy, the EC has granted MedImmune a marketing authorisation for FLUENZ for children from 24 months onwards up to 18 years. The SPC warns for the use of this vaccine below the age of 12 months for safety reasons: "In a clinical study, an increase in hospitalisations was observed in infants and toddlers younger than 12 months after vaccination. It is not recommended to administer FLUENZ to infants and toddlers 12–23 months of age. In a clinical study, an increased rate of wheezing was observed in infants and toddlers 12–23 months of age after vaccination". Further details on LAIV safety data are provided in the FLUENZ EPAR (below).

Data on FLUENZ from the EPAR[27]

In several studies, *solicited* AE were monitored by diary cards for 10 to 14 days post any vaccination in the paediatric population and for mostly 7 days post vaccination in adults. The difference in collection periods is based on the original hypotheses that titre and duration of vaccine virus shedding would be greater in children than in adults and that solicited adverse events would be temporally related to vaccine virus shedding, as suggested by data from clinical studies. However, this short surveillance period precludes any possibility to detect late AE detectable up to day 28

post administration (some of those late AE are taken into account in the efficacy studies as Influenza-Like Illness (ILI) symptoms from the classical start D14/D15 post vaccination surveillance for efficacy data). Obviously, due to the live attenuated character of the FLUENZ vaccine, solicited and unsolicited AE mimic an influenza illness episode.

Unsolicited AE were recorded for 14 to 42 days following each dose. Globally, all serious AE were recorded during the study period from the day of vaccination through day 42 post last dose since it was the most common data collection period and from day of vaccination until day 180 post last dose (that is, 180 days post dose 1 if only 1 dose was administered or 180 days post dose 2 if 2 doses were administered).

Reactogenicity could be evaluated after repeated vaccination in more than half of paediatric studies (two doses in the same year or one yearly single dose up to three annual revaccinations). Safety data were derived from over 141 000 subjects who received FLUENZ in 73 clinical and postmarketing studies conducted over more than a decade (from 1994 to 2008) in multiple regions of the world. Of these 73 studies, 57 contribute to FLUENZ exposure in 123 834 subjects. Among these 57 studies, 39 included more than 39 000 children aged 7 weeks to 17 years and, 18 studies included more than 8 500 adults aged 18 years to 97 years. Two of the 57 studies are postmarketing studies.

Additionally, more than 10 million doses of FLUENZ have been distributed commercially in the USA from initial licensure in 2003 until the end of the 2007-2008 influenza season. Overall, based on the available data from individual studies (stratified analysis by age groups), FLUENZ was considered safe and well tolerated with a safety profile similar to that of the comparator treatment group (TIV and placebo).

Based on individual studies, the use of antipyretics (for the children group) was more frequent in the FLUENZ group compared to the control group (TIV or placebo) with rate differences in some studies ≥ 2.0 percentage points. Reactogenicity was generally higher after the first dose of R-FLUENZ than after the second dose or after the yearly revaccination (up to 4 years). In fact in all age groups for FLUENZ, TIV, placebo groups, the incidence of reactions showed a tendency to decrease post the second dose and the yearly revaccination (the rate of events being then in between those of post dose 1 and post dose 2).

In subjects <18 years of age, among solicited AE runny or blocked nose was more commonly observed in the FLUENZ group than in either the TIV or placebo groups. Other solicited AE with rate differences ≥ 0.9 percentage points (FLUENZ>comparator) in both TIV and placebo controlled studies included decreased appetite, irritability, headache and fever ≥ 38.0°C. High fever (≥ 39.5°C) was no more common in FLUENZ subjects than in subjects who received placebo or TIV.

The most important unsolicited AE by rate difference were generally similar to events defined as solicited AE (e.g. rhinorrhoea and pyrexia). The most frequently reported solicited AE that occurred at a higher rate in FLUENZ than TIV or placebo subjects was pyrexia. The incidence of rhinorrhoea and upper respiratory tract infection were also usually higher in the FLUENZ treatment group than in the comparator treatment group. The use of antipyretics (for the children group) was more frequent in the FLUENZ group compared to the control group (TIV or placebo) with rate differences ≥ 2.0 percentage points.

Analysis of serious AE and death case-reports in any age did not reveal any significant safety concern with the use of FLUENZ. No death (119 cases for >141 000 recipients) was considered to be related to FLUENZ.

A significant increase in wheezing events was observed in subjects younger than 24 months of age (Study MI-CP111 including children aged from 6 to 59 months, comparing LAIV to TIV) but this risk seemed to be confined to those with a pre-existing history of wheezing or asthma.[38] No such increase in rates of wheezing was seen in subjects ≥ 24 months of age in this study.

Three other reviews of literature and post-marketing safety data on TIV and LAIV in children corroborated these data.[3, 50, 76] They conclude that TIV and LAIV are safe and well-tolerated, and that AE are usually mild to moderate. Overall, injection-site reactions (pain and inflammation) are the most common AE described for TIV while runny nose is the most common AE for LAIV. One also describes febrile seizures associated with a specific vaccine in Australia (from CSL limited) but these are not discussed here as this vaccine is not available in Belgium.[50]

3.2.2 Influenza vaccines safety in adults

In contrast to the discussion on influenza vaccination of children, few data are published in review articles on the safety of seasonal influenza vaccination of adults. However five recent sources provide relevant information: the 2010 report from the US Advisory Committee on Immunization Practices (ACIP), the meta-analysis published by Manzoli on H1N1 pandemic vaccines,[77] a report from the Center for Infectious Disease Research and Policy (CIDRAP) from Minnesota University,[50] the EPAR of the seasonal influenza vaccine Intanza,[78] and a technical report published by the ECDC on influenza vaccines in children and pregnant women.[76]

3.2.2.1 Seasonal influenza vaccine safety in adults

An extensive literature review was conducted by the team of Osterholm on TIV safety. They reported that TIV is safe and well tolerated.[50] Injection-site reactions, such as pain and inflammation, were the most common reported AE. TIV has also been associated with a few very rare and unique AE, which include Guillain-Barré syndrome (GBS) and narcolepsy discussed below. The ACIP 2010 report reported similar findings for mild AE.[3] TIV administration in older persons and persons with co-morbidities was not associated with higher rates of systemic symptoms compared to placebo or compared to younger age groups. In clinical trials, severe AE occurred after vaccination at a rate of <1%. Post-marketing surveillance in the US did not identify new safety concerns. The most severe AE reported after TIV in adults was GBS.

The EPAR for Intanza also provides useful insight on TIV safety, although the route of administration (intradermal (ID) application) is clearly different from the other TIV's, which are administrated via the intramuscular (IM) route. The AE profile of this vaccine might be somewhat different from the normal TIV's for the local AE's, but the overall difference in safety profile is not large (as shown in the EPAR).[76]

There was no safety signal regarding the solicited systemic reactions that occurred within 7 days after vaccination, whatever the dose level of the ID Influenza Vaccine and the delivery route.

The AEs categorized as common (i.e. with a frequency >1%) in the ID group were:

- Nasopharyngitis (3.9%)
- Headache (3.4%)
- Pharyngolaryngeal pain (2.6%)
- Rhinitis (1.4%)
- Back pain (1.3%)
- Cough (1.1%)
- Dysmenorrhea (1.1%)

In terms of severity, the highest proportion of subjects with unsolicited moderate or severe AEs occurred, in both the ID and the IM group, in the System Organ Class of Infections and Infestations (3.1% of ID subjects).

The ID vaccine is commonly associated with a range of local and systemic adverse reactions. These adverse events are not often of severe intensity and the safety profile would not preclude the use in adults 18 to 59 years and elderly aged > 60 years.

Although injection site reactions were as expected higher in subjects vaccinated by the ID route than by the IM route, no other data indicate that the safety of this vaccine is different from other authorized IM influenza vaccines.

From these data, it is concluded that seasonal influenza vaccines have an acceptable safety profile.

3.2.2.2 H1N1 influenza vaccine safety in adults

Manzoli et al searched Medline, Embase and nine clinical registries to find RCT's using a pandemic H1N1 virus to perform a meta-analysis to identify the best formulation that was used in the pandemic season 2009-2010 against the pandemic strain H1N1/2009/Califonia. They included 18 RCTs in their primary analysis with a total of 16 725 subjects. Primary outcome was the seroconversion rate according to hemagglutinination-inhibition (HI); secondary outcomes were adverse events. Therefore this review might be of interest as these vaccines should protect against an influenza virus infection.

Clearly, this review should be regarded very critically as most of these vaccines differ greatly from the seasonal as their composition, use of adjuvants, etc was different. However it is felt important as very few large safety datasets are available for seasonal influenza vaccines.

The authors summarise their findings as follows:

- The rate of serious vaccine-related adverse events was low for all 2009 H1N1 vaccines (0.013% overall).
- This meta-analysis does not have enough power to draw a conclusion for vaccine safety at the population level.
- For mild to moderate adverse reactions, these were clearly more (and very) frequent for oil-in-water adjuvanted vaccines, but the reporting of mild or moderate adverse events was lacking or suboptimal in many trials.

The results of such analyses must be interpreted with caution, but these vaccines seem to have a positive benefit-risk ratio.

3.2.2.3 Influenza vaccine safety in pregnant women

Tamma et al[79] conducted a review on influenza vaccination during pregnancy and discussed the data from 2 RCTs and 10 observational studies. They concluded: “Inactivated influenza vaccine can be safely and effectively administered during any trimester of pregnancy. No study to date has demonstrated an increased risk of either maternal complications or untoward fetal outcomes associated with inactivated influenza vaccination. In addition, no scientific evidence exists that thimerosal-containing vaccines are a cause of adverse events among children born to women who received influenza vaccine during pregnancy.”

Mak et al[80] concluded in their review that there are limited data on vaccine safety, but that the few prospective studies of pregnant women suggest that the vaccine is safe.

Blanchard-Rohner and Siegrist[81] showed in their review that no serious adverse events or increase in adverse pregnancy outcomes were found in any of the studies they identified.

At the moment, there are no indications that vaccinating pregnant women against seasonal flu causes harm. However, data on safety are scarce, especially for Europe, since there is no published information on RCTs or large observational studies in Europe.

A few papers have been published since the cited review studies were published. Some of these are related to the use of pandemic influenza vaccines, and are thus only partially of interest.

Recently Pasternak[82, 83] published two articles on the use of pandemic vaccines in pregnant women in Denmark. Both articles conclude the same: in Denmark 50 000 pregnant women were followed as part of their pregnancy after being vaccinated with the AS03 adjuvanted vaccine, and no adverse outcome was detected for the babies after delivery.

Several recent articles have supported more extensive vaccination in pregnancy, but these were not accompanied by formal systematic reviews.[84-86]

In sum, several papers have underlined the desirability of vaccinating pregnant women. Most of these recommendations are based on the morbidity of ILI in pregnant women and neonates. The Danish experience illustrates nicely that during the pandemic the vaccination of pregnant women did not harm mothers or children. Unfortunately the study was not sufficiently powered to conclude that the absence of harm (in terms of major birth defects, preterm birth, and small size for gestational age) could be extrapolated as a clear benefit for mother and infant. This experience was shown with an adjuvanted monovalent pandemic influenza vaccine. Many vaccinologists would accept that these data are also relevant for seasonal influenza vaccines.

In conclusion, sparse data are available for the use of seasonal vaccines in pregnant women; however the data that are published are reassuring.

3.2.3 Special potential issues for influenza vaccine safety

Since the Guillain-Barré syndrome (GBS) was found associated with influenza vaccination in 1976, much research has been done to verify whether seasonal influenza vaccination has an increased risk of this syndrome.[87]

A British self-controlled case series study, using 775 GBS episodes of all age groups, found no evidence of an increased risk of GBS after seasonal influenza vaccine, with a non-significant lower relative risk of 0.76 (95%CI 0.41–1.40) within 90 days after vaccination. In contrast, the study found greatly increased risks of GBS after influenza like illness (ILI), with relative

risks of 16.6 (95%CI 9.4–29.5) and 7.4 (95%CI 4.4–12.4) within 30 and 90 days after ILI, respectively.[88]

During the 2009 pandemic, in the Scandinavian countries many children were vaccinated with the H1N1 AS03 adjuvanted vaccine. Two published studies found a temporal association between vaccination and narcolepsy in children in England and Finland, but this association was not found in Canada where 2 million children were vaccinated with a comparable vaccine.[89, 90] Fang Han et al[91] have also shown that the wild influenza virus H1N1 could induce narcolepsy as well. Narcolepsy is a very rare, poorly understood neurological entity and the association is not understood. More research will be needed to elucidate any potential causal relationship between influenza vaccination and narcolepsy.

In summary, no important safety issues have been published for the large-scale use of seasonal vaccines in children. Narcolepsy has been temporally associated with H1N1 AS03 adjuvanted vaccine in some countries but this was not observed in other countries. More research is required to understand these observations.

3.3 Economic evaluations

3.3.1 Childhood vaccination options

A literature review was made of English-language economic evaluations of seasonal influenza vaccination in those aged less than 18 years, starting from a descriptive literature review up to the year 2006.[92] New publications up to October 2012 were identified through SCOPUS literature searches using the search terms (as keyword, title or abstract) 'influenza' AND 'vaccine' (or 'vaccin', 'vaccination', 'immunization', 'immunisation') AND economic (or 'cost-effectiveness', 'cost-benefit', 'cost-utility', 'cost effectiveness', 'cost benefit', 'cost utility'). The search identified 20 publications[4, 14, 15, 93-109] that met our criteria (i.e. "textbook" full economic evaluations[110]). Additional search updates were made up to March 2013, yielding another four publications, which are briefly discussed at the end of this section.

3.3.1.1 Clinical endpoint assumptions

As shown in Table 7, most studies used efficacy estimates against one of two outcomes: clinically diagnosed influenza-like illness (ILI) and/or laboratory confirmed influenza infection. However, several studies applied efficacy estimates against influenza-related healthcare resource use such as hospital admissions.[95, 97, 102, 104] One study also considered efficacy against otitis media.[93]

Several economic evaluations used estimates of vaccine efficacy and disease incidence based on a single clinical trial[4, 93, 95, 98, 99, 106] or observational study.[102, 104]

Adverse events associated with influenza vaccination were included in some but not all studies (Table 8). Where included they were generally not found to be influential in determining cost-effectiveness. Inclusions of such events are likely to be more important when assessing LAIV than TIV (see section on vaccine safety above).

3.3.1.2 Indirect effects

Influenza vaccination not only protects vaccine recipients but may also indirectly protect their social contacts. This effect is often represented using dynamic models, which aim to mimic the underlying transmission dynamics by relating the risk of infection to the proportion of infected people in the population. The risk of infection (or force of infection when it relates to susceptible individuals only) decreases as a result of vaccination. This contrasts with static models, which apply a fixed (or static) risk of infection which does not change as a result of vaccination in the model. Only one of the reviewed studies (Weycker et al)[14] used a dynamic model. It was based on an earlier agent-based microsimulation model.[111] The remaining studies used static models in which the risk of infection is independent of the proportion of the population that is infectious.

However, several of these studies incorporated a proxy indirect effect via a reduction in influenza or ILI among household contacts of vaccinated children based on clinical trial or observational studies.[93, 95, 98, 100, 106, 109] Estimating indirect effects using dynamic models is usually preferable to doing so based on results from clinical trials, since these are usually designed to estimate the short term effects of interventions on an individual level.[112] Observational post-licensure studies can be more informative in this respect, but the circulating strains, household structure and contact patterns can be country-specific, making inferences to other settings problematic.

Table 7 – Summary of the vaccination programmes evaluated and the efficacy assumed for each economic evaluation of childhood vaccination

Author (year), country	Vaccine	Age group	Efficacy (sensitivity range)	Endpoint
Riddiough (1983), USA[103]	TIV	0-14 years	60% (30-90%)	Influenza
White (1999), USA[109]	TIV	Schoolchildren	56% (43-75%)	Influenza
Cohen (2000), USA[93]	LAIV	6-59 months-4 years	83% (54-83%)	Influenza
			32%	Otitis media
Dayan (2001), Argentina[94]	TIV	High risk children 6-14 years	70% (10-90%)	Influenza
Fitzner (2001), Hong Kong[96]	LAIV	1-15 years	60% (60-70%)	Influenza
Luce (2001), USA[99]	LAIV	15-71 months	24%	ILI fever days
Turner (2003), UK[108]	TIV	0-12 years	81%	Influenza
Hall (2005), USA[97]	TIV	6-23 months	65% (65-85%)	Hospitalisation
Meltzer (2005), USA[101]	TIV	6 months-14 years	50-90%	Influenza
Weycker (2005), USA[14]	Not stated	6 months-18 years	70%	Influenza
			80%	Transmissibility
Esposito (2006), Italy[95]	TIV	2-5 years	33%	Upper respiratory tract infections
			22%	Lower respiratory tract infections
			26%	Febrile respiratory illnesses
			32%	Antibiotic prescriptions
			29%	Antipyretic prescriptions
			48%	Missed school days
Prosser (2006), USA[15]	TIV	6 months-17 years	69% (40-90%)	Influenza
	LAIV		84% (60-96%)	
Salo (2006), Finland[105]	TIV	6 months-13 years	80% (60-80%)	Influenza
Skowronski (2006), Canada[107]	TIV	6-23 months	66% (34-90%)	Influenza
Hibbert (2007), USA[98]	LAIV	6-35 months	84% (74-90%)	Influenza (season 1)
			85% (78-90%)	Influenza (season 2)

Author (year), country	Vaccine	Age group	Efficacy (sensitivity range)	Endpoint
Marchetti (2007), Italy[100]	TIV	6-24 months 25-60 months	25% (5-56%) 48% (40-95%)	ILI
Navas (2007), Spain[102]	TIV	3-14 years	59%	Acute febrile respiratory
			45%	Paediatric visits
			19%	Antibiotics, antipyretics
			33%	Work absence
Luce (2008), USA[4]	LAIV (vs. TIV)	24-59 months	54% (40-60%) vs. TIV	Influenza
Schmier (2008), USA[106]	LAIV	5-18 years	35%	ILI
Salleras (2009), Spain[104]	TIV	3-14 years	59%	Acute febrile respiratory
			45%	Paediatric visits
			19%	Antibiotics, antipyretics
			58%	School absences
			33%	Work absences

Source: Newall et al.[113]

3.3.1.3 Valuation of costs and benefits

The studies differed widely in terms of the costs and benefits that were included (Table 8). All but two of the studies were conducted from a societal perspective, considering benefits regardless of who received them.[97, 108] Of these, all but two considered the value of lost productivity due to caregivers missing work to care for sick children.[96, 103] Some studies also considered the value of lost productivity due to household contacts (e.g. caregivers) becoming sick,[14, 93, 95, 98, 100, 106, 109] to the children in the value of lost school attendance,[96, 104, 106] and the value of lost lifetime productivity due to premature death.[14, 101, 102]

The two studies that took a third party payer or provider perspective were among the few to conclude that vaccinating low-risk children was not cost-saving.[97, 108] Several other studies conducted sensitivity analyses which additionally adopted a payer or provider perspective. Of these, three[99, 102, 107] concluded that vaccination was no longer cost saving from this perspective, and only one[105] suggested that vaccination was still cost saving. This suggests that the more favorable conclusions drawn from studies conducted using a societal perspective need to be interpreted carefully in Belgium, given that the Belgian guidelines for health technology assessment indicate a preference for a payer perspective.[114]

The majority of studies[93-97, 99, 101, 102, 104-107, 109] present the net value or benefit/cost ratio of an intervention in monetary terms, i.e. the cost of the vaccination programme compared to the direct and indirect societal costs avoided through the intervention. However, several such studies[93, 94, 97, 99, 104-106, 109] can be regarded as incomplete cost-benefit analyses because they only valued benefits in terms of avoided morbidity (i.e. the value of healthcare costs and productivity saved), and not in terms of avoided mortality.[110]

A few studies[4, 15, 98, 100, 103] took an extra-welfarist approach, by measuring benefits in terms of non-monetised utilities such as quality-adjusted life years (QALYs). Estimating the quality of life in small children can be problematic, because none of the standard quality of life instruments were designed to be administered in children under the age of 5 years. These studies surveyed caregivers to act as proxies for the ill child. Most of these studies were relatively recent (all but one published after 2006), possibly reflecting the increasing preference for this approach by healthcare authorities. However, the benefits captured were not consistent between studies. Some studies[4, 100] included benefits in terms of both utilities (such as QALYs) in the denominator and productivity gains in the numerator of the cost-utility ratio. This practice has been questioned by some economists who believe that this can result in double counting.[115, 116]

Since the Belgian guidelines advocate the use of QALYs, a separate search for studies measuring the health-related quality of life (HRQoL) for influenza was undertaken (see Quality of life).

Several evaluations, particularly those targeted specifically at healthy children, did not include serious influenza complications (Table 8). Some[97, 104, 105, 109] argued for the exclusion of mortality on the basis that childhood deaths due to influenza are rare and/or difficult to observe in a single trial. However studies suggest that healthy children, while at a lower risk, contribute to influenza-related hospitalisations[117] and deaths.[118] The failure to include deaths may be problematic since the benefit of a single avoided child death is substantial in most economic evaluation frameworks. Only one study used a population dynamic model to account for the indirect protection to the elderly,[14] who have by far the highest risk of influenza-related death.[119, 120] This study based death rates on modelled rates of 'excess' disease and estimated that the majority of deaths prevented by childhood vaccination would be in those aged over 65 years. The future inclusion of modelled 'excess' disease rates demands further discussion around the accuracy and interpretation of such estimates.

3.3.1.4 Results of reviewed studies

In the studies reviewed, various methodological and modelling decisions seemed to be associated with vaccine programmes being found to be cost-saving (Table 8). Studies that included productivity losses (due to illness and care giving) appear more likely to be cost-saving, however in some cases reductions in time losses were offset by those incurred by caregivers to obtain vaccination for their child. The inclusion of indirect protection to other (non-targeted) age groups also appears to be associated with a programme being found cost-saving. The inclusion of influenza complications did not appear to be strongly associated with cost-effectiveness, but is likely to be more influential in models that incorporate indirect protection to the elderly.

Although all studies conducted some form of sensitivity analysis, several studies only conducted one-way sensitivity analysis (e.g.[102, 104]), which is generally considered inadequate to explore parameter uncertainty. Furthermore, many of the factors most influential to cost-effectiveness were methodological choices (Table 8), rather than those related to parameter estimation. In several of the studies these choices were not discussed in detail. Most of the economic evaluations of childhood influenza vaccination were conducted for the US and adopted a wider perspective (i.e. including productivity losses) than the reference case for economic evaluations used by many other governments, including Belgium. Hence, we cannot simply transfer their methods and results to the Belgian context.

An additional search update was made up to October 2012 (for a full description of the search and selection, see section adult vaccination options below), yielding another 2 economic evaluations of seasonal influenza vaccination in children.[121, 122] Prosser et al focused on the comparison of LAIV and TIV in children aged 6 months to 4 years using a static model, and thus bears little relevance to the purpose of our study (in which in line with the European license, we model children under age 2 years not to receive LAIV).[122] The other is an economic evaluation using an individual based model to analyse 3 vaccination options for children aged 6m-23m; 6m-36m; 6m-5y in Argentina, using vaccine efficacy estimates against ILI (i.e. not specifically influenza) at a single vaccination coverage rate of 50%.[121] They found all three children options they analysed to result in acceptable cost-effectiveness ratios, thus supporting Argentina's decision to implement seasonal influenza vaccination in children, after the 2009-2010 pandemic experience.

A final ad-hoc search update was undertaken in March 2013, yielding 2 additional economic evaluations of seasonal influenza vaccination in children.[123, 124]

Tarride et al[124] similarly to Prosser et al[122] and Luce et al[4] focused on the comparison between LAIV and TIV using a static decision tree model. They concluded that LAIV was preferable to TIV for children aged 2 to 17 years in Canada.

Pitman et al[123] used Vynnycky et al's[125] dynamic transmission model structure (see section model review below) to estimate the cost-effectiveness of vaccinating three broad age groups of children (2-4, 2-10, 2-18 years). There was no fitting involved, but the model was calibrated against historical data from different regions (face validation). Dynamic transmission parameters were thus not estimated but assumed for projections, and this over a time horizon of 200 years. Duration of natural and vaccine induced immunity was assumed equal and to last 6 years and 12 years for influenza A (H1N1 and H3N2) and B, respectively. TIV and LAIV vaccine efficacy estimates were assumed to be 60% and 80%, respectively, in line with those of previous studies assumed independent of age group and averaged over seasons. A limited range of vaccination coverage scenarios was presented and no simultaneous changes were assumed for the adult programme. A limited one-way sensitivity and extreme-value analysis showed robust qualitative results. The authors concluded that "Vaccinating 2-18 year olds was estimated to be the most cost-effective policy in an incremental cost-effectiveness analysis, at an assumed annual vaccine uptake rate of 50%".

Table 8 – Summary of relevant aspects included in each economic evaluation of childhood vaccination (base-case)

Author (year), country analysed	Caregiver time for child sickness	Productivity loss - death	Complications	Indirect protection	Adverse events	Cost saving
Riddiough (1983), USA[103]	N	N	Y	N	N	N
White (1999), USA[109]	Y	N	N	Y (static)	N	Y
Cohen (2000), USA[93]	Y	N	Y	Y (static)	N	Y
Dayan (2001), Argentina[94]	Y	N	Y	N	Y	Y
Fitzner (2001), Hong Kong[96]	N	N	Y	N	N	N
Luce (2001), USA[99]	Y	N	Y	N	Y	N (individual)
Turner (2003), UK[108]	N	N	Y	N	Y	N
Hall (2005), USA[97]	N	N	Partial^	N	N	N
Meltzer (2005), USA[101]	Y	Y	Y	N	Y	Variable*
Weycker (2005), USA[14]	Y	Y	Y	Y (dynamic)	N	Variable*
Esposito (2006), Italy[95]	Y	N	Y	Y (static)	Y	Y
Prosser (2006), USA[15]	Y (in QALYs)	N	Y	N	Y	N
Salo (2006), Finland[105]	Y	N	Partial^	N	Y	Y
Skowronski (2006), Canada[107]	Y	N	Y	N	N	N
Hibbert (2007), USA[98]	Y	N	Partial^	Y (static)	Y	Y
Marchetti (2007), Italy[100]	Y	N	Partial^	Y (static)	Y	Y
Navas (2007), Spain[102]	Y	Y	Y	N	Y	Y
Luce (2008), USA[4]	Y	N	Y	N	Y	Y
Schmier (2008), USA[106]	Y	N	N	Y (static)	Y	Y
Salleras (2009), Spain[104]	Y	N	Partial^	N	Y	Y

Source: Newall et al.[113]
Dark grey indicates the choice made about inclusion of the factor would likely be favourable to the cost-effectiveness of a vaccine programme and light grey indicates it would likely be unfavourable. The final column indicates if the study found vaccination to be cost-saving.
** Results reported for variable vaccination cost; ^ Deaths from influenza not included in the analysis.*

3.3.2 Adult vaccination options

In this section we report on the main features of economic evaluations applied to influenza vaccination of adult age groups. Since the original recommendations for influenza vaccination focused in practice primarily on adults (mainly otherwise healthy elderly or people (mainly adults) with underlying chronic conditions), many economic evaluations on this subject have been applied to this age group. We discuss the main results from already existing reviews for each of the main adult target groups. In order to identify relevant studies, we performed a search for all publications since 2006 (up to October 2012). The results of the search and selection process is shown in Figure 4. We used the general search string (cost OR costs OR cost-effectiveness OR cost-benefit OR cost-utility OR economic) AND influenza AND (vaccine OR vaccines OR vaccination OR immunisation OR immunization) in the title field in the databases Web of Science and Pubmed.

Our search identified 15 review articles of potential interest. These reviews focused on healthy (working) adults,[126-128] health care workers,[129] persons with underlying illness,[130] elderly,[130-133] children[92, 113, 134-136] and multiple target groups.[137, 138] We also identified 61 original research articles published in the same time period, many of which would have been covered by the various reviews. These original research articles can similarly be categorized as follows: healthy (working) adults,[139-148] health care workers,[149-152] persons with underlying illness,[153-160] elderly,[161-169] children,[4, 15, 95, 98, 100, 102, 104-107, 121, 122, 170] pregnant women and recent mothers,[171-176] and multiple target groups.[177-188]

It appeared that only the economic evaluations of the target group of pregnant women were not the specific subject of a published review in the time frame of our search. Therefore, we expanded the time period of our search to all available years and added the search term “pregnan* to our search. However, we were unable to identify additional individual analyses or reviews of economic evaluations on vaccinating pregnant women. Note however that De Waure et al[130] included two analyses on vaccinating pregnant women in their review.

Of the 15 reviews of potential interest, five covered childhood vaccination options, which were discussed in Section 3.3.1 above, together with the additional original papers on childhood vaccination retrieved with the search described in this section.[92, 113, 134-136] Three other reviews were excluded because upon closer inspection they did not formally review economic evaluations of influenza vaccination, but expressed opinions without a systematic review relevant for our purposes.[131, 133, 138] One other paper was also excluded because it was published in Mandarin.[137] This leaves us with six reviews that we use as a basis for discussing published economic evaluations on specific target groups (see Table 9).[126-130, 132]

3.3.2.1 Elderly

Postma et al[132] and de Waure et al[130] both reviewed this topic. Based on 18 studies, Postma et al[132] concluded that vaccination of the elderly is often found to be cost-saving, particularly when potential indirect productivity gains are included. If not, Postma et al[132] found the incremental costs to compare favourably to the incremental benefits. They identified the risks of death and hospitalisation in the target group, vaccination costs and vaccine effectiveness as the main drivers of these results. These findings were generally confirmed by the later review of De Waure et al[130] based on 12 studies in the elderly (1990 up to 2011), which also concluded vaccination of high risk and low risk elderly would be acceptable in terms of cost-effectiveness. The additional economic evaluations we identified[161, 164, 167] focused on older adults (>50y and >65y) in US emergency departments,[161] elderly (>65y) in Poland[161] and African American and Hispanic elderly (>65y) in the US.[164] These analyses all concluded these vaccination programmes were (very) cost-effective. Those that investigated the impact of parameters, found the same parameters to be important as mentioned in the review by Postma et al (see above).[132]

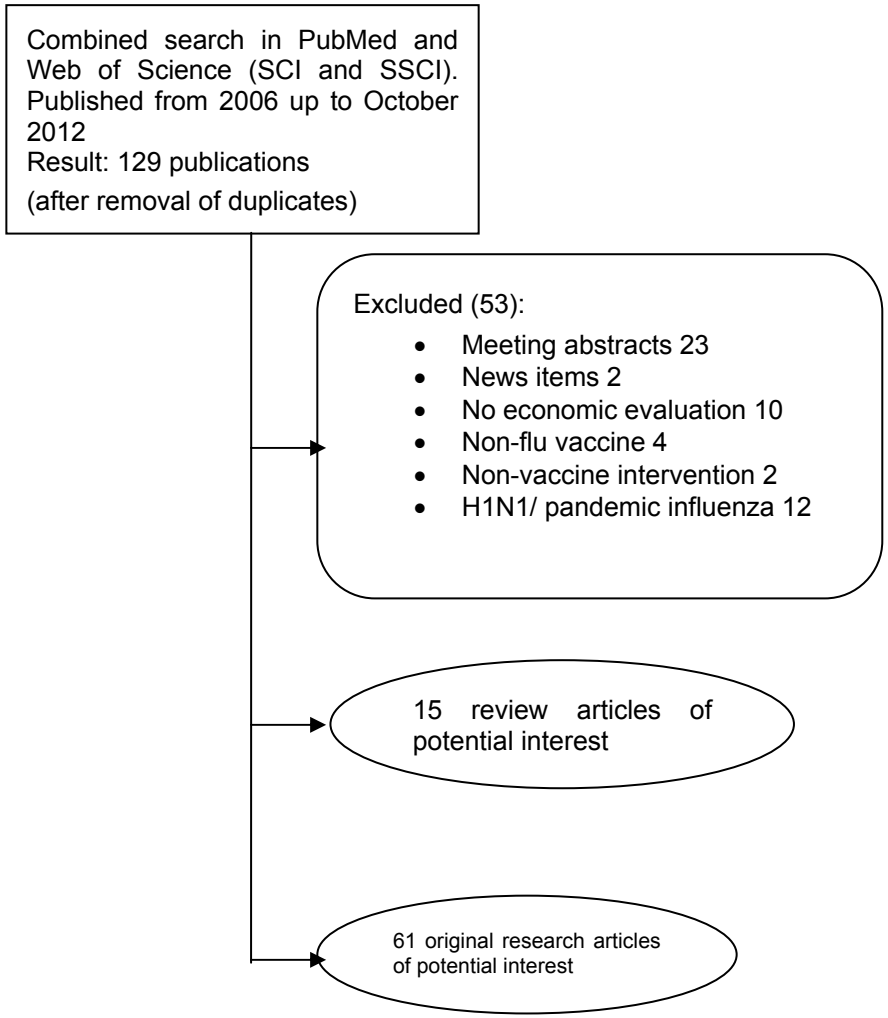
All analyses to date undertaken for this target group have used static decision tree or static state transition models.

Table 9 – Key issues considered in economic evaluations of seasonal influenza vaccination in adults

Paper	Target group	Number of studies reviewed	Main study conclusions	Key issues relating to outcomes					
				Herd	Endpt	Prod	VCost	VEff	Other key issues
Burls 2006[129]	Healthy adults, healthcare workers	14	10/14 cost saving (including 2/2 on health care workers)	x					Patient benefits for health care workers
Gatwood 2012[126]	Healthy adults 18-64 years	7	"Generally not cost saving"			x		x	Variability in outcomes Setting of vaccine delivery Severe adverse events Estimating less severe endpoints
Hogan 2012[127]	Healthy adults	10	8/10 favored vaccination	x	x		x	x	Perspective (employer only or employee as well)
Newall 2009[128]	Adults 50-64 years	6	All cost-effective		x	x	x	x	Life expectancy in people with co-morbidities
De Waure 2012[130]	Adults >50 years and high-risk populations	20	All cost saving or cost-effective in both elderly and high-risk groups	x		x			Life expectancy in people with co-morbidities
Postma 2006[132]	Elderly	18	15/18 cost saving, 16/18 cost-effective			x	x	x	Definition of influenza-attributable hospitalisation or death

Herd: herd protection; Endpt: use of different endpoints to estimate incidence and vaccine effectiveness (e.g. acute respiratory illness, influenza-like illness, laboratory-confirmed influenza); Prod: productivity loss due to influenza; VCost: drivers of vaccination costs (purchase and administration); VEff: drivers of vaccine effectiveness.
Source: adapted from Jit et al.[189]

Figure 4 – Selection of potentially relevant reviews and original articles on economic evaluations of seasonal influenza vaccination in adults



3.3.2.2 Healthy adults

Several authors reviewed economic evaluations of influenza vaccination in healthy adults.[126-128]

Newall et al[128] noted that individual studies on vaccination of adults aged 50-64 years concluded that seasonal influenza vaccination of this age group is likely to be cost effective, but that their results were dependent on several key assumptions. The most important one being the estimates of serious outcomes due to influenza and the estimates of vaccine effectiveness (VE), which were often mismatched in these analyses. Due to data limitations and lack of transparency they found that there is uncertainty that remains unstated or unexplored. Hence, Newall et al indicate the favourable conclusions of these studies should be interpreted with caution.[128]

The two more recent reviews focused on economic evaluations applied to the US. Gatwood et al[126] concluded that the results of these analyses were most sensitive to variations in wage rates, levels of worker productivity, the costs and effectiveness of vaccination, and the incidence of influenza. They asserted that seasonal influenza vaccination of healthy, working-age adults is generally not cost saving, and that its attractiveness depended on societal and payer (i.e. employer) value judgements. Hogan et al[127] also confirmed these findings in more general terms.

Like all the other studies in this section, the additional two studies we identified[144, 147] were based on static decision tree or static state transition models. Smith et al[147] found that universal dual pneumococcal polysaccharide and influenza vaccination at age 50 years would be cost-effective, whereas Mogasale and Barendregt[144] asserted that model structure, parameter assumptions and data limitations introduce uncertainties which are insufficiently accounted for in existing cost-effectiveness studies of influenza vaccination for people aged 50 to 64 years. They estimated increased vaccination of adults aged 50-64 years to range from very cost-effective to cost-ineffective, based on scenario analysis (without probabilistic sensitivity analysis).

3.3.2.3 Adults with underlying chronic illness

De Waure et al reviewed relevant articles on this topic.[130] These studies, as well as one other[157] their review did not retrieve, considered vaccination of cancer or asthma patients to be cost-effective or to result in cost-savings. However, in 1998 Hak et al[190] found there was insufficient evidence to support vaccinating all Dutch patients aged 18-64 years with chronic lung disease on the basis of cost-effectiveness (in contrast to those aged > 65 years with comorbidities). The reliability of these findings fundamentally depends on relating vaccine efficacy on appropriate outcomes to reliable estimates of the occurrence of such outcomes in the context of the envisaged target group. Furthermore, the reduced overall age-specific quality of life and life expectancy of this target group has often not been accounted for in the analyses on this subject.

3.3.2.4 Health care workers (HCWs)

Burls et al[129] reviewed evidence relevant to conduct economic evaluations of influenza vaccination in health care workers, and used this in an economic evaluation. They showed that economic evaluations published till then did not include patient benefits from vaccinating HCWs. They undertook an economic evaluation using UK data and found vaccination of health care workers to be cost saving. In their most pessimistic scenario they still found this programme to be cost-effective.

Later publications on this target group generally showed by empirical examination comparing sick leave records between vaccinated versus unvaccinated HCWs that influenza vaccination of HCWs can be cost-saving. This was shown for HCWs coming into close contact with cancer patients in Colombia,[149] for HCWs working on pediatric wards in Italy (especially efficient for young nurses),[152] in Italian HCWs in general[150] and in general university hospital staff in France. In these later analyses only Chicaiza-Becerra et al[149] included patient benefits in the estimation of the benefits from vaccination.

3.3.2.5 Pregnant women

We identified 6 economic evaluations on this subject, four for the US,[171, 172, 174, 175] one for Canada[176] and one for England & Wales.[173]

Roberts et al[175] published the first study in 2006 and estimated that, in comparison to supportive care, TIV vaccination of pregnant women would save approximately US$50 per woman, with a net gain of about 45 quality-adjusted hours.

Three years later Beigi et al[171] published an analysis for maternal vaccination in the US, concluding that it is a very cost-effective intervention for clinical attack rates that correspond to both seasonal influenza epidemics and occasional pandemics (i.e. when influenza prevalence ≥ 7.5% and influenza-attributable mortality is ≥ 1.05% (consistent with epidemic strains)). They found cost savings for a single dose strategy when the prevalence of influenza exceeded 30%.

These first two articles were crude in their approach to timing the vaccinations in relation to the availability of vaccines, the seasonal attack rate and the pregnancy stage.

Jit et al[173] found maternal influenza vaccination to fall within the range of acceptability of cost-effectiveness in The UK (<£30 000 per QALY gained), and that the cost-effectiveness improved considerably if (partial) vaccine protection would last into a second season, and vaccination efforts in pregnancy did not take place after the month of December. They considered the costs of vaccine delivery to be the main source of uncertainty, in addition to the quality of life detriment associated with a symptomatic influenza case.

Skedgel et al[176] estimated universal vaccination of pregnant women to be cost-effective when delivered at low marginal costs (at Public Health Clinics, or as part of a routine prenatal physician consult). They also found targeted vaccination of pregnant women with co-morbidities to be cost-saving. Myers et al[174] found seasonal influenza vaccination in pregnancy to be relatively cost-ineffective and noted that delay of vaccination beyond November reduced both effectiveness and cost-effectiveness, implying the most cost-effective approach would be to vaccinate pregnant women as quickly as possible after TIV became available in a given season.

Ding et al[172] found vaccination of pregnant women to be cost-saving if the annual maternal influenza attack rate was more than 2.8%, influenza vaccine efficacy was more than 47%, or if vaccine acquisition and

administration cost per dose were less than US$33. Again vaccine efficacy and costs were obvious influential parameters.

3.4 Dynamic transmission models

Several dynamic models of seasonal influenza vaccination in children have been published but most of these have not been linked to economic analyses. One of the challenges for dynamic models in this context is that their results are highly sensitive to the assumed social mixing patterns that enable transmission of infections. Ideally, these models require age specific data on effective contacts between susceptible and infectious hosts in various social situations. Due to important advances in the collection of social contact data to parameterise infectious disease transmission models over the last 5 years, such data are beginning to emerge for an increasing number of countries. The use of such data has been shown to provide better fits to empirical observations than was previously possible when researchers were forced to use more simplified and uncertain contact patterns in such models.

We distinguish between two classes of dynamic transmission models: mathematical models and individual based models. In mathematical models of infectious diseases, the flow of individuals through different compartments (e.g. susceptible, infected, recovered) is described using a system of partial or ordinary differential equations. Therefore these models are often referred to as compartmental (mathematical) models. The use of partial or ordinary differential equations allows for mathematical analyses investigating properties of the model such as for example the equilibrium states, local and global stability, etc. In these compartmental mathematical models, it is assumed that people mix at random and different levels of mixing within and between specific subpopulations can be assumed by adding compartments and thus equations to the model description. In individual or agent based models, more detail can be assumed but at the cost of complexity. Individuals are explicitly represented, they live in households, in communities, go to school or work etc.; people are allocated to specific locations between which they commute: during the night typically at home, during the day typically at home, school or work. There is a probability of transmission from infectious to susceptible individuals when they meet at the same place and at the right moment. Whereas mathematical models are described by systems of partial or ordinary differential equations, individual based models cannot be represented as such. The computational complexity of individual based models is much higher given the level of detail that is of interest. As a consequence, much more information is needed to properly inform these models. Given the lack of information, ad hoc assumptions are often made. Individual based models are important particularly in cases where stochasticity is of importance, i.e. in the initial phase of an outbreak or when specific mitigation strategies such isolation and containment are of interest.

Given the research question here and the aforementioned limitations of individual based models, we will only consider compartmental mathematical models here.

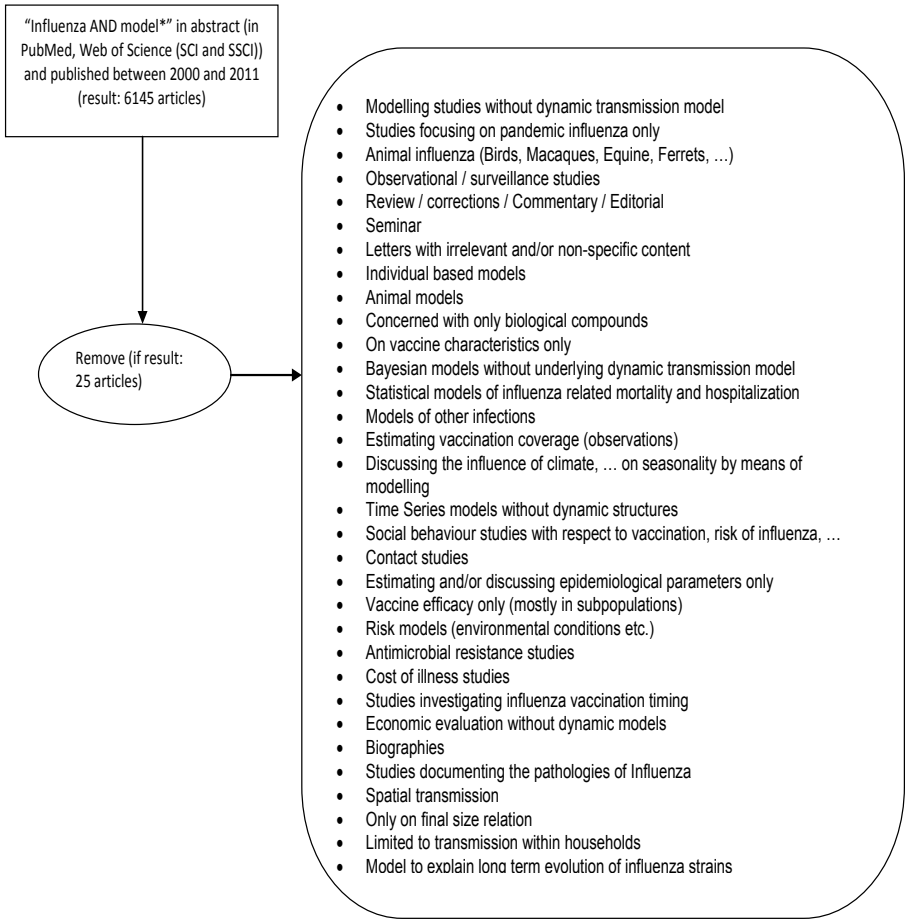
3.4.1 Search strategy

In order to gain insights into the existing modeling approaches for seasonal influenza, a thorough literature review was conducted. The search strategy started with entering the keywords “Influenza AND model*” and year from 2000 until 2011 into the search engines of PubMed and Web of Science (SCI and SSCI). Earlier years were excluded because of our interest in up-to-date modeling of influenza for example using social contact data. Note that the inclusion of social contact data was not conserved as selection criterion. Hence 6145 articles fulfilling these requirements were obtained.

The search strategy then focused on identifying articles, by looking at the title and abstract, presenting dynamic models as shown by the flowchart in Figure 5. We explicitly excluded spatial models given that our study focuses on Belgium for which there is no evidence of spatial patterns of influenza incidence. As a result of this selection, 25 articles were eligible for further assessment.

All 25 articles included a mathematical dynamic model. We further differentiated between articles and identified 4 main groups based on the modeling approach used: standard mathematical models, multistrain models, models using adaptive parameters for seasonality, and comparative modeling papers. In the following sections we discuss the characteristics (Table 10) and the models belonging to each of these main groups, in light of their usefulness for the analysis we want to do to address the objectives of this report.

Figure 5 – Flowchart of search and selection process for articles on modeling



3.4.2 Results

3.4.2.1 Standard mathematical models

These articles applied standard deterministic mathematical models such as for example SIR (susceptible-infectious-recovered), SEIR (susceptible-exposed-infectious-recovered), SVIRS (susceptible-vaccinated-infectious-recovered-susceptible) with some differentiation based on the estimation approaches and assumptions made.

These standard mathematical models are able to capture single outbreaks, but require additional aspects (sinusoidal contact patterns, changing parameters with seasons…) to mimic seasonal characteristics. The papers discussed in this section present models mainly involving single strains that are only able to capture single outbreaks and require additional aspects such as loss of immunity,[191] changing contact patterns or changing strains to mimic the seasonal characteristics as observed in influenza incidence. It has been shown that the aforementioned factors are important drivers for seasonality. Another aspect is the incorporation of vaccination. The methods of incorporating vaccination are different; nonetheless it is mostly assumed that susceptible individuals are vaccinated.

Pradas-Velasco et al[185] report an economic evaluation of influenza vaccination, using both a dynamical model for the disease process and a static model for the economic evaluation. They use vaccine efficacy and coverage values specific for Spain. They assume vaccination is only efficaciously given in particular periods of the year to susceptible individuals. Dushoff et al[192] divide the study population in a core group, being more effective in spreading the disease, and a vulnerable group, which is more vulnerable to the disease. They investigate how to protect the population under these circumstances. Vaccination is assumed to be given before the influenza season and its effect is assumed to last until the end of the season. Vaccine efficacy values are assumed and focus is more on the simulation. Alexander et al[191] report on a theoretical study of an SVIRS model and apply this model in two settings: elderly in a personal care home and office workers. In their model they assume that susceptible individuals are vaccinated, but that these vaccinated individuals not necessarily confer immunity and hence may become infected at a lower rate. The vaccine efficacy values used are vaccine efficacy for susceptibility as well as vaccine efficacy for susceptibility to disease. The

authors indicate that their model can be extended to long-term multi-season dynamics of influenza infection by employing time dependent parameters, furthermore they indicate that with a known vaccine efficacy, their model provides the vaccination rate necessary to control the spread of influenza infection in a population. However, caution is necessary since this rate is predetermined by the duration of infectiousness and the rate of contact between susceptible and infected individuals. Glasser et al[193] use a SEIR model and add vaccination with age-specific efficacy. They use effective contact rates based on results from the 1957 pandemic to study the effect of vaccination on mortality. A comparison between alternative strategies with respect to vaccination was also performed. Hsieh[194] uses an age-dependent compartmental model allowing for the inclusion of vaccination, quarantine, asymptomatic and symptomatic infections, hospitalizations and disease deaths. Estimates of the age-dependent hospitalization rates and per contact transmission probabilities were obtained by least-squared curve fitting using pneumonia and/or influenza data and using MATLAB software. The authors indicate that their resulting fit might be affected by low efficacy when vaccines do not match the circulating strain. Furthermore, the values for the duration of the infectious period and the latent period are based on pandemic influenza results. Qiu & Feng[195] adapt a SIR model to allow for drug-resistant strains and vaccination. The authors mainly discuss the theoretical aspects of this model and furthermore shortly discuss a numerical simulation in which they do not discuss a value for the vaccine efficacy. Zhang et al[196] set up a model to simulate data of hospitalizations, hence their model is a SEIR model which includes infectious but not hospitalised as well as infectious and hospitalised compartments. They further calculate the loss of antigenic relatedness and use this value for the ratio of recovered individuals losing their immunity. Furthermore the birth and death rate are assumed and the other model parameters are estimated using the minimum sum of square. This study involved multiple influenza seasons and the goodness of fit is ascertained for each of the seasons.

3.4.2.2 Multistrain models

These models are built on the premise that multiple strains are responsible for seasonality in influenza transmission and deal with cross-immunity and thus the impact of the associated (partial) immunity. Many of the papers are mainly of a theoretical nature and only include simulations but no empirical validation vis-a-vis the observed evolutions. Furthermore, these models require a sufficient amount of data (e.g., data on the circulating strains, detailed strain-specific incidence data of influenza-attributable disease) from various sources to be employed. Due to the lack of sufficient information these models are not applicable for the current study. Furthermore, vaccination is only applied in 2 of these papers. Alexander & Kobes[197] allow in their two-strain model for vaccination. They assume that vaccination can fail and hence incorporate a probability to get infected when vaccinated. Nevertheless, it is unclear how the vaccine-efficacy is implemented and which values are adapted. Prosper et al[198] also implemented vaccination in their multi-strain model but assume that the vaccine-efficacy is 100%, which is unrealistic. The other papers in this group, which do not implement vaccination, are Lavenu et al,[199] Andreasen,[200] Omori et al[201] and Nuno et al.[202]

3.4.2.3 Models using adaptive parameters for seasonality

These articles explicitly include the seasonality in various ways. Stone et al,[203] Qiu,[204] and Olinky et al[205] used a sinusoidal contact rate, with the last one differentiating explicitly between high and low seasons. The last authors studied recurrent dynamics, but focused on measles. Casagrandi et al[206] added an additional compartment to their model for the cross-immune individuals and used a sinusoidal changing contact rate. Kwok et al[207] also used a sinusoidal changing contact rate while incorporating household information into their SEIR model. Boni et al[208] used a SIR-model with cross-immunity for the epidemic phase and an additional model for the season-to-season phase, hence formulating a year round model. Their results are rather theoretical. Grassly & Fraser[209] use seasonality in a SIR model to get information on the changes in R0. Finkenstadt et al[210] include the possibility to become susceptible after being recovered in their model. They also fit their model to observed weekly incidences using likelihood methods and Monte-Carlo sampling methods of simulated annealing. From the current group, Vynnycky et al[125] were the only authors including vaccination in their model. Furthermore, they include changing contact rates in their model, using data from the POLYMOD contact study (Mossong et al[211]) to inform the contact rates. The models in this subgroup are of interest due to their explicit inclusion of seasonality, which can be modified through parameter changes to fit observations. Unfortunately only the last one models vaccination as well as the seasonality. Vynnycky et

al[125] are furthermore the only authors using data to inform the contact rates.

3.4.2.4 Comparative modeling papers

Lastly some authors focused on the comparisons of various dynamic models: Ballesteros et al[212] compare the serial SIR to the SIRS model, Wearing et al[213] show the influences on a SEIR model when ignoring certain assumptions and Reluga & Medlock[214] compare 4 SIR models. Although these articles give interesting insights, they do not contribute novel information for the formulation of our model and hence are not considered to specify our model structure.

Table 11 shows the values used for the duration of infectious period, duration of latent period and waning rates. It can be observed that these values differ per article, indicating the uncertainty. For this reason, this research project will allow these parameters to be estimated from the available data.

The group of models of interest for the current research is the models including seasonality. The problem with the multi-strain models is the lack of data to inform the model, the comparative modeling papers do not add additional information. From the standard mathematical models, Alexander et al[191] might offer inspiration as they allow for the loss of immunity and incorporate seasonality as such. Since seasonality is an important aspect in modeling influenza, due to the observed seasonal influenza incidence, we are mostly interested in the models, which include this seasonality. Within this group, only Vynnycky et al[125] incorporated vaccination and their surplus is the use of data to inform the contact rates. Additionally Finkenstadt et al[210] also allow for loss of immunity and ideas can be used from this paper as well. We start with a thorough investigation of the model from Vynnycky et al[125] with the aim to develop a model useful for our specific research questions.

Table 10 – Summary of studies on mathematical models for seasonal influenza

Reference	Dynamic model	Stoch (S) / Determ (D)	Contact data? (Y/N)	Theoretical/ applied[a]	Country	Years of influenza data	Strain	Interv-ention[b]	Who targeted	Vaccine effect	Vaccine efficacy	VE [c]: VE_S or VE_SP
Multistrain models												
Lavenu et al[199]	2-strain SIR with cross-protection	D	N	S	NA	NA	NA	N	NA	NA	NA	NA
Andreasen [200]	SIR model with cross-immunity	D	N	T	NA	NA	NA	N	NA	NA	NA	NA
Alexander & Kobes[197]	2-strain model with partial immunity	D	N	S	NA	NA	NA	V	NA	Leaky	NA	NA
Omori et al [201]	SIR with cross-immunity and co-infection for strains	D & S	N	T	NA	NA	NA	N	NA	NA	NA	NA
Prosper et al[198]	SAIR SIR 2-strain	D	N	T & S	US	2009-2010	H1N1 & seasonal	V, D, AV	People who did not have symptoms yet and did not receive the vaccine yet	Effective against seasonal but not against pandemic influenza	100% (assumed)	NA

Reference	Dynamic model	Stoch (S) / Determ (D)	Contact data? (Y/N)	Theoretical/ applied[a]	Country	Years of influenza data	Strain	Interv-ention[b]	Who targeted	Vaccine effect	Vaccine efficacy	VE [c]: VE_S or VE_SP
Nuno et al [202]	1 and 2-strain models	D	N	T & S	NA	NA	NA	O	NA	NA	NA	NA
Models using adaptive parameters for seasonality												
Stone et al [203]	Classical seasonally forced SIR model	D	N	T & A[d]	US UK	1928-1963 1948-1968	NA	NA	NA	NA	NA	NA
Vynnycky et al[125]	SEIRS model + seasonal FOI	D	Y	S	UK	1972-1986 1997-2005	H3N2 H1N1 B	V	From 2000 individuals aged ≥65 years; From 2005 programmes involving children	All-or-none	50% elderly[215] 65% child[216]	VE_SP
Casagrandi et al[206]	SIRC, seasonally forced SIRC	D	N	A	Singapore England and Wales	March 1993 –March1994 1987–1997	A (H3N2)	N	NA	NA	NA	NA
Boni et al[208]	SIR model with cross-immunity	D	N	T	NA	NA	NA	N	NA	NA	NA	NA
Grassly & Fraser[209]	SIR model with seasonally changing transmission	S	N	T & A[e]	UK	1905-1916 1944-1964	NA	NA	NA	NA	NA	NA
Olinky et al[205]	SIR model with contact rates different for high and low season	D	N	T & A[d]	US, UK, Denmark	1930-1960 1950-1965 1930-1965	NA	NA	NA	NA	NA	NA
Finkenstadt et al[210]	SIRS with changing contact rate	S	N	A	France	Week 44, 1984-week 21, 2002	NA	N	NA	NA	NA	NA
Kwok et al[207]	SEIRS model with seasonally changing transmission	D	N	S	NA	NA	NA	N	NA	NA	NA	NA
Qiu[204]	SPIR with seasonal beta	D	N	T & S	NA	NA	NA	AV	NA	NA	NA	NA

Reference	Dynamic model	Stoch (S) / Determ (D)	Contact data? (Y/N)	Theoretical/ applied[a]	Country	Years of influenza data	Strain	Interv-ention[b]	Who targeted	Vaccine effect	Vaccine efficacy	VE [c]: VE_S or VE_SP
Standard mathematical models												
Pradas-Velasco et al[185]	SIR	D	N	A	Spain	NA	NA	V	NA	All-or-none	Less favorable: 0.4 Basal: 0.67[217, 218] More favorable: 0.9[219-221]†	VE_SP
Dushoff et al[192]	SIR model	D	N	S	NA	NA	NA	V	Vulnerable or core group	Leaky model	0.8 in protecting core group; 0.5 in protecting vulnerable group (assumed)	NA
Alexander et al[191]	SVIRS model	D	N	T & S	NA	NA	NA	V	Health office workers, geriatric population in care home	Leaky model	Office: 0.8[222, 223]*, Personal care home: 0.3[224, 225]	VE_S[222, 223]*, VE_SP[224, 225]
Glasser et al[193]	Age-structured SEIR model	D & S	N	A	US	1918 (1913-1917)	NA	V	No vaccination; 60% of infants <1 year and adults ≥ 65 years or children 1-9 years, adolescents 10-19, young adults 20-29 vaccinated	Leaky model	35% among infants, declined linearly with age over 64 years (60% among people aged 65-59 years, 50% among those 70-74 years)[226]	VE_S
Hsieh[194]	Age-structured compartmental model	D	N	T & A	Taiwan	2004-2005	NA	V, D	0-2 years, 3-5 years, 6-7 years, 8-14 years, 15-21 years, 22-64 years, ≥65 years	Leaky model	0.7 for 0-2 years; 0.7 for 3-5 years; 0.7 for 6-7 years; 0.7 for 8-14 years; 0.5 for 22-64 years; 0.4 for ≥65 years[216, 227]*	VE_S
Qiu & Feng[195]	$SVI_{SU}I_{ST}I_RR$	D	N	T & NSim	NA	NA	NA	V	NA	Leaky model	NA	NA
Zhang et al[196]	SEIJP - P is recovered or partial immunity	D	N	S	US	2001-2006 seasons	H3N2	V	NA	Unclear	NA	NA

Reference	Dynamic model	Stoch (S) / Determ (D)	Contact data? (Y/N)	Theoretical/ applied[a]	Country	Years of influenza data	Strain	Interv-ention[b]	Who targeted	Vaccine effect	Vaccine efficacy	VE [c]: VE_S or VE_SP
Comparative modeling papers												
Ballesteros et al[212]	Test serial SIR model against SIRS model	D & S	N	T & S	New York	1992–1993 1993–1994 1994–1995 1995–1996	Beijing/1993 (BE93) cluster & Wuhan/1995 (WU95)-like	N	NA	NA	NA	NA
Wearing et al[213]	SEIR (influence of ignoring some assumptions)	D& S	N	S	UK	NA	NA	NA	NA	NA	NA	NA
Reluga & Medlock[214]	Comparison of 4 SIR models	D	N	T	NA	NA	NA	NA	NA	NA	NA	NA

Models: S=susceptible; I=infectious; E=exposed; P=prophylaxis; R=recovered; A=asymptomatic infected; V=vaccinated; C=cross-immune; J=hospitalised.
$SVI_{SU}I_{ST}I_RR$: Susceptible – Vaccinated – Infected with the sensitive strain and untreated – Infected with the sensitive strain and treated – Treated infected with the resistant strain – Recovered.
NA: Not available; FOI: Force of infection.
a: Possible nature of methods: Applied (A), Calculations (C), Numerical Simulations (Nsim), Simulations (S), Theoretical (T).
b: Possible interventions: Vaccination (V), antivirals (AV), social distancing (D) (school closure etc), no intervention (N) and other (O).
c: VE: vaccine efficacy; VE_S is the vaccine efficacy value that measures how protective vaccination is against infection; VE_SP measures how protective vaccination is against disease, ignoring asymptomatic cases.
d: Applied to measles, not to influenza (but relevant for influenza).
e: Theoretical on the reasons for seasonality, applications to measles.
f: A model for each population is made.
** Value used is not exactly the same as from the original reference.*
† This reference could not be checked since it could not be retrieved or it was not written in English.

Table 11 – Parameter values of potential interest in dynamic models of influenza transmission

Reference	Waning rate after infection	Waning rate after vaccination	Duration latent period	Duration infectious period	Main findings	Influential parameters on findings
Multistrain models						
Lavenu et al[199]	NA	NA	NA	3 days[228, 229*,†]	Cross-protection of 50% between two strains is sufficient to explain single influenza peak in temperate countries	Cross-protection
Andraesen[200]	NA	NA	NA	NA	Mathematical analysis of influenza model far from complete	NA
Alexander & Kobes[197]	NA	NA	NA	1/0.244 days[230-232*]	Pre-vaccination is more effective than vaccination during outbreak	Cross-immunity, vaccination level
Omori et al[201]	NA	NA	NA	NA	Majority of antigenic drift in influenza is expected to occur in earlier part of each transmission season	Cross-immunity, basic reproduction number
Prosper et al[198]	NA	NA	NA	5 days[233] 33-100 days[234*]	Implementation of antiviral treatment might reduce number of influenza cases by up to 60% under reasonable seasonal vaccination strategy	Interventions used
Nuno et al[202]	NA	NA	NA	NA	NA	Strategies implemented in model
Models using adaptive parameters for seasonality						
Stone et al[203]	NA	NA	NA	NA	NA	NA
Vynncyky et al[125]	1/6 per year for influenza A 1/12 per year for influenza B[210, 235-238†]	Same as after infection Or 1/3 per year for A and 1/6 per year for B[13]	2 days[239-241†]	2 days[239-241†]	Consistently high levels of vaccination coverage among pre-school children has the potential to bring benefits to both those vaccinated and the community	Contact patterns, vaccine efficacy
Casagrandi et al[206]	1/0.5-1 year[242, 243]	NA	NA	2-7 days[244, 245†]	Comparison with empirical evidence shows that the simulated regimes are qualitatively and quantitatively consistent with reality, both for tropical and temperate countries	Cross-immunity
Boni et al[208]	NA	NA	NA	NA	In particular, for diseases with antigenic drift, vaccination may be doubly beneficial	Antigenic variation
Grassly & Fraser[209]	NA	NA	NA	NA	Reasons for seasonality remain unclear	NA

Reference	Waning rate after infection	Waning rate after vaccination	Duration latent period	Duration infectious period	Main findings	Influential parameters on findings
Olinky et al[205]	NA	NA	NA	NA	Analysis reveals a new threshold effect that gives clear conditions for the triggering of future disease outbreaks or their absence	Susceptibility of population
Finkenstadt et al[210]	After few years[246†]	NA	NA	NA	The SIR-S approach adopted here can also be shown to improve forecasting in comparison to conventional methods.	NA
Kwok et al[207]	1/(2.5*365) [assumed]	NA	1.4 days[247]	1.2 days[248, 249]	Proportion of infections that occur within households was only partially influenced by the hazard h of infection within household relative to the hazard of infection outside the household	Basic reproduction number
Qiu[204]	1/0.003 day[250]	NA	NA	7 days[5]	NA	NA
Standard mathematical models						
Pradas-Velasco et al[185]	NA	NA	NA	3 days[251]	The indirect effect of vaccination on the non-vaccinated individuals (the 'herd immunity effect') can be greater than the direct effect on individuals vaccinated	NA
Dushoff et al[192]	NA	NA	NA	NA	While switching vaccine to more active groups may protect vulnerable groups in many cases, switching too much vaccine, or switching vaccine under slightly different conditions, may lead to large increases in disease in the vulnerable group.	Assortativity of mixing, reproductive number
Alexander et al[191]	1/1 year [assumed]	1/1 year [assumed]	NA	5-7 days: 4 days for office situation and 20 days for personal care home[252*]	Spread of influenza can be controlled if the combined effect of the vaccine efficacy and vaccination rate reaches a threshold determined by the duration of infectiousness and the rate of contact between infected and susceptible individuals	Vaccine efficacy
Glasser et al[193]	NA	NA	1 day[253]	3.8 days[253]	Simulations, vaccinating older children, adolescents, and young adults averts the most cases, but vaccinating either younger children and older adults or young adults averts the most deaths	Age distribution of mortality
Hsieh[194]	NA	NA	1.48 days[248]	2.85 days[254]	Satisfactory model fit	Asymptomatic infections
Qiu & Feng[195]	1/0.003 day	1/0.003 day	NA	6 days[5]	Analytical results of the model show that the control reproduction numbers of the sensitive and resistant strains, provide threshold conditions that determine the competitive outcomes of the two strains	Rates of vaccination and resistance development

Reference	Waning rate after infection	Waning rate after vaccination	Duration latent period	Duration infectious period	Main findings	Influential parameters on findings
Zhang et al[196]	1/0.0018 days [estimate]	NA	NA	NA	Chi-square test of goodness of fit indicates that our model fits the data reasonably well	NA
Comparative modeling papers						
Ballesteros et al[212]	NA	NA	NA	Theoretical: 8 days[255] Empirical: 2.77 days[199]	Our results reveal that the replacement of a resident antigenic cluster by a mutant cluster, as observed in data, is reproduced only by the status based model integrating the reduced infectivity assumption	NA
Wearing et al[213]	NA	NA	1-4 days [256†]	4-5 days[256†]	When developing models for public health use, we need to pay careful attention to the intrinsic assumptions embedded within classical frameworks	NA
Reluga & Medlock[214]	1/6 years [257†]	NA	NA	6 days[257†]	Comparative study illustrates the importance of the sometimes subtle bookkeeping issues associated with resistance mechanisms in epidemiological models	NA

Latent period: The time period between infection and onset of infectiousness. Sometimes referred to as the 'pre-infectious' period.
Infectious period: The time period during which individuals are infectious.
** Value used is not exactly the same as from the original reference; † This reference could not be checked since it could not be retrieved or it was not written in English.*

3.5 Quality of life

This section reviews and assesses the published quality of life (QoL) weights used to describe the influenza or influenza-like illness (ILI) burden of disease.

3.5.1 Search strategy

Electronic databases were consulted to identify original publications on QoL estimates of ILI and influenza. Systematic searches were carried out up to November 2012 in Medline(OVID), Embase(OVID), HTA(CRD), NHS EED (CRD) and Psycinfo(OVID). The search strategies and terms used are presented in Supplement 1.

Identified references were assessed (Table 12) in a two-step procedure: initial assessment of the title, abstract and keywords; followed by full-text assessment of the selected references. Reference lists of the selected studies were scrutinized for additional relevant citations.

The searches on the databases returned 620 citations of which 9 were primary studies reporting original QoL weights on the burden of influenza/ILI.[108, 188, 258-264] Two articles presented the results of the same study.[258, 264] The flowchart of the selection process can be found in Supplement 1.

Table 12 – QoL studies selection criteria

	Inclusion criteria	Exclusion criteria
Population	Influenza patients	Primary condition is not influenza
Intervention	Any	Not applicable
Outcome	Unique QoL weights	Multi-dimension HRQoL scores, DALYs
Design	Direct (TTO, SG) or indirect (EQ-5D, SF-6D…) valuation methods in primary studies	Letters, secondary studies…

QoL: Quality of Life. HRQoL: Health-Related Quality of Life. DALY: Disability-Adjusted Life-Year. TTO: Time-Trade-Off. SG: Standard-Gamble.

3.5.2 Results

3.5.2.1 Methodological assessment

The main characteristics of the 9 selected studies are presented in Table 13.

Table 13 – Overview of the primary studies valuing the health-related quality of life associated with influenza/ILI

Author, year, country	Methods						Baseline (no symptom)			Disease				
	Instrument	Study timing	Focus group	Sample size	Age (years)	Data collection period	Health state	Time	QoL weight	Health state	Time	QoL weight	Duration (days)	QALD
Van Hoek, 2011, UK[264] & Baguelin, 2010, UK[258]	EQ-5D	Pro-spective[a]	Patients	83 (ILI)	Adults & children (11-15)	2009	No ILI	Post ILI/H1N1 recovery	0.97	ILI *	Worst day of illness	0.34	Mean 8.7	2.7
				186 (H1N1)			No H1N1		0.96	H1N1 §		0.96	H1N1 §	0.96
Sander, 2010, Canada[188]	Turner's weights combined with unpublished disease duration	See Turner	See Turner	See Turner	See Turner	See Turner	-	-	-	ILI *	See Turner	See Turner	NS	5.33 (0-19y)[e] 6.35 (20-64y) 10.69 (65+y)
Pradas Velasco, 2009, Spain[262]	EQ-5D	Pro-spective	Patients	50	Mean: 40.34 (SD: 9)	2004-2005	No ILI	Post ILI recovery	0.941 (SD: 0.12)	ILI *	Once during illness	0.294 (SD: 0.43)	Mean 10.5 (Min 7 – Max 14)	6.8 #
Turner, 2003, UK[108]	Likert scale (0-10) transformed to Visual Analogue Scale VAS scores transformed to Time-Trade-Off	Pro-spective[b]	Patients	309 (adults) 387 (elderly and high-risk)	Adults (18-65) Elderly (65+) High-risk (13+) h	01-03/ 1998	-	-	-	ILI * - adults	Day 1	0.068	Mean 7.69	-
											Day 2	0.245		
											Day 3	0.397		
											Day 4	0.526		
											Day 5	0.612		
											Day 6	0.659		
											Day 7	0.705		
											Day 8	0.758		
											Day 9	0.778		
											Day 10	0.787		
											Day 11	0.796		
											Day 12	0.798		
											Day 13	0.799		
											Day 14	0.803		
											Day 15	0.808		
											Day 16	0.810		
											Day 17	0.810		
											Day 18	0.811		
											Day 19	0.812		
											Day 20	0.814		

											Day 21	0.865		
										ILI * - elderly and high-risk	Day 1	0.117	Mean 9.985	-
											Day 2	0.197		
											Day 3	0.270		
											Day 4	0.349		
											Day 5	0.401		
											Day 6	0.433		
											Day 7	0.460		
											Day 8	0.464		
											Day 9	0.494		
											Day 10	0.502		
											Day 11	0.532		
											Day 12	0.543		
											Day 13	0.562		
											Day 14	0.573		
											Day 15	0.576		
											Day 16	0.613		
											Day 17	0.616		
											Day 18	0.627		
											Day 19	0.641		
											Day 20	0.651		
											Day 21	0.669		
O'Brien, 2003, Canada [261]	Likert scale (0-10) normalised to 0-1 QoL weights	Pro-spective[c]	Patients	262	16-64	01-03/ 1998	-	-	-	ILI *	Day 1	0.40	Mean 6.97 (95%CI 6.10–7.87)	4.36
											Day 2	0.48		
											Day 3	0.58		
											Day 4	0.65		
											Day 5	0.71		
											Day 6	0.76		
											Day 7	0.78		
				630						ILI+ †	Day 1	0.40	Mean 6.83 (95%CI 6.43–7.21)	4.24
											Day 2	0.44		
											Day 3	0.54		
											Day 4	0.64		
											Day 5	0.70		
											Day 6	0.75		
											Day 7	0.79		
Rothberg, 2003, USA [263]	HUI-3	Retro-spective[f]	Patients	15	Working-age	2001-2002	-	-	-	ILI *	Most recent ILI episode	0.25	-	-
Brady, 2001,	HUI-3	Hypothetic scenario[g]	Healthy adults	11	NS	NS (2000?)	No ILI	-	1	ILI-OP	-	0.636	-	-

Canada[259]														
Griffin, 2001, UK[260]	EQ-5D	Retro-spective[d]	Patients	21	18+	1999-2000	No ILI	-	0.817	ILI+ †	Most recent ILI episode	- 0.066	Mean 2.48	-
		Hypothetic scenario[g]	Healthy GPs	8	NS		No ILI	-	0.720	ILI	-	- 0.720	Mean 2.48	-

a: From disease onset to recovery. b: From the day of ILI onset up to 21 days after. Based on the placebo arm of 8 Oseltamivir RCTs from Hoffmann la Roche, with study centres in Europe, Canada, the USA and China. c: From the day of ILI onset up to 7 days after. Based on the placebo arm of 4 Oseltamivir RCTs from Hoffmann la Roche, with study centres in Europe, Canada, the USA and China. d: Patients suffering from ILI within the last 3 months. e: Children were assumed to have the same QALY weights as the adults in Turner et al.[108] f: Patients with a history of influenza-like illness, the recall period is not reported by the authors. g: The description of the scenarios to be considered and valued is not reported by the authors. h: Patients with chronic cardiac (excluding chronic idiopathic hypertension) or pulmonary disorders (including bronchopulmonary dysplasia and asthma but excluding cystic fibrosis) severe enough to require regular medical follow-up or hospital care.
*VAS: Visual Analogue Scale, TTO: Time-Trade-Off, OP: Out-Patient, IP: In-Patient, HUI: Health Utility Index, GP: General Practitioner, ILI: Influenza-Like Illness, QALY: Quality-Adjusted Life-Years, QALD: Quality-Adjusted Life-Days, NS: Not Stated. * Clinically diagnosed ILI, § PCR confirmed influenza A/H1N1, † Virus culture or serology confirmed influenza, # Self computation.*

Prospective versus retrospective design - All studies were prospective, with the exception of two retrospective studies.[260, 263] In the first retrospective study, the recall period is not reported.[260] In the second one, patients were asked to remember their ILI episode as far as in the last 3 months.[263] In contrast with prospective QoL studies, retrospective designs may lead to serious recall bias, especially for transient diseases such as ILI/influenza.

Sample size - The three eldest studies of Rothberg,[263] Brady[259] and Griffin[260] used very small sample sizes (between 8 to 21 respondents) to elicit QoL weights. Most recent studies enrolled 50 to about 600 subjects. The validity of QoL weights obtained from small sample sizes may be questioned.

QoL instrument - Almost all studies used validated generic instruments to derive QoL weights, i.e. the EuroQoL EQ-5D[258, 260, 262, 264] and the HUI-3.[259, 263] In the study of Turner,[108] patients were asked to daily value their health on a Likert ordinal scale (0 to 10) from the day of ILI onset up to 21 days after.[108] Data were then recalibrated to a visual analogue scale (VAS - from 0 to 100) and converted to Time-Trade-Off scores[265] in order to map the original disease-specific scale onto a QALY scale. In O'Brien,[261] QoL values were derived from a Likert ordinal scale (0 to 10). The raw scores were then normalised to 0-1 and used as QoL weights.

Respondent - In most studies, ILI/influenza patients themselves were asked to value their own ill-health by marking a scale or by filling in questionnaires. In two studies, this task was performed by healthy adults who were presented hypothetical scenarios describing an ILI episode.[259, 260] As there is evidence that experts' opinions are not always close to the patients experiences, the use of healthy adults to value patients' health states is not recommended.

Stratification - In three studies, the age of the respondent was not reported.[259, 260, 263] In two other studies, age limits were reported but the ranges were wide or imprecise (18+,[260] 11-15 and adults[264]). It is clear though that the severity and duration of ILI symptoms differ with the age and general status of the patient. When sample sizes allow it, stratification of the QoL results by age categories (adults, elderly) or health status (otherwise healthy, co-morbidities…) is thus important. This was done in the study of Turner[108] that reported QoL results separately for otherwise healthy adults (18-65 year), the elderly (65+) and a high-risk population (13+) consisting of ILI patients with chronic cardiac or pulmonary disorders. This is also the case in O'Brien that distinguished the results according to the severity of disease (ILI versus laboratory confirmed influenza).[261]

Timing – ILI/influenza is a transient disease whose symptoms rapidly evolve. QoL values will not be constant during the whole ILI/inflenza

episode and may considerably differ according to the point in time where they were measured. Two studies asked patients to assess their ILI episode as a whole.[260, 263] One study asked them to value any day during their ILI episode,[262] while another study valued the worst day of illness.[258, 264] By contrast, O'Brien[261] and Turner[108] assessed the daily evolution of the ILI/influenza episode, up to 7[261] or 21[108] days after disease onset.

Health state definition – Table 14 lists the clinical criteria used by the studies to enrol their patients. According to those criteria, the health states to be valued can be classified as clinically diagnosed ILI (ILI) or (laboratory) confirmed influenza (ILI+). In most studies, patients were enrolled based on clinical symptoms only (ILI). A significant difference among those studies is whether fever is a required symptom[108, 188, 258, 261, 263, 264] or not.[262] It has been shown that studies including fever in their ILI definition result in a higher proportion of influenza-confirmed ILI cases.

Table 14 – Health state definition: clinically diagnosed influenza (ILI) versus confirmed influenza (ILI+) cases

Author, year, country	Data collection year	Criteria for patient identification	Diagnostic	ILI or ILI+ health state
Van Hoek, 2011, UK[264] & Baguelin, 2010, UK[258]	2009	Fever + at least 1 other influenza-related symptom (blocked/runny nose, cough, sore throat, headache, muscle/joint pain, chest pain, stomach ache, diarrhoea, nausea, chills, weakness or eye irritation)	Clinical	ILI
Sander, 2010, Canada[188]	See Turner	See Turner	See Turner	ILI
Pradas Velasco, 2009, Spain[262]	2004-2005	GP diagnostic with no further criteria specification	Clinical	ILI
Turner, 2003, UK[108, 266-268]	1998	Adults and elderly: fever + 1 respiratory symptom (cough, sore throat or nasal congestion) + 1 systemic symptom (headache, malaise, myalgia, sweats or chills, fatigue). Children: fever + cough or coryza	Clinical	ILI
Rothberg, 2003, USA[263]	2001-2002	Fever + 2 of 4 symptoms (cough, myalgia, sore throat, headache)	Clinical	ILI
O'Brien, 2003, Canada[261, 266-268]	1998	Adults: Fever + 1 respiratory symptom (cough, sore throat or nasal congestion) + 1 systemic symptom (headache, malaise, myalgia, sweats or chills, fatigue). Children: Fever + cough or coryza	Clinical	ILI
		Virus culture or serology among ILI patients	Influenza confirmation	ILI+
Brady, 2001, Canada[259]	Not reported	Hypothetic scenario to be valued by healthy adults. Description of the scenario not reported.	-	?
Griffin, 2001, UK[260]	1999-2000	GP diagnostic with virus culture	Influenza confirmation	ILI+
		Hypothetic scenario to be valued by healthy adults. Description of the scenario not reported.	-	?

Influenza season - Not all the influenza seasons are alike. They mainly differ in circulating strains, which show different attack rates, severity, affected age groups and degree of matching with the vaccine strains. In the studies selected, the years of data collection spanned from 1998 to 2009, covering various intensity seasons. When choosing a set of QoL data to feed our model, we should pay attention that the season characteristics (i.e. severity) during the data collection year matches our expectations for the coming Belgian ILI seasons.

3.5.2.2 Selection of QoL data for the Belgian simulation model

Based on the previous section, QoL data from Turner[108] and O'Brien[261] appear to be the most adequate to feed our Belgian simulation model.

Both studies are prospective and are performed on a large sample of patients (300-600 patients per group). In both studies this sample size represented a large proportion of the patients enrolled in the clinical trials along which QoL data were collected (i.e. 65-67% in Turner and 96.5% in O'Brien).

In Turner, patients are stratified according to age and health condition (healthy adults (18-65 year), the elderly (65+) and a high-risk population (13+)). In both studies, QoL values are reported daily, up to 7[261] or 21[108] days after disease onset. The health state valued is ILI, equally defined in both studies as documented fever of 38° or higher plus 1 or more respiratory symptom (cough, sore throat or nasal congestion) and 1 or more systemic symptom (headache, malaise, myalgia, sweats or chills, fatigue). This definition matches closely with that used by the IPH (Scientific Institute of Public Health) influenza surveillance in Belgium. Besides the valuation of ILI, O'Brien also report QoL values for influenza confirmed ILI+ cases, allowing the model to be fed with the most adequate data. In both studies, the data collection period was January to March 1998, with data collected mainly from Europe and North America (Canada and the USA). In both Europe and the USA, the 1997-1998 ILI season was of relatively low intensity, which corresponds to the intensity of the seasons we experience now.

4 DATA COLLECTION AND INTERMEDIARY ANALYSES

4.1 Epidemiological and burden of disease data

4.1.1 ILI and influenza surveillance, hospitalization rates and deaths

An overview of the Belgian ILI and influenza surveillance, hospitalization and death data is provided in the part I report by Hanquet et al.[23]

4.1.2 Estimation of influenza related admissions and deaths through regression analyses

A major problem is that admissions and deaths coded as influenza represent a minority of the true influenza hospitalisation and mortality burden.[269, 270] Indeed, only a minority of cases is confirmed by laboratory testing or recognized as due to influenza. Furthermore, there is no ICD code for influenza-like-illness. The most common influenza-related severe outcome is pneumonia, which may also be caused by other infections (viral or bacterial).

Several studies have addressed this problem by estimating the burden of severe influenza disease with the use of multivariate regression analysis, using the underlying temporal variations of influenza and pneumonia, as well as other co-variates of interest to attribute outcomes to these causative agents.[269-276]

For this reason, a regression analysis has been conducted to determine the number of hospitalization and deaths that are attributable to influenza in Belgium. Full details of this analysis are provided in Supplement 2 and the main features are summarized below.

Our analysis, using Belgian data, is based on two major outcomes:

- Deaths from pneumonia and/or influenza (P+I),
  - Coded as principal (or underlying) cause of death
  - Coded as any of the different causes of death

- Admissions for pneumonia and/or influenza,
  - Codes as principal diagnosis
  - Coded as any diagnosis

We also conducted an analysis on all respiratory and/or circulatory admissions for the sensitivity analysis.

4.1.2.1 Methods

A multivariate linear regression analysis has been conducted. As dependent variable, we use the weekly number of admissions coded as pneumonia and/or influenza (P+I) from the Minimal Clinical Data (MCD) on hospitalisation and the weekly counts of deaths coded as P+I from the death certificates. For both outcomes, we analysed separately P+I as principal diagnosis/cause of death and P+I as any diagnosis/causes of death.

Independent variables were the weekly counts of respiratory pathogens that are the most frequent cause of influenza-like-illness or pneumonia: influenza A and B viruses, *Streptococcus pneumoniae*, adenovirus, RSV, *Mycoplasma pneumoniae,* parainfluenza virus, *Haemophilus influenza.* Pathogens data were provided by the sentinel laboratory network and the National influenza Centre of the Scientific Institute of Public Health (IPH) and the KUL Reference Laboratory for *Streptococcus pneumoniae*. Other parameters were holidays and returns from school breaks (i.e. first week after Christmas holidays and first week of September), a seasonal term and population size. We also tested whether including time lags between pathogen counts and outcome and whether adjusting pathogen data for the respective surveillance coverage (of sentinel and reference laboratories) and trends in blood cultures over time would improve the models. Selection of parameters was based on stepwise regression, based on Wald tests ($p<0.20$).

Separate models were built for each age group. We restricted the analysis to the 5 calendar years 2004-2008, which includes 4 influenza seasons (from 2004-05 to 2007-08), as this was the period in which all data were available. Model selection was based on the goodness-of-fit, as measured by the deviance divided by the degrees of freedom (dev/df) and the distribution of residuals. Several distribution models have been tested, and the over-dispersed Poisson models with identity link were the most appropriate to fit our data. All analyses were run in STATA 12.0, and we used generalized linear model regressions (glm) for over-dispersed Poisson.

For all outcomes, a better fit was generally found in models including one influenza parameter by season (instead of a single influenza parameter for the whole period), interactions between pathogens, holidays and break returns, and a population term in some age groups. Lagged variables improved the models in the regression on deaths. Models that adjusted for pathogen surveillance coverage and blood culture trends did not improve the models and provided very similar estimates of influenza attributable admissions and deaths.

For admissions, as not all relevant parameters could be fitted into one final model (i.e. interactions of each pathogen with separate influenza parameters by season) as none of them was clearly superior, we ran two models

- Model 1, with influenza parameterized by season and breaks;
- Model 2, with interactions between pathogens and breaks.

4.1.2.2 Prediction of influenza attributable admissions

Final models showed a reasonable goodness-of-fit and a minor level of serial correlation of residuals, except in the 75+ in which the fit was inferior. The number of predicted influenza admissions is very similar in both models 1 and 2. Interestingly, adding or changing some parameters that decreased substantially the level of autocorrelation and improved the fit did minimally change the predicted numbers.

When the outcome is P+I as principal diagnosis, around 2100 influenza admissions are predicted in an average season, representing an admission rate of 20/100 000 persons or a 6% of admissions for P+I as principal diagnosis (Table 15). When the outcome is any P+I admissions, above 3000 influenza admissions are predicted by season, representing an admission rate of about 30/100 000 persons or 4-5% of any P+I admissions. The admission rates vary largely across age groups (range 6–93/100 000 by age group for P+I main).

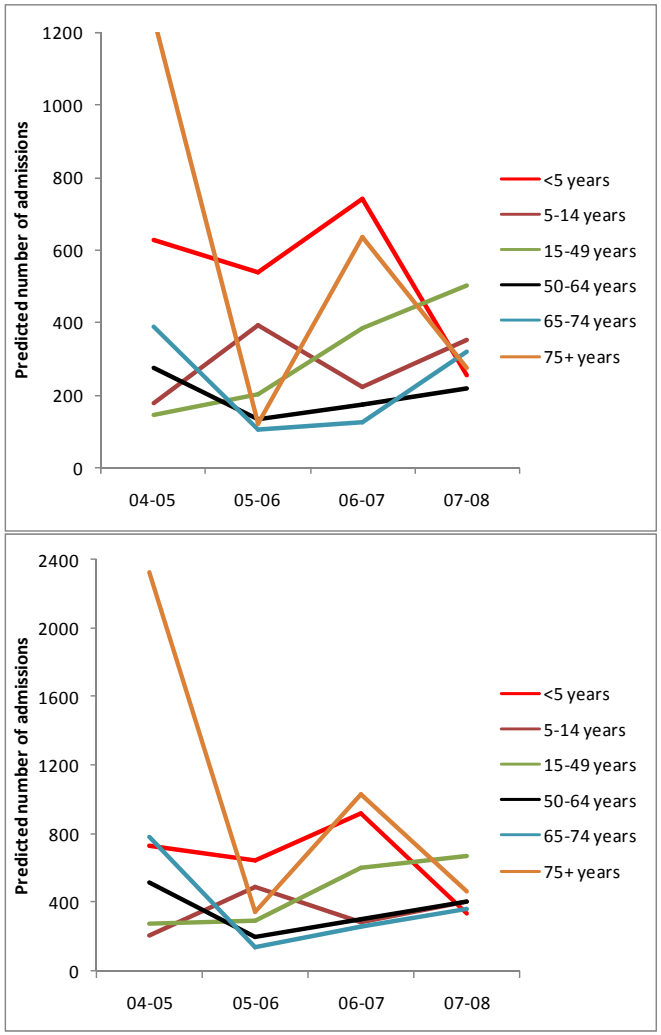
Table 15 – Predicted admissions, rates and % P+I admissions in an average influenza season, by age group and model

	Average number admissions (range by season)		Admission rate per 100 000		% of P+I admissions (average)	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Model based on P+I as principal diagnosis						
<5 years	540 (255-742)	600 (538-673)	92.7	103.0	8%	8%
5-14 years	287 (178-394)	290 (279-304)	23.6	23.9	11%	11%
15-49 years	309 (147-503)	301 (174-441)	6.2	6.0	7%	7%
50-64 years	201 (134-277)	178 (102-241)	10.5	9.3	5%	4%
65-74 years	234 (104-388)	179 (56-373)	24.8	18.9	5%	4%
75+ years	568 (121-1238)	554 (204-1088)	66.2	64.5	4%	4%
Total	2140	2102	20.3	20.0	6%	6%
Model based on P+I as any diagnosis						
<5 years	661 (338-925)	690 (630-798)	113.4	118.4	8%	8%
5-14 years	348 (208-489)	362 (354-369)	28.7	29.8	11%	12%
15-49 years	462 (277-673)	429 (257-598)	9.2	8.6	6%	6%
50-64 years	356 (198-517)	316 (191-480)	18.7	16.6	4%	3%
65-74 years	386 (137-785)	305 (72-655)	40.8	32.2	3%	3%
75+ years	1043 (345-2323)	1019 (376-2001)	121.5	118.6	3%	3%
Total	3256	3120	31.0	29.7	5%	4%

P+I: Pneumonia and/or influenza admissions.

The predictions vary substantially across seasons, with a range of 13-27/100 000 by season for all ages (Table 15 and Figure 6), especially with Model 1 as it parameterizes influenza by season. The four included seasons presented different levels of intensity: the 2004-05 and 2006-07 seasons were characterized as moderate intensity, and the 2005-06 and 2007-08 seasons were considered as low intensity. No season with a high level of intensity could be included in the analysis.

Figure 6 – Influenza admissions by season and age, predicted by model 1 for P+I main diagnosis (top) and any (bottom)



x-axis: season year.

In general, the proportion of P+I admissions that are attributed to influenza by the models is low (6% for P+I main; 4-5% or any P+I) compared to the TIV vaccine efficacy values against ICD-coded P+I admissions (8-32%, see part I). This could be partly due to differences in coding systems, admission patterns and higher intensity influenza seasons in the settings that published efficacy studies (mostly US). The numbers of influenza admissions predicted by the P+I main diagnosis model are on average 40% higher than the number of ICD coded influenza admissions in the MCD dataset, confirming that outcomes coded or diagnosed as influenza are an underestimation of the true influenza burden. The difference is highest in the elderly 75+, in which the models predict 4 times more admissions than the MCD dataset.

A first sensitivity analysis predicted 46% more admissions if our models would only include influenza and RSV as independent parameters. In the elderly 75+ years, this model would predict 70% more admissions than our final selected model. Another analysis considered all respiratory and respiratory coded admissions as outcomes and predicted around 5000 admissions by season, representing 2.3-fold more admissions overall than P+I model 1 (principal diagnosis). This analysis predicted lower numbers of admissions in children but a 3.5-fold higher number in adults ≥50 years of age. However, most of these models showed a poor goodness-of-fit and the results of these are therefore not included in the analyses in this report.

4.1.2.3 Prediction of influenza attributable deaths

No model could be run among children when regressing P+I deaths as main cause, and the models in P+I deaths as any cause found no deaths in the 5-14 years. Indeed, the numbers of coded P+I deaths in these groups were extremely low (<10/season). One model was selected in each age group as being clearly superior to others in terms of goodness-of-fit and residual distribution. In the 65+, the best models included a time lag for the dependent variables. All final models showed a good fit, and a minor level of auto-correlation of residuals was only observed in the 75+.

When the outcome is P+I as principal cause of death, 244 influenza deaths are predicted in an average season, representing a death rate of 2.3/100 000 persons and 6% of all P+I deaths as principal cause (Table 16). When the outcome is P+I as any cause of death, 356 influenza deaths are predicted by season, representing a death rate of 3.5/100 000 persons and 3% of P+I deaths as any cause. The death rate is low in young adults and highest among the elderly as expected, at 23.7–31.0/100 000 when regressing on P+I as principal cause or as any cause.

Table 16 – Predicted influenza deaths, death rates and % of P+I deaths by influenza (average across seasons) by age group

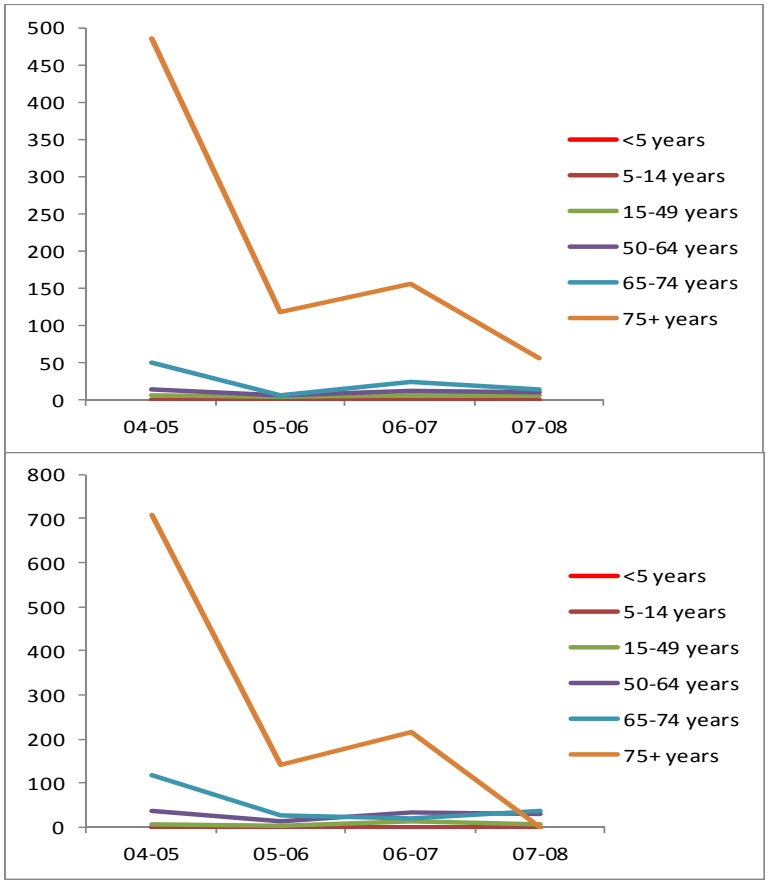
Age	Number deaths		Death rate		% of P+I deaths	
P+I cause of death	Main cause	Any cause	Main cause	Any cause	Main cause	Any cause
<5 years	0	2	0.0	0.3	NA	15%
5-14 years	0	0	0.0	0.0	NA	0%
15-49 years	5	8	0.1	0.2	11%	3%
50-64 years	11	30	0.6	1.6	6%	4%
65-74 years	24	51	2.5	5.4	6%	3%
75+ years	204	266	23.7	31.0	6%	3%
Total	244	356	2.3	3.4	6%	3%

P+I: Pneumonia and/or influenza admissions.

The prediction varied substantially across seasons (Figure 7), with 86-132 deaths in low intensity seasons and 200-556 deaths in moderate intensity seasons. The numbers of predicted influenza deaths are in average 3-fold higher than the number of ICD coded influenza deaths for both types of outcome (principal or any cause of deaths).

A sensitivity analysis predicted the number of deaths in models would include influenza as sole pathogen. We found 40% more deaths in the 75+ for P+I as principal cause of death. When regressing on P+I as any cause of deaths, 80% more deaths would be predicted in the 65+, including 89% more deaths in the 75+.

Figure 7 – Predicted influenza deaths by season and age for P+I as main cause (left) and any cause (right)



x-axis: season year.

4.1.2.4 Conclusions

The final models to predict the number of influenza attributable admissions and deaths show a relatively good goodness of fit and residual distribution, with the exception of the elderly ≥75 years. In these four seasons with moderate and low intensity, we predict a range of 2000-3000 influenza admissions and 250-350 influenza deaths by mean influenza season. A high variability of these outcomes across season is observed: the number of admissions in the highest season represented more than the double than those in lowest season, and the number of deaths predicted in the highest season accounts for 6 to 12-fold those predicted in the lowest season. This high variability of the influenza predicted numbers across seasons and age groups confirms the known variability and changing severity of influenza strains.

The estimates of influenza admissions and deaths also vary with the selected outcome. When regressing on any P+I diagnosis, we estimate around 50% more admissions and deaths by season compared to predictions based on P+I as principal cause models. When modeling all respiratory and circulatory admissions as dependent variable, we found a 2.3-fold higher number of admissions compared to estimates from P+I models (principal cause).

These results are difficult to compare with those from other studies, due to differences in outcomes, seasons, independent parameters, indicators reported, type of health system and health seeking behavior. In general, our admission estimates are in line with those from prospective studies, though only recent studies among children were found.[277, 278] Other regression studies predicted overall higher influenza admission and mortality rates in the elderly and lower admission rates in the younger groups.[269, 271, 274-276, 279, 280] However, most seasons covered by these studies were in the nineties when higher intensity seasons were observed, and many studies only involved influenza (and sometimes RSV) as pathogens. When we compared similar seasons and conducted analyses with similar outcomes and pathogens, our estimates were in line with those predicted by these studies. For instance, our death estimates were comparable with those predicted by two studies using a similar outcome and the same methodology, when we compare seasons with similar intensity;[119, 120] similarly, our admission estimates were similar to US and Australian studies when we compared rates in seasons of low or moderate intensity.[269, 280, 281]

Our study has two major limitations. One is a remaining level of auto-correlation of residuals, especially in the elderly. However, changes in the model that improved the independence of residuals did hardly affect the

predicted influenza-related outcomes. The other limitation is that our study period involves four low to moderate intensity seasons, it is thus not representative of high intensity seasons in Belgium. This likely underestimates the influenza burden on admissions and deaths.

4.2 Cost data

4.2.1 Out of hospital costs for Influenza Like Illness (ILI) and clinically diagnosed influenza

4.2.1.1 Survey methods and participation

With the aim to collect data on out of hospital health care use for influenza-like-illness in Belgium we conducted a retrospective survey during the 2011-2012 influenza season. To this end, between January and March 2012 roughly 10 000 Belgian telephone numbers were dialled by random digit dialling on mobile and landlines. After contact was made (i.e. someone answered the phone) 9170 potential respondents expressed a willingness to participate and check a list of potential symptoms for ILI. These symptoms were: (a) rapidly rising fever, (b) high fever (>38°C for an adult and >38.5°C for a child), (c) sore throat, (d) runny or blocked nose, (e) cough, (f) sore muscles, (g) shivering, (h) nauseous/vomiting, (i) tired and exhausted. About halve of the potential respondents (4537) complied with the criteria of the checklist (having someone in the household (including themselves), who experienced at least three symptoms on the checklist during the previous 4 weeks). The process of recruitment was also following set quota targets, in order to approximate by pre-defined groups, the gender specific population of the respective regions, in accordance with national statistics. Age quota were set to allow exploring age-specific cost differences and making sure robust estimates could be made for the most vulnerable in the population (i.e. by oversampling children under 12 years and the elderly) as follows: <12y (25%), 12-17y (5%); 18-49y (25%); 50-69y (25%); >70y (20%). This implies respondents were excluded if their background did not comply with the sought after characteristics at the time of sampling. It is noteworthy that these quota were met a first time in mid February 2012, at which point the sample was expanded. In other words, this process of quota sampling was started in midstream again from scratch (i.e. the inclusion process is not substantially different between the different months of recruitment, and the sample population is comparable over time).

We aimed to collect information on 2250 people who experienced ILI, but oversampled by 10% to replace questionnaires in the original sample, with invalid or incomplete answers (a total of 496 records were replaced). The remainder were removed starting with the last one obtained, so that we have a final sample size of 2250 eligible and complete questionnaires. All respondents were contacted and recruited by telephone, but these could each choose to complete further questions by phone, through the internet (they would then receive a survey-link by email within 10 minutes), or in writing (through the post services, with a pre-stamped return envelope). Recruitment and surveys were administered in both prevailing Belgian languages (Dutch and French). Consistency of recruitment protocols and surveys was verified by back translation.

ILI was defined as the occurrence of at least 3 symptoms of the symptom list above during the previous four weeks. Survey respondents with ILI were also asked whether their physician had explicitly diagnosed them with influenza or not. Those reporting to be diagnosed with influenza by their physician were assumed to be clinically diagnosed influenza cases, although no standard information was available on the diagnosis and on potential laboratory tests.

4.2.1.2 Characteristics of respondents

We collected information on 2250 persons who experienced ILI. The majority completed the questionnaire in writing by post (n=925), through the internet (n=844), or orally on the phone (n=481). Slightly more than half (54%) was female (1232 female versus 1018 male). The age distribution is depicted in Figure 8. Figure 9 indicates that a peak in ILI reports occurred in January. Of the 1116 patients who visited a GP and who were not hospitalised, 38% (n=429) were diagnosed by their physician with influenza.. Overall, 4 respondents who were hospitalised reported to be diagnosed with influenza. Health care use was similar across ages, although for children slightly more often a medical doctor was consulted. The majority of hospitalized patients were either very young or older than 70 years (Figure 10). Reported duration of symptoms is longer for hospitalized as compared to ambulatory patients, and is shortest for persons not seeking medical care (Table 17).

Figure 8 – Age distribution of respondents of the influenza survey

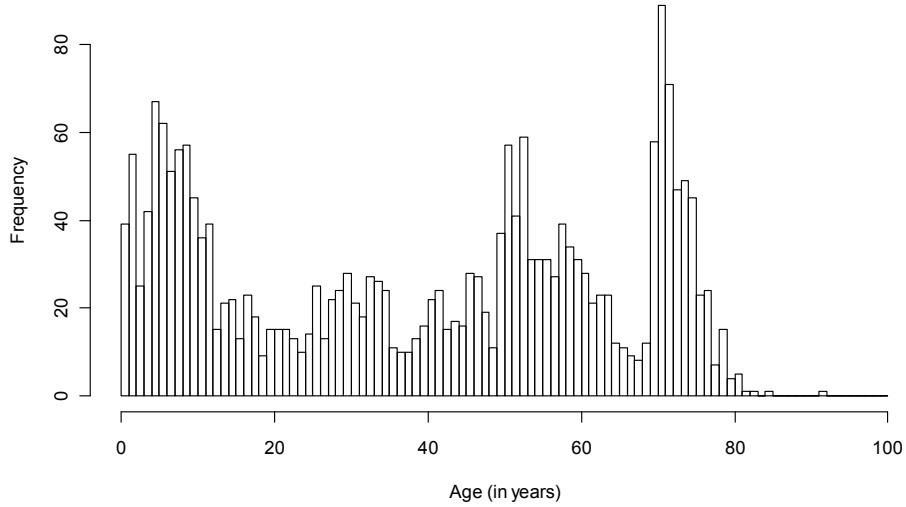


Figure 9 – Months during which survey respondents experienced ILI symptoms

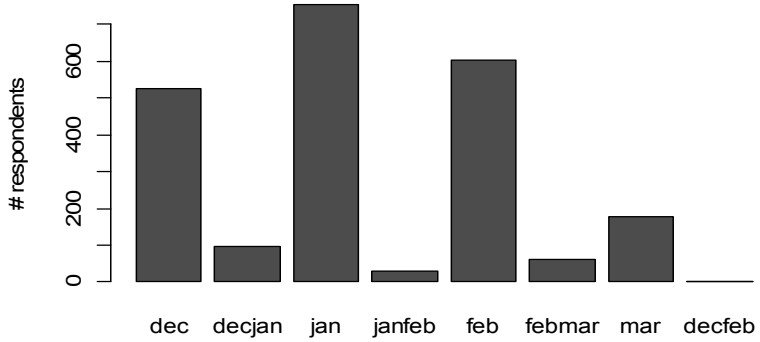
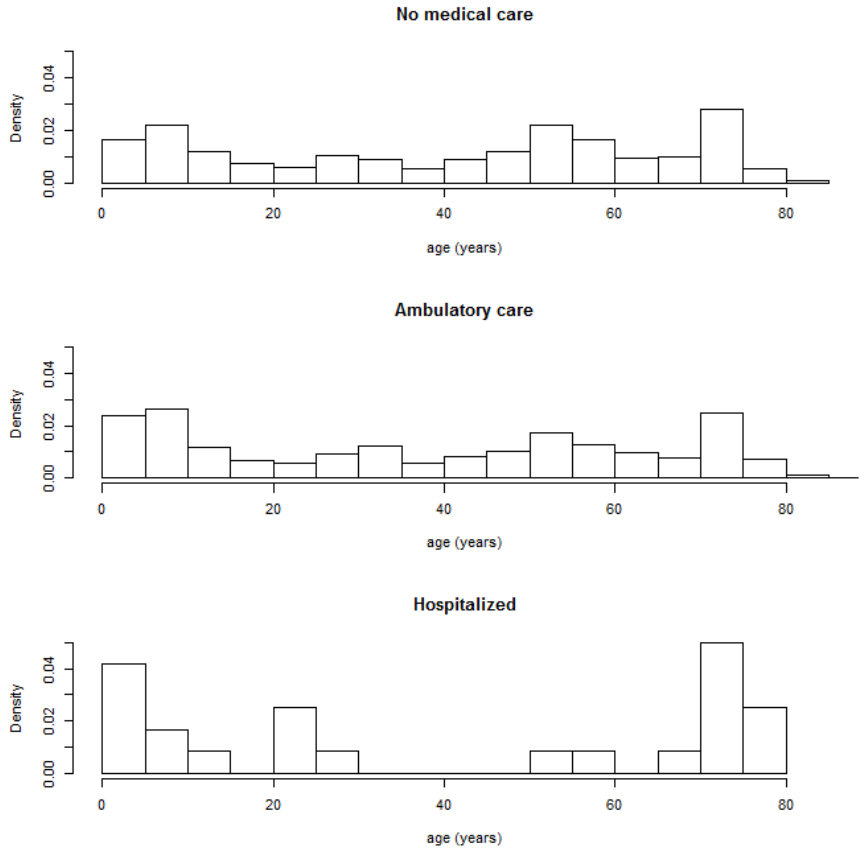


Figure 10 – Age distribution of persons with ILI by health care use



4.2.1.3 *Cost estimates based on the survey*

The total direct medical cost of persons with ILI is obtained, separately for patients not seeking medical care, patients seeking ambulatory care, and hospitalised patients (costs outside the hospital). Costs for ambulatory patients are calculated with and without including the 18 patients with emergency visit and/or consultation in a hospital (Table 17). Total direct medical costs of a person include the cost of medication purchased and the cost of consultations (costs paid by the National Health Service (NHS) as well as co-payments).

Table 17 – Health care use and duration of symptoms of survey respondents (n=2250)

Patients' behaviour	N	Duration of symptoms (mean days, standard deviation)
Did not consult a medical doctor ('no medical care')	1107 (49.2%)	5.51 (0.14)
Consulted at least once a medical doctor ('ambulatory')	1098 (48.8%)	6.43 (0.14)
Hospitalised and stayed at least one night in hospital ('hospitalised')	24 (1.1%)	8.5 (1.04)
Went to hospital but did not stay overnight (emergency visit and/or consultation in hospital)	18 (0.8%)	8.9 (4.5)
Went to hospital but unclear if they stayed overnight	3 (0.1%)	NA

The next paragraphs explain in detail how the direct medical costs outside the hospital are obtained.

Consultation frequency and costs

We analysed the consultation frequency for 1141 persons, who consulted at least once a medical doctor (including 43 persons who went to hospital). For the majority of respondents this was the general practitioner. The type of medical doctor they visited as well as the frequency are presented in Table 18 below.

Table 18 – Consultation frequency of respondents who sought medical care for their ILI episode

	consultations at the doctor's practice (or in the hospital)									visits at home							telephone consult						
# consultations	1	2	3	4	5	6	7	8	total	1	2	3	4	5	6	total	1	2	3	4	5	6	total
general practitioner	708	183	28	9		1			**929**	210	44	8	3	1	3	**269**	80	20	2	4	2		**108**
pediatrician	42	12	4		4		2		**64**	2	3	1				**6**	4	6					**10**
pneumologist	19	5	1					1	**25**	5						**5**	1						**1**
otorhinolaryngologist	46	1	1						**48**	9	1	1				**11**							**0**
other specialist	28	23	1	2					**54**	2				3		**5**	9	2			3		**14**

Note: respondents could fill in more than 1 cell; 'other specialist' was not further specified. Table includes hospitalised patients.

Unit costs for consultations are taken from the Belgian reimbursement scheme ("Tarieven; geneesheren - raadplegingen en bezoeken: honorarium fees ; 01-02-2012", http://www.inami.fgov.be/insurer/nl/rate/index.htm#medecins). Standard fees were used for regularly insured patients (i.e. according to Belgian guidelines[114]), see Table 19. The following assumptions were made:

- General practitioners and specialists are 'accredited'.
- Patients have a Global Medical File ('GMF').
- Consultation is not because of the GMF.
- Assume all general practitioners are 'acknowledged'.
- In the Belgian reimbursement scheme, no specific information was found on the cost of a consultation with an otorhinolaryngologist ('neus-keel-oorarts/nez-gorge-oreille') (info was available only on 'technische geneeskundige verstrekkingen/prestations techniques médicales'). We assume the same cost as for the other specialists (pediatrician and pneumologist).
- Visits at home were assumed to occur during normal hours (i.e. not in the evening, during the weekend or urgent).

- Visits at home were assumed to occur for a single person (and not simultaneously for multiple persons).

Of the 1041 respondents, 27 reported a home visit from a specialist. However, this seems very unlikely (possibly a mistake was made by completing the questionnaire, or patients had a visit from a family member who is a specialist). Therefore we assume for all visits at home, the cost of a visit at home from a general practitioner.

For telephone consults, there is no information on costs in the Belgian reimbursement scheme, and this is not covered in the KCE guidelines.[114] For an individual person with influenza-like symptoms, it is likely that the cost for telephone consults are low at the margin, though at the height of the influenza season, the cumulative opportunity costs to an individual physician may be high. Nonetheless, we assume here conservatively that these consults occur at no cost.

To estimate the level of reimbursement, we assume that all patients are persons without preferential reimbursement (i.e. unit costs are based on 'tegemoetkoming rechthebbenden zonder voorkeurregeling/intervention bénéficiaires sans régime préférentiel').

Table 19 – Unit cost for different types of medical doctor and consults (NHS+co-payments), costs based on the Belgian reimbursement scheme on 1/2/2012

Type of medical doctor	Consultations at the doctor's practice (or in the hospital)	Visits at home	Phone consult
General practitioner	€23.32	€35.03	€0
Pediatrician	€35.02	Assume same as general practitioner	
Pneumologist	€35.01		
Otorhinolaryngologist	Assume same as pneumologist		
Other specialist	€23.32		

The average cost per person for consultations (Table 20) is obtained by multiplying the number of consults of a certain type by the unit cost for that type. Excluding the records for which the total cost for consultations is possibly right-censored (i.e. persons who were still sick at the moment the questionnaire was completed, n=355), results in slightly lower average costs, but the effect is very small (not shown).

Table 20 – Average cost (€) per person for consultations for an ambulatory person with ILI (n=1098)*

Based on unit costs for medical doctors who are:	Min	1st quartile	Median	Mean	3rd quartile	Max
Accredited	0	23.32	23.32	42.52	46.64	595.2
Not accredited	0	19.93	19.93	38.19	39.86	551.3

** Persons who went to hospital were excluded here. There are 6 persons who specified only a telephone consultation, for these persons the cost is €0.*

Medication frequency and costs

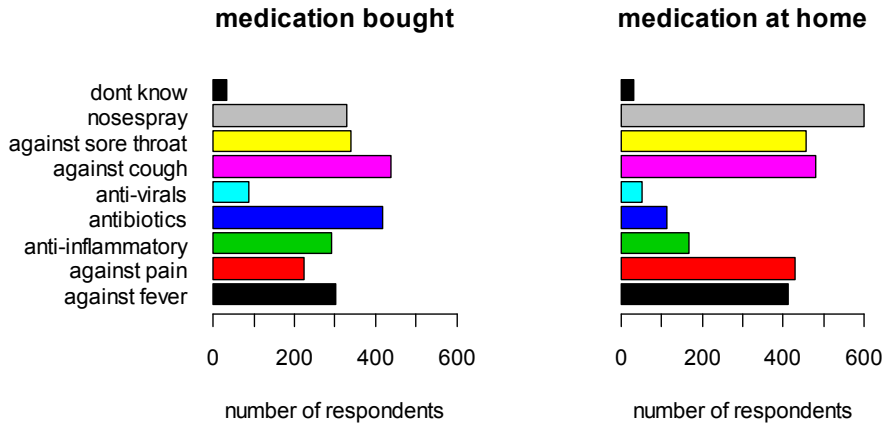
In the survey, two questions were related to medication use/costs:

- Question 7: about the type of medication taken, and if it was purchased or not for the particular episode (i.e. depending on whether the person had it at home).
- Question 8: about how much was paid for medication (i.e. the cost that the persons had to pay themselves at the drugstore). The persons had to choose between 5 categories ('between €0 and €25', between '€25 and €50', and so on).

To estimate the total cost paid for medication per person, we use the first question (7)'s responses, as it contains more detailed information and it is not restricted to co-payments only. However, the results are also compared with the responses on the second question (8).

For 1710 of the 2250 patients with ILI included in the survey, it was stated that they used medication.

Figure 11 – Number of respondents who used different types of medication, separately for medication bought in the pharmacy and medication that the respondents had at home



Each respondent could specify several types of medication. 'Don't know' refers to medication taken but not sure which type.

The unit price for each medication group is derived from the 'Gecommentarieerd Geneesmiddelen Repertorium/Répertoire Commenté des Médicaments' (www.bcfi.be, accessed May 2012). For each medication group, the reference price for the generic pharmaceutical product is taken (if it existed) (i.e. in accordance with the KCE guidelines[114]), with the exception of antibiotics (see below). If more than one generic product is available for a specific medication group, the lowest and highest price is recorded. If no generic product is available for a specific medication group, the product appropriate for the general population (e.g. not restricted to children) is taken with the lowest and highest price being recorded, irrespective of specific characteristics of each product (e.g. tablets or spray, number of tablets per package, ...). To determine for each medication group specified in the questionnaire from our survey, the appropriate medication group as defined in the 'Gecommentarieerd Geneesmiddelen Repertorium/Répertoire Commenté des Médicaments', we used GRACE data[282] and expert opinion. As part of the GRACE project (www.grace-lrti.org), an observational study assessed medication use of patients with acute cough and lower respiratory tract infections in primary care in 13 countries, including Belgium.[282] The drugs data for Belgium were classified into the different medication groups used in our survey (i.e. cough medicine, antivirals and so on, classification done by dr. Samuel Coenen). As such, the data give an indication on which drugs were used in Belgium within each medication group. However, these data could not be used directly to estimate the unit cost per medication group, as not all medication groups specified in our survey, are presented in the GRACE data, and as the sample size for some of the medication groups are rather small (n=20). As from the GRACE data it was clear that the same type of drugs are used for 'fever' and 'pain', we applied the same unit cost to these two mediation groups.

For each medication group in the survey, the relevant medication group from 'het Gecommentarieerd Geneesmiddelen Repertorium/Répertoire Commenté des Médicaments' is detailed below. The choice of lowest and highest unit price for each of the medication groups are also detailed below.

As part of the European Surveillance of Antibiotic Consumption (ESAC) project the weighted average price for prescribed antibiotics in Belgium in 2008 was obtained (i.e. €15.96). This price is inflated to the year 2012 (based on the consumption price index for medication, http://statbel.fgov.be/nl/statistieken/cijfers/economie/consumptieprijzen/, accessed 6 June 2012) and is used as such as the unit cost for antibiotics.

Respondents could also specify 'I don't know' or 'Other medication' when they were asked about which medication was taken. These records were handled as follows:

- "Other medication": If specified which other medication and if this belonged to one of the 8 medication groups as defined in the questionnaire, the cost as assessed for that medication group was applied (only when the respondent did not also specify they took medication from that medication group). In all other cases, the medication cost was set at zero, but analyses were made with and without including these records.
- "I don't know": The medication cost was specified as zero, but the analyses were made with and without including these records.

Table 21 – Unit cost per medication group (NHS + co-payment, €2012)

Medication group (as specified in questionnaire)	Medication group (as specified in Folia Therapeutica 'Gecommentarieerd Geneesmiddelen Repertorium/Répertoire Commenté des Médicaments')	Lowest price§	Highest price§
Against fever#	8.2.1 Paracetamol + 8.2.5 Combined preparations (excluding drugs for infusion)	5.89	13.15
Against pain#			
Anti-inflammatory#	9.1.1.2.3 Ibuprofen	6.01	13.67
Antibiotics		15.48*	
Anti-virals (for influenza treatment such as Tamiflu and Relenza)	11.4.2 Middelen tegen respiratoire virussen	28.21	29.49
Against cough (cough sirup…)	4.2 Antitussiva, mucolytica en expectorantia	4.80	11.77
Against sore throat (sucking tablet, throat spray…)	17.4 Orofaryngeale aandoeningen	3.70	9.79
Nosespray	17.3.2.2 Vasoconstrictoren + 17.3.2.4 Varia	3.87	11.45

§ Irrespective of way to administer, size of single pill, number of pills or volume.
** Weighted average of prescribed antibiotics in Belgium in 2008 (€15.96, GRACE data), inflated to year 2012 based on consumption price index for medication.*
 # Generic products available.

To calculate the average cost for medication per person with ILI (Table 22), the following assumptions are made:

- We only include medication that was purchased and taken for the ILI episode.
- Per medication group, only 1 unit of the product is assumed to have been taken, except for pain and fever (as these 2 groups were merged), and other medication (but only 4 records).

Additionally we specified if costs were right-censored. That is, we know *for certain* the costs should be higher than what was specified, but we do not know how much higher (i.e. the product was taken and bought, but we could not determine the medication group, and hence not the cost) (n=83):

- Type of medication is not known.
- 'Other medication' specified to be taken and bought, but no name given for this 'other medication'.
- 'Other medication' specified to be taken and bought and a name was specified, but not possible based on that name to assign it to a particular medication group.

Additionally we specified if costs were *possibly* right-censored. That is, for these costs it is not possible to determine with certainty whether they should be higher than what was specified, and for none of the other medications for the particular ILI episode 'censored' was specified (n=422):

- Medication was taken but unclear if bought.
- Medication was bought, but unclear if taken.
- Persons were still sick at the moment the questionnaire was completed (n=355).

Excluding the records for which the total medication cost is (possibly) right-censored, results in slightly lower average costs. However, the effect is very small when compared to the difference in average cost when using the lowest as compared to the highest unit price for each medication (see Figure 12).

Figure 12 – Median cost for medication bought per person with ILI, for different assumptions: lowest or highest unit cost for a drug, including all respondents or only the ones which are not right-censored

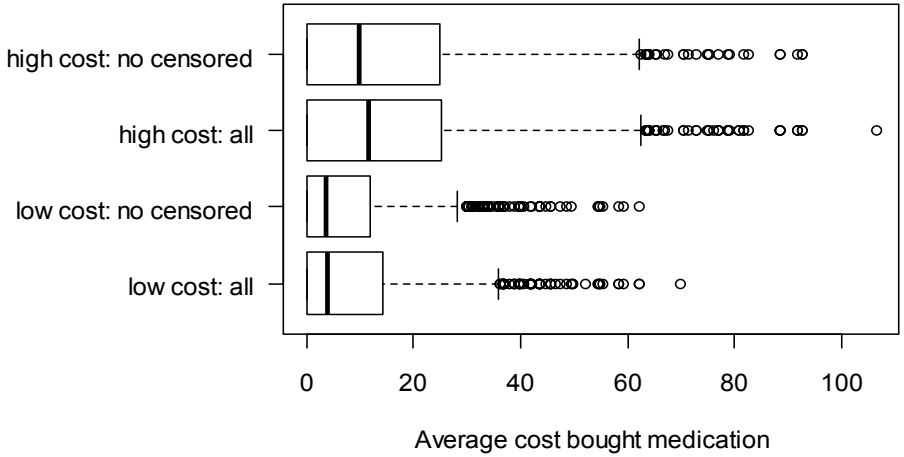
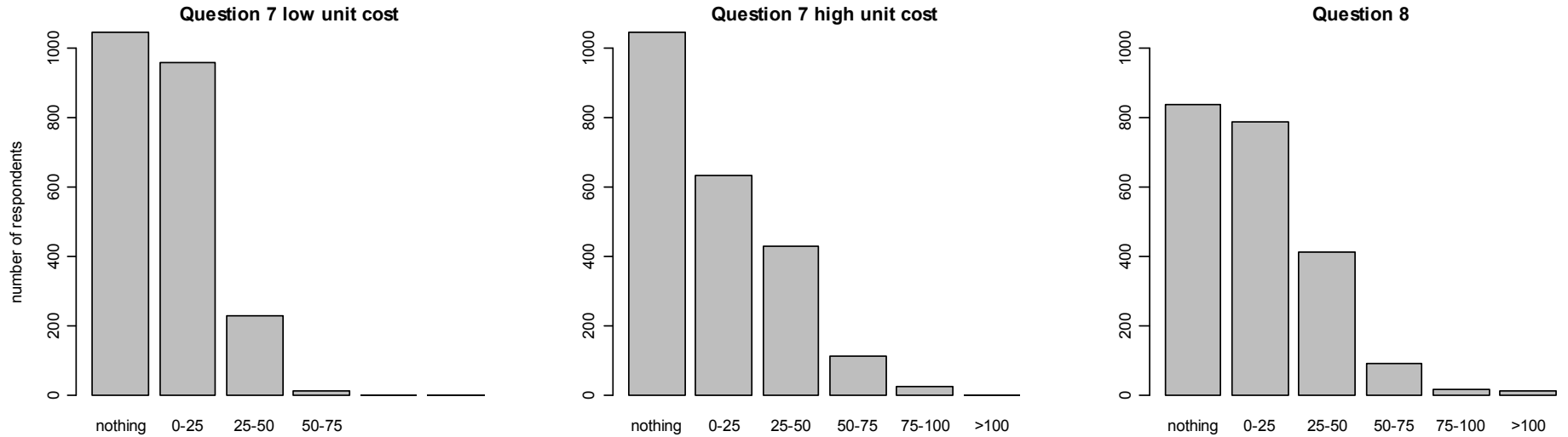


Table 22 – Average cost (€2012) for medication bought per person experiencing an ILI episode, assuming lowest or highest unit cost for a drug (excluding respondents for which costs are right-censored)

	Min	1st quartile	Median	Mean	3rd quartile	Max
Lowest cost	0	0	3.70	7.81	11.30	62.07
Highest cost	0	0	9.79	13.75	24.92	92.68

The average cost for medication per person experiencing an ILI episode as assessed through question 7 in the survey (on the amount paid for medication in the pharmacy), lies in between the lowest and highest average cost as assessed based on question 8 (about type of medication taken and bought) of the flu survey (Figure 13). For further analyses, the average lowest and highest costs based on the question 7 are used.

Figure 13 – Average cost for medication bought based on question 7 (about type of medication taken and bought) and question 8 (about amount paid for medication at pharmacy), N=2250 for question 7, N=2163 for question 8 (i.e. excluding respondents that answered 'don't know'), lowest or highest units costs are assumed for the different medication groups specified in question 7



Note: Based on Question 7: more respondents without costs for medication, because they (n=163) specified for question 7 that they took medication but did not buy it, but for question 8 that the amount they paid for medication was larger than €0 or not known.

4.2.1.4 Direct medical ambulatory cost

In this analysis, the direct medical treatment costs consist of consultation costs and the costs of medication purchased specifically for the ILI episode. In this analysis both the direct medical costs borne by the NHS and co-payments borne by the patients and their family are taken into account. Uncertainty is accounted for by calculating a 'low' and 'high' cost per person-episode, i.e. if uncertainty exists about the unit price for a consultation or a medical drug, the lowest and highest probable cost was specified (see above). The costs are calculated separately for patients with no medical care, ambulatory patients and hospitalised patients (costs outside the hospital). The direct (out of hospital) medical costs for a person experiencing an ILI episode are summarized in Table 23 (patients not seeking medical care) and Table 24 (patients seeking ambulatory care). Excluding patients for whom the costs are right-censored results in slightly lower average costs, but the effect is very small (not shown). We include these records for further analysis. As including the 18 patients who went to hospital but did not stay overnight has only a very small impact on these costs (not shown), we chose to exclude them from further analysis.

Table 23 – Average cost for a person with ILI not seeking medical care (NHS + co-payments, €2012), assuming lowest or highest unit cost for drugs

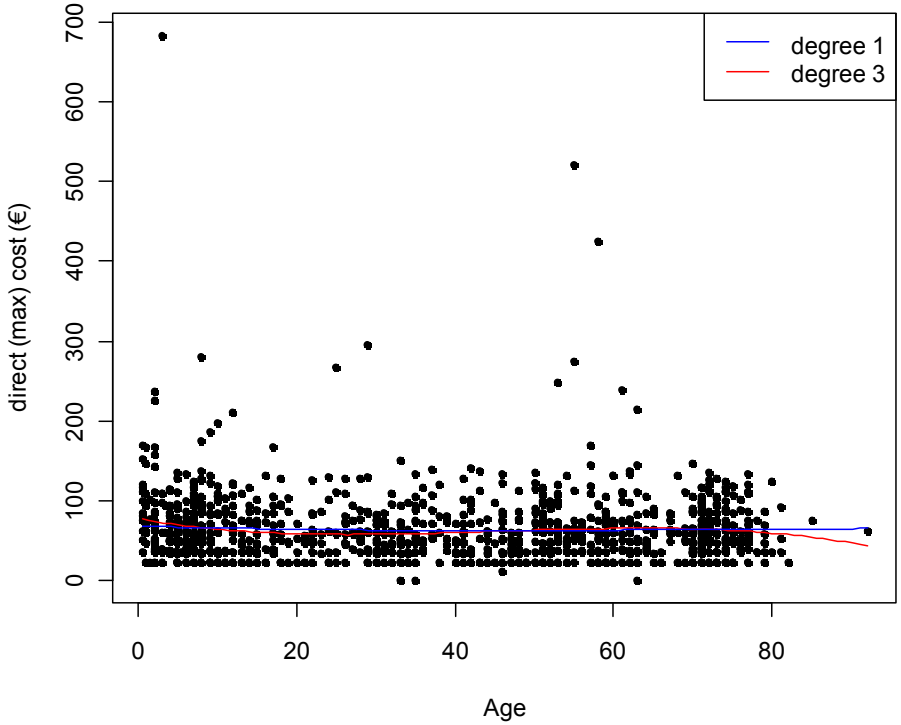
	Min	1st quartile	Median	Mean	3rd quartile	Max
Lowest cost	0	0	0	3.39	4.80	49.87
Highest cost	0	0	0	7.17	11.77	80.91

Table 24 – Average cost for an ambulatory patient with ILI (NHS + co-payments, €2012), assuming lowest or highest unit cost for drugs

	Min	1st quartile	Median	Mean	3rd quartile	Max
Lowest cost	0	25.82	41.30	51.04	63.62	596.90
Highest cost	0	36.47	52.81	63.81	80.77	683.70

Perhaps, somewhat surprising, the average costs for an ambulatory ILI patient does not differ by age (Figure 14). It also does not differ substantially between patients who were diagnosed by their physician with ILI and patients who were diagnosed by their physician with influenza (Table 24 and Table 25).

Figure 14 – Maximum direct cost by age (in years) for ambulatory patients with ILI



The blue and red lines represent fitted local regression with degree of local polynomial being 1 and 3, respectively ('locfit' in R).

Table 25 – Average cost for an ambulatory patient with a clinical diagnosis of influenza (NHS + co-payments, €2012), assuming lowest or highest unit cost for drugs

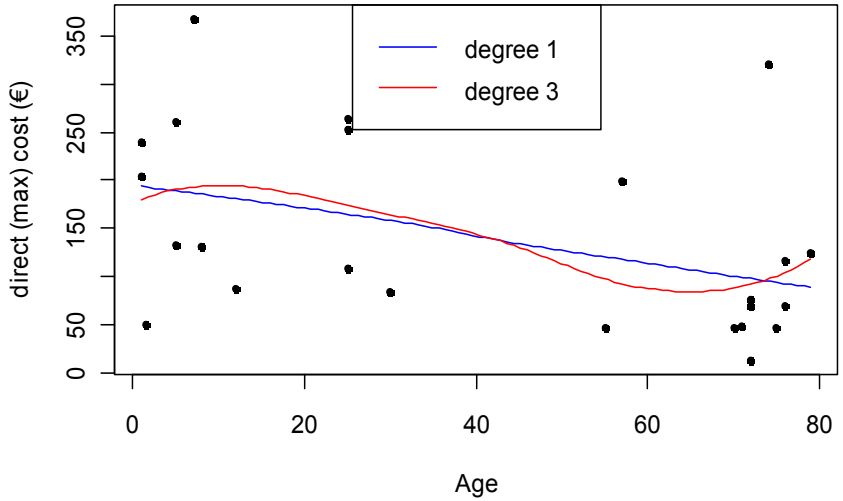
	Min	1st quartile	Median	Mean	3rd quartile	Max
Lowest cost	4.80	25.94	41.42	52.73	65.18	477.00
Highest cost	11.77	36.47	58.21	65.77	81.62	520.70

The average (lowest and highest) ambulatory costs (Table 26) for a hospitalised patient with ILI seems to decrease with increasing age (Figure 15). This is because for younger patients who are hospitalised for ILI, on average more consultations with a specialist (mostly pediatricians and/or pneumologists) and/or visits at home are requested, whereas older people seem to visit more often a general practitioner before and/or after their stay in the hospital for ILI (not shown). This contrasts with the independency of age of the costs for patients who seek medical care, but are not hospitalised.

Table 26 – Average cost for a hospitalised person with ILI (NHS + co-payments, €2012), assuming lowest or highest unit cost for drugs

	Min	1st quartile	Median	Mean	3rd quartile	Max
Lowest cost	5.89	56.29	97.81	119.70	188.90	313.20
Highest cost	13.15	65.09	112.30	139.90	212.80	367.60

Figure 15 – Direct maximum ambulatory cost by age (in years) for hospitalised patients with ILI



Blue and red lines represent fitted local regression with degree of local polynomial being 1 respectively 3 ('locfit' in R).

4.2.1.5 *Direct treatment costs for ILI patients accounting for uncertainty*

The average cost for an ambulatory patient with ILI is presented in Table 24. To account for sample size uncertainty around the average cost, we use normal distributions as input for the economic model, with as mean the sample mean and as standard deviation the sample standard error (i.e. in accordance with Briggs et al[283], Table 27).

Table 27 – Average cost for a person with ILI seeking ambulatory care: mean and standard deviation of normal distributions representing sample size uncertainty

Based on:	Uncertainty distribution
Lowest cost units	Normal (mean=€51.04, standard error=€1.18)
Highest cost units	Normal (mean=€63.80, standard error=€1.34)

The average cost outside the hospital for hospitalised ILI patients seems to decrease with increasing age (see above). Therefore a generalized linear model was fitted with cost as outcome and age as covariate, assuming the error terms are gamma distributed (gamma is the best-fitting distribution for costs) and using an inverse link function (gives better fit than log or identity link, based on likelihood). As in a gamma regression the dispersion parameter is estimated, the significance of the impact of dropping of parameters from a model is given by an approximate F test (Table 28).[284]

Table 28 – Test for dropping the age covariate from the out-of-hospital costs model

Cost data	Model	Res. Df	Res. Dev	Estimated dispersion	Df	Dev	F	Pr(>F)
Low	Intercept	23	15.473					
	Intercept + age	22	12.974	0.5555236	1	2.499	4.50	0.0449
High	Intercept	23	12.999					
	Intercept + age	22	10.854	0.5143032	1	2.145	4.17	0.0528

Res: Residual; Df: Degree of freedom; Dev: Deviation.

Table 28 shows that the out-of-hospitals cost model including age as covariate is borderline (not) significantly better than the model without age as covariate (Table 26). Hence, as input for the economic model, we use age-independent estimates of the average costs outside hospital (Table 29).

Table 29 – Average ambulatory cost of a person with ILI who was hospitalized: mean and standard deviation of normal distributions representing sample size uncertainty

Based on:	Uncertainty distribution
Lowest cost units	Normal (μ=€119.65, σ=€17.69)
Highest cost units	Normal (μ=€139.94, σ=€20.19)

4.2.1.6 Direct treatment costs for influenza patients accounting for uncertainty

Total costs for ambulatory patients with a clinically diagnosed influenza do not differ from total cost estimated for ambulatory patients with ILI (see above). Hence, the same means and uncertainty distributions apply as for ambulatory patients with ILI. As mentioned before, the average costs for ambulatory patients do not depend on age. In view of this, no age-dependent ambulatory cost parameter was used as input for the models.

Total costs outside the hospital for hospitalised patients with a clinical diagnosis of influenza cannot be estimated as a function of age, because the sample size of this subgroup is too small (n=4). Lowest/highest costs outside the hospital for these patients are €41.04/€48.70, €68.07/€76.13, €70.45/€83.71 and €108.96/€124.47 (note that all of these costs are lower than the mean costs outside the hospital for hospitalised patients with ILI, Table 26). Normal distributions with sample mean as mean and sample standard error as standard deviation are used to reflect uncertainty around the mean cost outside the hospital for patients with influenza (Table 30).

Table 30 – Average ambulatory cost of a person with diagnosis flu who was hospitalised: mean and standard deviation of normal distributions representing sample size uncertainty (n=4)

Based on:	Uncertainty distribution
Lowest cost units	Normal (μ=€72.13, σ=€13.97)
Highest cost units	Normal (μ=€83.25, σ=€15.66)

4.2.2 *In-hospital costs for hospitalised influenza patients*

The registration of MCD (Minimal Clinical Data, or 'Minimale Klinische Gegevens/Résumé Clinique Minimum') is mandatory for every hospital in Belgium since 1991. This means that for each hospitalised patient, information such as birth year, postcode, gender, and other information such as length of stay (LOS) in the hospital, diagnosis, techniques used and treatments have to be recorded and sent to the FOD (Federal Government Administration). Data are stripped from patient-identifying information. These data are coupled with the HBD (Hospital Billing Data), which records the (public) health insurance costs of each hospital stay. This means that the relationship between treated pathology and the costs to the health care system can be studied. The advantage of the coupled MCD-HBD data is that it is obligatory for all hospitals. However, one should keep in mind that we do not know how accurate each hospital reports the obligatory MCD data, nor how reliably the data are gathered. Hence, interpretation of the data should be done with care.

From this database, we retained influenza-associated hospitalizations (using ICD9 codes starting with "487" or "488" or "480") for the period 2004-2007. The year 2004 was the earliest year for which we have the unit costs per hospital day (i.e. hotel costs). Although the year 2008 was present in the database, its format was different and it was not merged with data of preceding years, so we decided to use 2007 as the last year for the analysis of hospitalisation costs.

A distinction was made between primary influenza (at least one influenza code in the primary diagnostic field for a hospitalization) and secondary influenza (at least one influenza code in the secondary diagnostic field and no such code present in the primary diagnostic field). In addition to these hospitalizations the combination of influenza and several comorbidities were extracted on the basis of the ICD 9 codes listed in Supplement 1.

In this report, we are interested in estimating the impact of vaccinating broad population age groups, which should have - at sufficiently high coverage - a homogenous impact across subgroups with comorbidities. Hence the hospitalization costs arising from influenza in any person are important. However, we are equally interested in estimating the cost-effectiveness of vaccinating (as currently recommended) relatively focused risk groups, suffering from the comorbidities we listed in Supplement 1. For these specific subgroups other costs may apply, an issue we explore in this section.

For each hospitalization, the cost of the hospital stay (HOSP) was calculated by multiplying the length of stay, with the weighted average daily hospitalization cost depending on the hospitalization type and year of hospitalization (see KCE guidelines[114] p. 102). This information was only available from 2004 onwards (see above). We removed the data from burn centers, palliative care, rehabilitation and psychiatric wards to retain only those of acute, surgical and geriatric wards. Hospitalizations with an extremely long length of stay (> 1000 days) were identified as outliers and removed. Additional cost categories listed in Table 31 were included.

Table 31 – Cost categories extracted from the MCD-HBD database

Cost category	Description	Methodology costs extraction
HOSP	Hospitalization cost, cost of staying at the hospital	Length of stay multiplied by weighted average daily hospitalization costs.
BPMR	Blood plasma, mother's milk, radio-isotopes	Sum of patient share and RIZIV share.
DELIVER	Medical deliveries	To the RIZIV share €6.20 per admission was added to account for the patients' share for medical imaging acts. Note that no patient share was included for other costs than medical imaging, which is a limitation of the database.
PHARMA	Pharmaceutical products	Patient and RIZIV share were added. For non-forfaitised drugs other than D-category drugs the fictive patient share was removed. The real lump-sum of €0.62 per hospital day was included.

Cost category	Description	Methodology costs extraction
IMPL	Implantations	RIZIV shares were summed (this is an underestimation, but a drawback of the database used).
CM&NM	Clinical microbiology and nuclear medicine	To the sum of all RIZIV costs, €7.44 per admission was added to account for the patients' share.

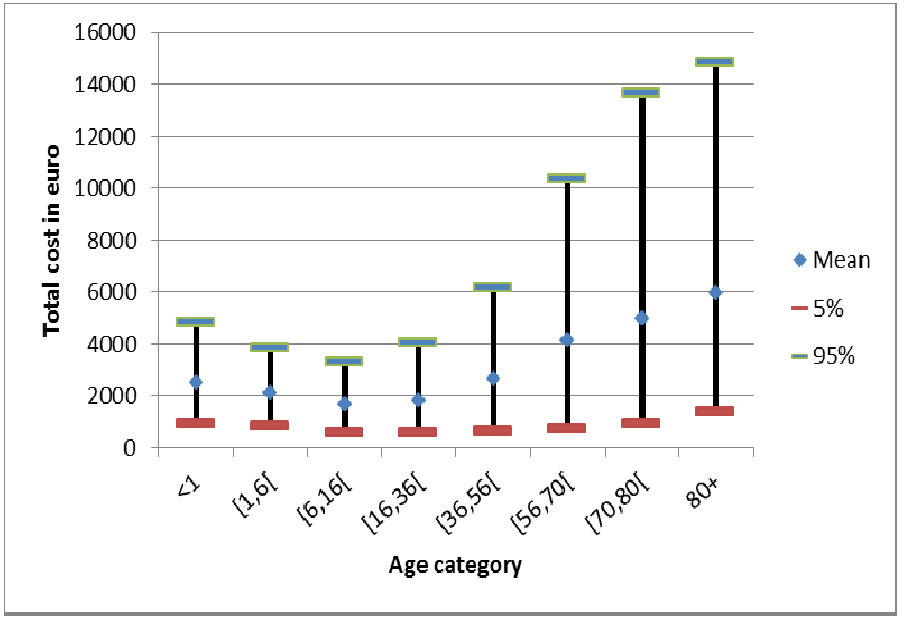
All cost were adjusted for inflation to the January 2012 level (based on the consumption price index for hospitalization costs, http://statbel.fgov.be/nl/statistieken/cijfers/economie/consumptieprijzen/, accessed 6 June 2012). The additions to account for patient share (€0.62 per hospital day for PHARMA, €7.44 per admission for CM&NM, €6.22 per admission for DELIVER) were added after correcting for inflation, since they represent current estimates of patients' share.

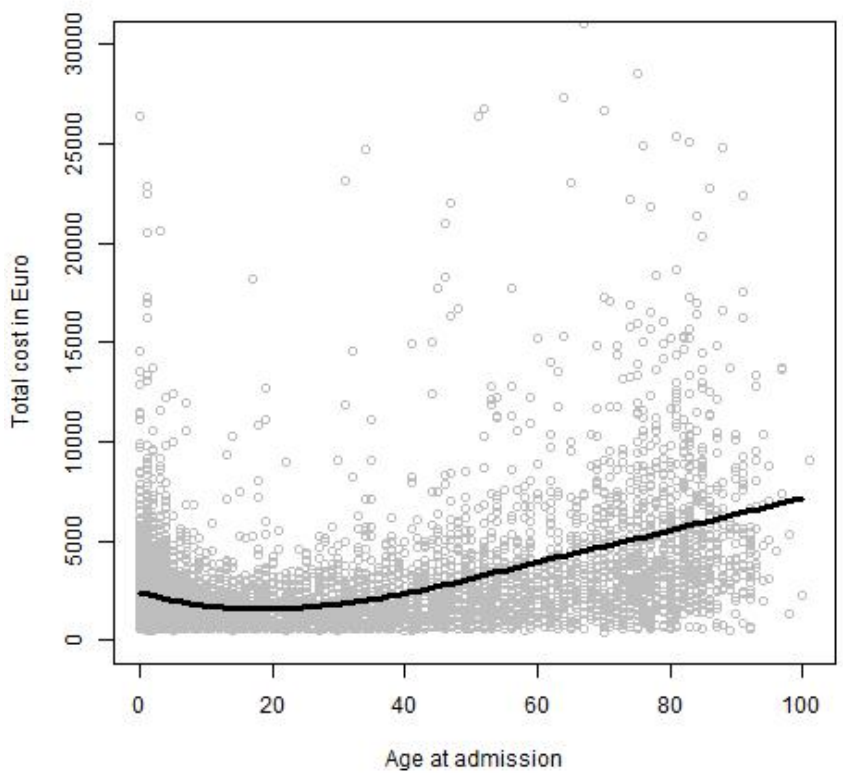
Summary statistics per diagnostic group of the total direct hospitalisation costs per age category and the average distribution of these costs per age group of a patient were calculated and displayed in the plots below and in Supplement 1. The average cost was also smoothed by a spline fit according to age. In Supplement 1, tables are given that summarise this information for each of the diagnostic groups by age group. Note that these data represent census data. That is, this comprises all the information for all admittances to all Belgian hospitals during four years (2004-2007), and statistical uncertainty related to sample size is thus absent from these data.

4.2.2.1 Patients with a primary diagnosis of influenza

In our dataset, we collected information on 9705 admissions with a primary diagnosis of influenza.

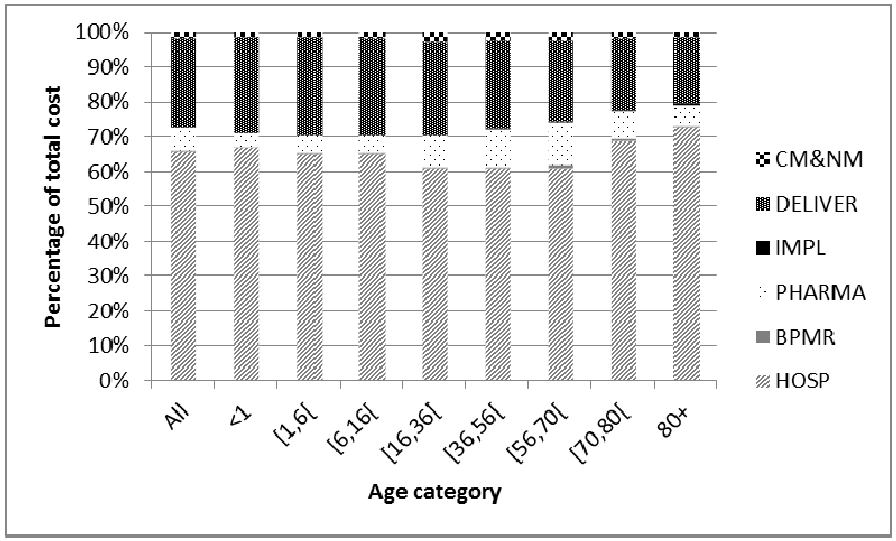
Figure 16 – Age-specific hospitalization costs for patients with a primary diagnosis of influenza, upper panel: age groups (mean and 5th and 95th percentile); lower panel: spline smoothed estimate





The mean and median costs for these patients are €2599 and €1922 (for details by age group, see Supplement 1), respectively. As can be observed in figure above, there is a trend for higher costs with age (observed at the mean as well as at the 5th and the 95th percentile), but also a strong association between variation in costs incurred and age at admission. Figure 17 below also shows that the costs consist mostly (about two thirds) of the costs of the hospital stay itself (i.e. "hotel costs"), and for about a quarter to a fifth for medical deliveries. The third most important cost category is that of pharmaceutical products.

Figure 17 – Age-specific hospitalization cost distribution per cost category for patients with a primary diagnosis of influenza



Note that the costs of hospital stay (associated with the length of stay) increase with age in adults, whereas those of medical deliveries decrease.

4.2.2.2 Patients with a secondary diagnosis of influenza

In patients with only a secondary diagnosis of influenza, the trend in increasing costs with age saturates at a relatively young age (see Supplement 1). That is, the costs incurred by adults over 55 years of age are independent of age, if influenza is indicated to be a secondary diagnosis only. These patients incur substantially higher mean (€5015) and median (€2766) costs than those with a primary diagnosis of influenza. Figures are provided in Supplement 1.

4.2.2.3 *Patients with an influenza diagnosis associated with other conditions*

We also conducted a cost analysis on patients coded with influenza, either as primary or secondary diagnosis, and associated with other conditions:

- Pneumonia, including a sub-analysis for patients with pneumococcal pneumonia;
- Co-morbidities: any comorbidity, and separate analyses for the major comorbidities: asthma, cardiovascular disease, chronic obstructive pulmonary disease (COPD), diabetes, hypertension, stroke, HIV;
- Secondary respiratory tract infections;
- Pregnant women: women with a primary or secondary diagnosis of influenza, woment with a primary diagnosis of influenza combined with pregnancy complications, woment with a seconday diagnosis of influenza combined with pregnancy complications (the list of pregnancy complications can be found in Supplement 1).

Supplement 1 provides some details on the cost distributions for these patients, while the main characteristics are summarized below.

Among patients admitted with diagnoses of both influenza and pneumonia, there is a trend towards substantially higher costs in the age group 56-70 years of age (with a peak around age 65 years). The mean and median costs for these patients are €4153 and €2594, respectively.

It is of interest to investigate the impact of co-infection with *Streptococcus pneumoniae*. In this group we show costs incurred for patients admitted with a combined diagnosis (primary or secondary) of influenza and pneumococcal pneumonia. The number of observations in this group (n=79), versus the previous one (n=5086) clearly indicates that interpretation of these results is problematic for some age groups. The mean and median costs in this group are substantially higher than in the previous group combining influenza with any pneumonia (€7025 and €3550, respectively), but the sheer size of the previous group absorbs the impact of these higher costing pneumococcal pneumonia cases.

4.2.2.4 *Patients with an influenza diagnosis associated with no comorbidity*

Additionally, an analysis was conducted for patients with influenza (primary or secondary diagnosis) for whom no comorbidity was recorded during their admission.

By excluding all the above comorbidities (in addition to the hospital departments we excluded at the onset), we are left with a dataset of 6449 admissions, at a mean and median cost of €2150 and €1581, respectively. That is, the costs are substantially lower than for the preceding groups, but to a much lesser extent lower than all admissions with a primary diagnosis of influenza (€2599 and €1922, respectively).

4.2.2.5 *In-hospital costs as inputs for the economic evaluations*

The nature of the hospital dataset does not allow to infer with certainty that the patient would not have been admitted to hospital if they did not acquire an influenza virus infection.

However, these data provide the best estimates for hospital costs we can obtain for Belgium, and is exhaustive for the entire hospital patient population.

In the analyses we undertake for the current report, we will use these data as follows:

- For vaccination of broad age groups, we implicitly assume that the prevention of unvaccinated cases through herd immunity is be non-discriminatory (as one can generally expect for a close contact infection borne by air and respiratory droplets). Therefore we apply the in-hospital costs for these cases, based on the selection of admissions for which influenza is indicated as a primary or secondary diagnosis (see Table 44).
- For vaccination of specific target groups (persons with comorbidities, pregnant women and health care workers) which do not have impacts beyond these target groups, the computation of in-hospital costs to be used in the static models is described in Section 5.5.2.3 below.

5 METHODS

Overall, the cost-effectiveness of the different target groups is explored through two main types of models:

- Dynamic transmission model: for vaccination options in age groups in the general population (without further specific subgroup targeting). That is, for various age groups in children (<18 years), adults (18-64 years) and the elderly (≥65 years),
- Static (fixed risk) model: for vaccination options in the following specific subgroups: pregnant women, persons with comorbidities and health care workers.

The rationale is that the dynamic model can account for changes in the transmission dynamics of influenza that would occur due to herd immunity effects when large groups in the population are vaccinated. The costs and effects occurring for the specific subgroups, such as pregnant women can be addressed by static models, which are used routinely in economic evaluations of non-infectious diseases. The latter approach will lead to small underestimates of the benefits of vaccination (e.g. within-household transmissions from adults to children or between adults is ignored), though some aspects of indirect protection are explored within the context of these static models (e.g. by vaccinating health care workers it is likely that the patients they contact are less likely to acquire influenza in some specific settings, such as homes for the elderly).

5.1 Options for vaccination

We use two types of models, static and dynamic models, depending on the options for vaccination considered. These models are described in more detail below.

In terms of vaccine dosages, we have opted to follow the most recent recommendations of the US Advisory Committee on Immunization Practices (ACIP),[285] which are likely to be taken over in Belgium, if we were to expand our influenza vaccination programme. More specifically, we assume two doses of TIV or LAIV are required for the first vaccination under age 8 years, whereas one dose is required for those aged over 8 years. As discussed in the review sections LAIV options are only explored between 2 and 18 years, and TIV options for all ages from 6 months to 105 years. Subsequent vaccinations are given under a single dose schedule. A simple algorithm was made based on the expected proportion of vaccinated persons in one year who would be revaccinated in the next year, and thus need only one dose, instead of two. In order to formulate this algorithm, an assumption was made that 90% of those aged less than 8 years who receive influenza vaccination in a particular year will also have received vaccination in the preceding year, while adjusting the vaccination coverage at each age in line with the option under consideration (throughout the considered childhood options vaccination coverage varies from 10% to 90% in 10% steps, see next section and section results).

5.1.1 Using the dynamic transmission model

After deliberation with the expert committee for this report and members of the Vaccination Section of the Superior Health Council, we consider a large number of options for vaccination across all age groups, and include options comparing TIV versus LAIV in age groups between 2 and 18 years.

The options for children and adult vaccination are separately compared to the current situation (Table 42 and Table 51), as well as combined. For the definition of options for vaccination we defined the following age groups:

- Children: 0.5-2, 2-5, 5-12 and 12-18 years;
- Adults: 18-50, 50-65, 65-75, 75-85, 85-95 and 95+ years.

Based on these distinctions and using the different vaccines, we model a total of 651 different vaccination options, an important part of which is also subjected to additional changes in vaccine coverage rates (such that we model effectively 5667 vaccination scenarios with the dynamic model).

More specifically, in discussing our results, the following groups of options are distinguished in addition to the current situation:

- Modified children options + current adult vaccination: 19 options at 9 different uptake levels for children (i.e. 171 scenarios).
- Current children vaccination + modified adult options focusing on targets as defined in Table 35: 23 options.

- Modified children options + modified adult options focusing on targets as defined in Table 35: 437 options at 9 different uptake levels for children (i.e. 3933 scenarios).
- Modified children options + modified adult options focusing on reducing vaccination in adult age groups: 171 options at 9 different uptake levels for children (i.e. 1539 scenarios).

These options are specified in more detail in the respective results section to assist the reader in the interpretation of the results.

5.1.2 Using the static models

The cost-effectiveness of risk groups is estimated separately using static models. Specifically we analyse the vaccination of pregnant women, health care workers and people with comorbidities using static models.

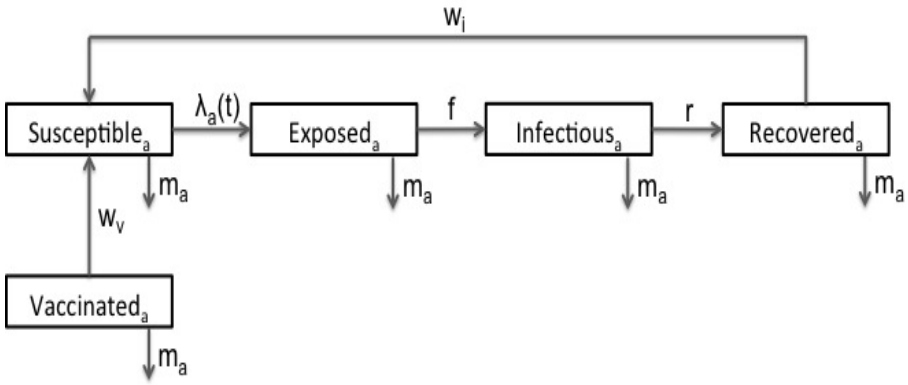
5.2 Description of the dynamic transmission model

5.2.1 Model structure

5.2.1.1 SEIRS model with vaccination

The model developed by Vynnycky et al[125] is considered the most suitable to build on, since it is the only model considering seasonally forced transmission rates, using data from social contact surveys to inform transmission rates, and including a vaccination component (see model review above). In this section we describe the similarities between our and Vynnycky's model, as well as the ways in which we depart from their approach. The model is structured according to compartments of Susceptible, Exposed (assumed not yet infectious), Infectious, Recovered (assumed immune after infection) and Vaccinated (assumed immune after vaccination) individuals, and is henceforth referred to as a SEIRS model with vaccination. Figure 18 displays the transitions between the compartments. Both vaccinated and recovered individuals are assumed fully protected until their immunity wanes. Finkenstädt et al[210] show that influenza incidence data from France support the presence of immunity loss, favoring the use of an SEIRS model rather than a 'lifelong immunity' SEIR model. After receiving the vaccine and before their immunity wanes, effectively vaccinated individuals are assumed to have complete immunity against infection and are unable to infect others (i.e. an all-or-none vaccine model). Vynnycky et al[125] consider vaccination for 3 strains: A (H1N1), A (H3N2) and B. Their model parameters are chosen such that annual influenza is due to influenza A, either by H1N1 or H3N2, and every 2 years by influenza B.

Figure 18 – Transition diagram for the SEIRS model with vaccination, based on Vynnycky et al[125]



The population is stratified into age classes of length 1 year (0-99 years). Belgian demographic data from 2009 (source: Eurostat, 2011) are used to initiate the model population and to estimate an age-specific daily mortality rate. The SEIRS model with vaccination is considered for each of the age classes, and the model is run over time steps of 1 day to ensure high precision while maintaining computational feasibility. Additionally, at each time step, the sign of the age-stratified number of individuals in each compartment is checked in order to avoid negative values (which never occurred in our extensive range of simulations). The definition of the model variables and parameters are presented in Table 33 and Table 34. The final two columns of these tables display the values of the model parameters adopted by Vynnycky et al,[125] together with their source references.

The equations describing the dynamic model for each age class are as follows:

For a = 0, 1, …, 99 years:

$$\frac{dS_a}{dt} = -\lambda_a(t)S_a(t) - m_a S_a(t) + w_v V_a(t) + w_i R_a(t)$$
$$\frac{dE_a}{dt} = \lambda_a(t)S_a(t) - m_a E_a(t) - f E_a(t)$$
$$\frac{dI_a}{dt} = f E_a(t) - m_a I_a(t) - r I_a(t)$$
$$\frac{dR_a}{dt} = r I_a(t) - m_a R_a(t) - w_i R_a(t)$$
$$\frac{dV_a}{dt} = -m_a V_a(t) - w_v V_a(t)$$

5.2.1.2 Time points of transition

Each year, there are three time points of transition at which individuals are assumed to move to another stage in the compartmental model. First, to capture the ageing process, all individuals move to the next age group on August 31st of each year, and the individuals in the final age group are removed from the population (i.e. the so-called Realistic Age-Structured or RAS model). This date reflects the start of the school year and allows approaching the clusters formed by children and adolescents in grades. We assume that the number of births equals the total number of deaths from the year before, such that the population size remains constant. Note that Vynnycky et al[125] assume a constant number of births and use a 'container' age class of +95 years with an adjusted mortality rate to ensure a constant population size.

Second, on October 10th of each year, individuals may be administered influenza vaccine, independent of their disease or vaccination history. In Belgium, influenza vaccines are generally administered in the 2nd or 3rd week of October.

Third, a number of newly infectious individuals are introduced as a seed into the population to ensure that the influenza epidemic takes off. The seeding date tseed is included as an unknown parameter and estimated from ILI incidence data. Following Vynnycky et al,[125] 200 individuals are seeded in each age band of 5-50 years (see Table 34). Alternative values for the size of the seed and the target age group for seeding were explored as well, but this did not influence our results.

Note, by contrast, that Vynnycky et al[125] assume all these three time points of transition (ageing, vaccination and seeding) to co-occur on August 31st of each year.

5.2.1.3 Seasonality

The seasonality in influenza incidence has been attributed to many factors, e.g. increased viral production in winter and changes in temperature and humidity, or changes in contact patterns, e.g. because of school holiday closures.[125] Results of a stochastic model by Finkenstädt et al[210] support the conjecture that transmission rates are subject to seasonal variation, indicating the importance of this component. Vynnycky et al[125] consider a seasonal force of infection by incorporating a sinusoidal function (the seasonality function z(t)) into the mass action principle), reflecting the deviation from the average basic reproduction number (see Table 33). In their approach, the seasonally forced transmission rates are chosen such that an average basic reproduction number (R0) value of 1.8 is obtained each year on September 21 and March 21, with a peak R0 value of 2.6 on December 21. In contrast, we estimate the average R0 value and the timing and height of the peak, from ILI incidence data. Furthermore, we explore season-specific amplitude, which might reflect between-season variability due to antigenic drift.

5.2.1.4 Contact rates

Susceptible individuals acquire influenza infection through effective contact with an infectious individual, and this process is highly age heterogeneous. Age-dependent transmission rates are assumed to be proportional to rates of making (conversational) contact involving skin-to-skin touching and taking longer than 15 minutes, as estimated from the Belgian POLYMOD data.[286-288] Previous modeling work revealed that this type of contact fits very well the observed seroprevalence profiles for endemic close contact infections such as varicella zoster virus and parvovirus B19.[288] Note that Vynnycky et al[125] use traditional WAIFW matrices based on data from an influenza pandemic, and the POLYMOD matrix based on all recorded contacts in the UK.[211] The estimated contact rates are kept fixed in the model. Accounting for the uncertainty on the contact rates would require bootstrapping the contact data. It is computationally infeasible to propagate

this uncertainty into the model projections for all vaccination options considered.

The proportionality factor q relates the transmission rates to the contact rates estimated from the POLYMOD data, and is determined by the value of the average R0. We make the common assumption of a constant proportionality factor q, the so-called `social contact hypothesis'.[289] A sensitivity analysis could be conducted towards this assumption. An age-dependent q might reflect heterogeneity between age groups regarding inherent susceptibility and infectiousness for influenza, or age-specific discrepancies between the contacts recorded in the diaries and the true events by which influenza transmission may occur.[288, 290]

Table 32 – Variable definitions for the SEIRS model with vaccination, based on Vynnycky et al[125]

Variable	Definition
Sa(t)	Number of susceptibles of age a at time t
Ea(t)	Number of infected (but not yet infectious) individuals of age a at time t
Ia(t)	Number of infectious individuals of age a at time t
Ra(t)	Number of individuals with naturally acquired immunity of age a at time t
Va(t)	Number of individuals with vaccine induced immunity of age a at time t
$\lambda_a(t)$	Force of infection for individuals of age a at time t: $\lambda_a(t) = z(t) \sum_{a'} \beta_{a,a'} I_{a'}(t) = z(t) \sum_{a'} q c_{a,a'} I_{a'}(t)$, where: The transmission rate is denoted by $\beta_{a,a'}$, the average per capita rate at which an individual of age a' makes effective contact with a person of age a, per day; q is the proportionality factor of the social contact hypothesis: transmission rates are assumed to be proportional to rates of making (conversational) contact $c_{a,a'}$
z(t)	Seasonality function: the factor by which the basic reproduction number at time t differs from the average basic reproduction number $\overline{R_0}$ at time t0, with amplitude δ, $z(t) = 1 + \delta \sin\left(\frac{2\pi(t - t_0)}{365}\right)$

Table 33 – Fixed parameters in the SEIRS model with vaccination

Parameter	Definition	Value	Source	Vynnycky et al[125]	
				Value	Source
Na	Initial size of the population of age a	Belgium in 2009	Eurostat (2011)	England and Wales in 2003	Office for National Statistics (2005)
ma	Mortality rate of individuals of age a	Belgium in 2009 (model-based estimate)	Eurostat (2011)	England and Wales in 2003	Office for National Statistics (2005)
va(t)	Effective vaccination coverage for individuals of age a (vaccination coverage x VE_{SP})	Coverage for the current and the new vaccination strategy in Belgium VE_{SP} estimates from literature review	Coverage: Hanquet et al (2011)[23] VE_{SP}: literature review (Table 36)	30% for ≥65 years from the year 2000; 60% for children from the year 2005	VE_{SP} elderly[215] VE_{SP} children[216]
tvacc	Time of vaccination each year	October 10	In Belgium, influenza vaccines are generally administered in the 2nd or 3rd week of October	August 31	NA
aseed	Target age group for seeding of infectious individuals into the population each year	5-50 years	Vynnycky et al[125]	5- 50 years	In previous influenza pandemics, very few of the earliest cases occurred outside this age range, and older individuals are unlikely to be the first cases during a typical influenza season
pseed	Number of susceptibles that are introduced as a seed into the population each year	200 individuals in each age band of a seed	Vynnycky et al[125]	1000 individuals (<6% of the susceptible population)	Selected to ensure that epidemics of a similar size occur every two years
f	Daily rate at which infected individuals become infectious, calculated as 1/(average latent period)	1/1 per day	Literature review (Table 38)	1/2 per day	[239-241]

Parameter	Definition	Value	Source	Vynnycky et al[125]	
				Value	Source
r	Daily rate at which infectious individuals recover and become immune, calculated as 1/(average infectious period)	1/3.8 per day	Literature review (Table 38)	1/2 per day	
wi	Yearly rate at which naturally infected individuals lose their immunity, calculated as 1/(average duration of protection)	1/6 per year	Vynnycky et al[125]	1/6 per year for influenza A; 1/12 per year for influenza B	Monto et al[13]
wv	Yearly rate at which vaccinated individuals lose their immunity, calculated as 1/(average duration of protection)	Assumed to be equal to wi	Vynnycky et al[125]	Assumed to be equal to wi or half of wi	NA
$c_{a,a'}$	Daily per capita rate at which an individual of age a makes contact with a person of age a'	Age-specific (too complex to show), see[286]	Estimated from POLYMOD contact data for Belgium on contacts involving skin-to-skin touching and taking longer than 15 minutes[287, 288]	Four WAIFW matrices and a POLYMOD contact matrix based on all recorded contacts for the UK	WAIFW matrices: Vynnycky and Edmunds[291] POLYMOD matrix[211]

Table 34 – Flexible parameters in the SEIRS model with vaccination

Parameter	Definition	Estimation range	Vynnycky et al, Vaccine (2008)	
			Value	Source
$\overline{R_0}$	Average basic reproduction number, i.e. the dominant eigenvalue of the next generation matrix with elements where D represents the average infectious period. Determines the value of the proportionality factor q.	[1.0–3.5]	1.3, 1.8 and 2.5	Value of 1.8: Vynnycky and Edmunds[291]
δ	Amplitude of the seasonality function z(t). Determines the peak value for the basic reproduction number.	[0–1]	0.43	Cooper et al (2006)[292]
t0	Reference time for the seasonality function z(t), at which the basic reproduction number equals . The seasonal peak of transmission is three months later.	July 1st until December 31st	September 21	Cooper et al (2006)[292]
tseed	Time of the year at which a number of infectious individuals are introduced as a seed into the population.	September 1st until March 31st	August 31	NA
α	Correction factor to calibrate model-based infection incidence rate to observed ILI incidence rate. Alpha may reflect several effects, among which the proportion symptomatic, GP consultation rate, ILI reporting rate, etc.	[0.01–2.00]	Not applicable	Not applicable

5.2.2 Fundamental differences between our and Vynnycky et al's approach

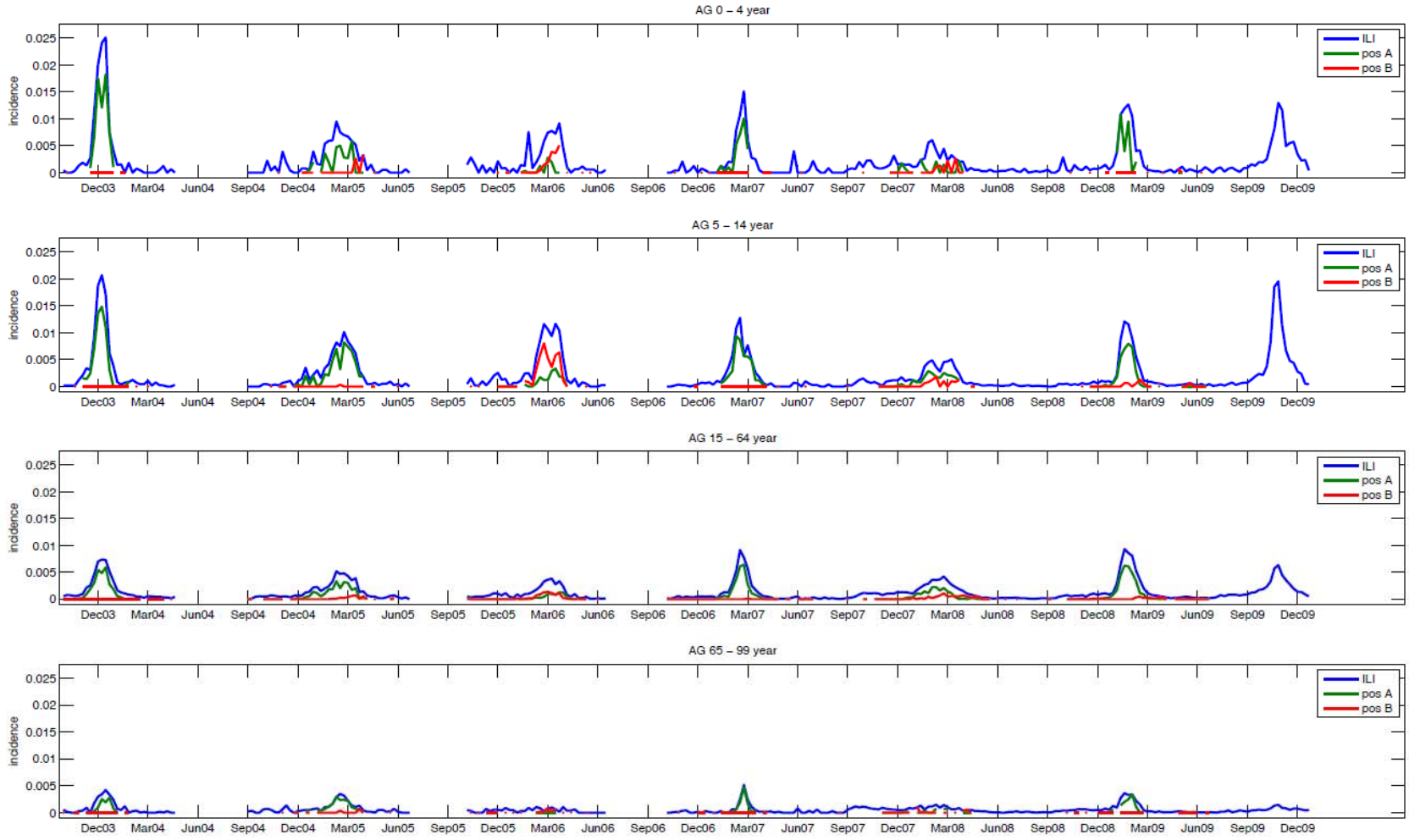
5.2.2.1 Imputation versus estimation

Vynnycky et al[125] fix pre-specified values for all model parameters, i.e. literature-based or chosen ad hoc, and do not fit model predictions to incidence data. In contrast, we estimate model parameters, which are less certain and about which there is no general consensus, from reported ILI cases. Other parameters that are well recorded, such as demographical information and vaccination parameters, are included in the model as fixed values. Preliminary analyses indicated that the dimension of the parameter space needed to be reduced. Using symbolic regression analysis, we chose to additionally fix the following parameters that had limited influence on the fit to the ILI incidence data: the timing of vaccination, the target age group and fraction of seeding, and the average latent and infectious period (Table 33).

5.2.2.2 Influenza A and B

Vynnycky et al[125] run the SEIRS model with vaccination for influenza A and influenza B independently, assuming no cross-protection. When using the data from Belgium (as we have to in this analysis applied to Belgium), it is not feasible to fit the model to influenza A and B positive cases separately, due to the sparseness of the lab-confirmed ILI incidence data (see Figure 19). There are very few positive cases for influenza B and numerous missing data due to the limited number of swabs taken in specific age groups, even during influenza epidemics. Therefore, we have no choice but to assume one generic influenza virus/strain, encompassing both influenza A and B, and fit our dynamic model both to ILI incidence data and lab-confirmed ILI incidence data (proportion positive based on a subset swabbed). It is important to conduct both analyses. Indeed, the ILI incidence data are more complete and accurate than the lab-confirmed ILI incidence data. Additionally, swabbing practices of ILI cases in the Belgian GP surveillance network, on which these data are based, are carried out 'ad hoc' (i.e. without using objective or consistent criteria). This would imply that the GPs were/are less likely to swab young children and elderly than healthy adults, simply because of considerations regarding the ease of administration. An advantage of using lab-confirmed data is that they would be less confounded by other pathogens circulating before the influenza epidemic. However, the flexibility we built in to accommodate season-specific parameters in our model is likely to capture at least partly such season-specific heterogeneities.

Figure 19 – Observed ILI incidence rates in Belgium, 2003-2009



Source: WIV–ISP.

5.2.3 *Dynamic model parameter imputation by fitting to past observations*

5.2.3.1 *Basic dynamic model assumptions and fixed parameters for fitting*

Multi-season versus single season model

In general, the few studies that fit an influenza transmission model to epidemiological data, consider one single influenza epidemic or model multiple seasons independently. In contrast, we fit our model to a series of multiple influenza seasons simultaneously (referred to as `multi-season model'). This facilitates making predictions for future influenza seasons and evaluating the cost-effectiveness of a new vaccination program. In the model building process, we do fit single season models as well to assess which parameters vary substantially by season. Some parameters might be included in the multi-season model as season-specific parameters if the fit to the data is significantly improved and if out-of-sample prediction is still warranted, for instance by running simulations.

All-or-none vaccine model

Each year on October 10, part of the population is assumed to receive influenza vaccination, independent of disease or vaccination history. Following Halloran et al,[293] we distinguish between three types of vaccine efficacy:

- Vaccine efficacy for susceptibility (VE_S): a measure of how protective vaccination is against infection;
- Vaccine efficacy for susceptibility to disease (VE_{SP}): a measure of how protective vaccination is against disease, thus ignoring asymptomatic cases;
- Vaccine efficacy for infectiousness (VE_I): which measures the reduction in the ability of a vaccinated infected person compared to an unvaccinated infected person to transmit the infectious agent to others.

Our model assumes an all-or-none vaccine, which means that the vaccine effectively protects a fixed proportion of these individuals, i.e. providing complete immunity against infection, while it completely fails in the remaining part. The 'effective vaccination coverage' is then the product of the vaccination coverage and the vaccine efficacy for susceptibility (VE_S), and determines the fraction of the population that moves to the vaccinated stage. Vaccine efficacy for infectiousness (VE_I) for inactivated trivalent influenza vaccines (TIV) is found to be non-significant based on experimental challenge studies in seronegative adults.[294] This indicates that vaccinated infected individuals are as infectious to others as unvaccinated infected individuals are. In view of these findings, it is not useful to extend the all-or-none vaccine model to a leaky vaccine model.

Both the vaccination coverage and VE_S are included in the model as set parameter values, because these are intervention-related and will be adjusted when the model is used for projections given different options for intervention.

Vaccination coverage

Table 35 presents the age-stratified values for the current vaccination coverage in Belgium,[23] which are used in the baseline scenario. In children of age 6m-17y, the vaccination coverage is 0% in children without co-morbidities and 1% in children with co-morbidities. Because the prevalence of co-morbidities in this age group is 6.6%,[23] this entails a global coverage of 0.066% in all children of age 6m-17y. In accordance with Table 1, Table 35 also shows the vaccination scenario's which will be evaluated using model projections.

Table 35 – Current and aspired influenza vaccination coverage by age in Belgium

Age group	Current vaccination coverage	Proposed vaccination coverage
6 months-17 years	0.066%	Different scenario's
18-49 years	11%	0%
50-64 years	28%	38% 48%
65-74 years	50%	75%
75+ years	71%	75%

Vaccine efficacy

In this section dealing with fitting the model to past data, we do not include data on LAIV as this vaccine is not yet used in Belgium. The description of efficacy parameter below thus only concerns TIV.

For seasonal influenza, VE_S estimates are only available from experimental challenge studies in seronegative adults.[294] Therefore, we use estimates of vaccine efficacy for infection-confirmed influenza illness (VE_{SP}) obtained from randomized controlled trials and observational studies, as a proxy for VE_S. The latter studies cover a broader age range and allow us to stratify VE estimates by type of season, according to influenza intensity (high-medium versus low) and matching of the vaccine (good-relative versus poor). The proportion of effectively vaccinated is then likely overestimated, since experimental challenge studies show that the proportion of symptomatic illness in the vaccinated infected is smaller than in the unvaccinated infected, and thus $VE_S < VE_{SP}$.[294] To compensate a corresponding decrease in model-based infection incidence, the estimate of the correction factor α (see below) would however increase.

The following procedure is used to obtain VE_{SP} estimates for TIV from lab-confirmed ILI cases, i.e. with confirmed influenza infection based on culture and/or PCR (not by serology), stratified by age and type of season:

- For each age group and type of season (intensity and matching) considered, relevant studies are selected by means of a literature review;
- Estimates are obtained by pooling,[23] averaging, or from a single study;
- Estimates are truncated according to the following biomedical premise: VE_{SP} in 6m-17y olds and elderly +65y should, on average, for the same type of influenza season, not be higher than in healthy adults 18-64y;
- If no data are available for a specific age group by type of season stratum, relative season-specific differences from another age group are used to obtain an estimate.

Table 36 presents the final VE_{SP} estimates obtained using this procedure. The corresponding references are listed in Table 37.

Table 36 – Influenza VE_{SP} estimates for TIV per age group, type of intensity and vaccine match (for references see Table 37)

Age group	Intensity: high-medium Match: good-relative 04-05, 06-07, 08-09 (01-02, 02-03, 10-11)	Intensity: high-medium Match: poor 03-04
6 months-17 years	65% (single* [6])	48% (mean [3, 13, 14])
18-64y (healthy)	65% (pooled [2, 10, 11])	60% (single [5])
≥65 years	60% (mean [8, 9])	55%***
Age group	**Intensity: low Match: good-relative 07-08 (00-01, 11-12)**	**Intensity: low Match: poor 05-06**
6 months-17 years	30% (mean [4, 6])	16%**
18-64y (healthy)	45% (Part I pooled [7, 12])	22% (part I single [1])
≥65 years	42%***	20%***

** Truncated estimate according to the following biomedical premise: VE_{SP} in 6m-17y olds cannot be higher compared to healthy adults 18-64y.*

*** Averaged estimate based on the relative VE_{SP} differences estimated in healthy adults 18-64y for the two other season categories, with overlapping intensity or matching (mean of 17.6% (22%/60%)*48% = 17.6% and 14.7% (22%/45%)*30% = 14.7%).*

**** Estimate obtained by multiplying the estimate for high-medium intensity and good-relative match season in elderly with the relative VE_{SP} difference estimated in healthy adults 18-64y.*

Table 37 – Reference studies for the influenza VE_{SP} estimates presented in Table 36

First author, year	Age	Country	Season	Intensity	Match	VE_{SP} (95%CI)
[1] Beran, 2009[295]	18-64y(healthy)	Czech	2005-2006	low	poor	22% (49–59%)
[2] Beran, 2009[296]	18-64y (healthy)	Czech, Finland	2006-2007	high-medium	good-relative	62% (46–73%)
[3] Eisenberg, 2008[297]	6-59m	US	2003-2004	high-medium	poor	44% (-42–78%)
[4] Heinonen, 2011[298]	9-40m	Finland	2007-2008	low	good-relative	66% (29–84%)
[5] Herrera, 2007[299]	50-64y (healthy)	Colorado, US	2003-2004	high-medium	poor	60% (44–72%)
[6] Hoberman, 2003[43]	6-24m	US	1999-2000	high-medium	good-relative	66% (34–82%)
			2000-2001	low	good-relative	-7% (-247–67%)
[7] Jackson, 2010[300]	18-49y (healthy)	US	2005-2006 2006-2007	low	good-relative	49%
[8] Kissling, 2009[52]	+65y	5 EU countries (I-Move)	2008-2009	high-medium	good-relative	59% (15–80%)
[9] Kissling, 2011[64]	+60y	8 EU countries (I-Move)	2010-2011	high-medium	good-relative	60% (17–81%)
[10] Monto, 2009[301]	18-49y (healthy)	US	2007-2008	high-medium	good-relative	68% (46–81%)
[11] Ohmit, 2006[302]	18-49y (healthy)	US	2004-2005	high-medium	good-relative	75% (42–90%)
[12] Ohmit, 2008[303]	18-49y (healthy)	US	2005-2006	low	good-relative	16% (-171–70%)
[13] Shuler, 2007[304]	6-59m	US	2003-2004	high-medium	poor	49% (30–60%)
[14] Szilagyi, 2008[305]	6-59m	US	2003-2004	high-medium	poor	52% (-100–90%)

M: Month, Y: Year.

Prior immunity

Starting from a completely susceptible population, we pre-run the model over five influenza seasons to a steady state (i.e. a so-called burn-in period), to generate an age-specific background immunity due to historical infection or vaccination. Vynnycky et al[125] did not mention whether they used a similar approach.

Average latent and infectious period

Estimates for the mean latent period (time from infection to infectiousness) and the mean infectious period (during which an infected may infect a susceptible by means of physical contact) are based on the literature review of dynamic transmission models for influenza, described in Section 3.4. For all selected studies, if available, the values used for the average latent and infectious period are recorded; the corresponding primary data sources are identified and discarded if:

- Not published in a peer-reviewed scientific journal;
- Published before 1990;
- Estimates based on flu epidemics before 1990 or pandemic flu data;
- Values based on ad hoc choice (not established empirically).

This search strategy likely entails the most relevant estimates of the mean latent and infectious period available for seasonal influenza. We found two eligible primary data sources (Table 38). The first is a review of experimental challenge studies by Carrat et al,[253] measuring viral shedding as a proxy for infectiousness. Glasser et al[193] use a value of 1 day for the mean latent period and 3.8 days for the mean infectious period, based on the observation that healthy volunteers shed virus for 4.8 days on average, with amounts increasing during the first day post-inoculation.[253] Because the other eligible primary data source, Cauchemez et al[232] also estimate a mean infectious period of 3.8 days based on a case follow-up study in households, we adopt the same values as Glasser et al[193] for the average latent and infectious period. Although it has been suggested that children on average have a longer infectious period than adults, there is no actual data to support this assumption.

Table 38 – Primary data sources to the selected studies of transmission models with corresponding estimates for the mean latent and infectious period

Mean duration in days	Carrat et al (2008)[253] review challenge studies	Cauchemez et al[232] case follow-up study in households
Latent period	~1.0†	NA
Infectious period	~3.8†	3.8 (0.8–8.6)
First detection of viral shedding	1.1	NA
Duration of viral shedding*	4.8 (4.3–5.3)	NA
Generation time**	2.5	NA

** Time from inoculation to the first negative nasal wash with no subsequent positive washes.*
*** Average time between an individual becoming infected and infecting others.*
† Proxy estimates derived by Glasser et al (2010) based on the results from Carrat et al (2008).

Waning immunity

Genetic variation produces antigenic novel strains at such a high rate that most people who have had influenza, are susceptible to a new circulating strain of flu within a few years of infection.[246] In our model, this process is partially captured by allowing for waning immunity after natural infection or vaccination. Because precise information is lacking, the two waning rates are assumed to be equal and age-independent. The literature review by Skowronski et al[306] does not support the historic concern that vaccine-induced antibodies wane more quickly in the elderly compared to the young.

An average duration of immunity of 6 years has been used in several published dynamic transmission models for the circulating strain of seasonal influenza (e.g. Vynnycky et al and Reluga and Medlock).[125, 214]

Vynnycky et al argued that no conclusive estimates for the duration of protection could be found in the literature and they motivated the assumption of 6 years in their model for (the circulating) influenza A by empirical assessment. More specifically, the assumption of 6 years led to predictions of an age-specific infection incidence which was compatible with that observed in Tecumseh in 1977-1978, and it induced a 2-year inter-epidemic period for a specific influenza A strain.[13] Reluga and Medlock refer to Dushoff et al for assuming a mean duration of immunity of 6 years,[257] who at their turn refer to Fine[307] for using a range of 4-8 years. The literature review of models also indicated that studies modeling a single influenza strain assumed a shorter duration of immunity, i.e. around 1 year for a generic strain (see Table 11).[191, 195, 204, 206]

Correction factor alpha

The correction factor alpha calibrates the model-based infection incidence rate (number of newly infectious individuals / total number of individuals) to the observed ILI incidence rate.[308] This factor may reflect several effects, among which the proportion symptomatic, the consultation rate, i.e. the probability to consult a GP in case of ILI, and the reporting rate, i.e. the probability that a GP reports a symptomatic case as ILI. Since alpha might also absorb incorrect model assumptions or parameter misspecifications, we prefer to keep alpha constant (not season or age-specific) during model fitting.

5.2.3.2 Parameter estimation

We implemented the dynamic age-structured model in MATLAB and performed parameter estimation using a weighted least squares (WLS) approach. Let Ca(wk) denote the number of reported ILI cases of age a in calendar week k, and let Pa(wk) denote the corresponding catchment population, i.e. the number of patients of age a in calendar week k. The observed age-specific ILI incidence rate in calendar week k is then calculated as follows: Ya(wk) = Ca(wk)/Pa(wk). After running the model, we obtain the number of individuals in each of the compartments stratified by age and time. To simplify notation, we suppress the dependency of the model outcome on the input parameters. Let EIa(t) denote the number of new infectious individuals of age a at time t, and let Na(t) denote the total number of individuals of age a at time t. The model-based influenza infection incidence rate in calendar week k, then equals:

$$Z_a(w_k) = \frac{\sum_{t \in w_k} EI_a(t)}{\frac{1}{7}\sum_{t \in w_k} N_a(t)}$$

We estimate the model parameters by minimizing the weighted sum of squared differences between the observed ILI incidence rates and the model-based infection incidence rates, calibrated using the correction factor α:

$$\sum_i \sum_k \nu_{a_i}(w_k)\left[Y_{a_i}(w_k) - \alpha Z_{a_i}(w_k)\right]^2,$$

where the weighted sum is taken over all weekly ILI observations per age group: 0-4, 5-14, 15-64, and 65-99 years. The (post-stratification) weights ν_{a_i} are proportional to the corresponding catchment population $P_{a_i}(w_k)$ and correct for the unequal population sizes represented by the different age groups. The WLS score is a direct measure of goodness-of-fit, with smaller values indicating a better fit to the ILI incidence data.

Initially, we aimed to estimate eleven model parameters by fitting to the observed age- and time-specific ILI incidence over six seasons simultaneously: tvacc, tseed, t0, pseed, aseed, $\overline{R_0}$, α, δ , wi, r and f (see Table 33 and Table 34). First, a Latin hypercube design with 75 000 and 100 000 points were sampled for the eleven parameters and each parameter combination was used to run the dynamic model. Increasing the sample size of the Latin hypercube design did not necessarily lead to a better model according to the WLS score and parameter estimates were highly variable, indicating the need for a dimension reduction. Therefore, we performed feature selection by analyzing the input-response data with Pareto-aware symbolic regression.[309, 310] We observed that five model parameters did not contribute substantially to the model output (tvacc, pseed, aseed, r and f) and opted to include these parameters as fixed values, based on literature estimates (Table 33). We also investigated the influence of w_i, by estimating the parameter set through the fitting separately using a fixed value for w_i (based on literature, see below).

A new grid search was performed with the five remaining parameters with season specific tseed, t0, $\overline{R_0}$ and δ. As explained above, one correction

factor (α) for all reference seasons was used. The model scores did decrease with season-specific parameters but since we still had twenty-five parameters, a grid search was not optimal. Therefore, we used a global search algorithm implemented in the Matlab Optimization Toolbox. The global search solver uses gradient-based methods to return local and global minima. A local solver was initiated from multiple starting points and returned the solution found during the search process. To reduce the chance to end up with a local minimum, many global searches were performed with different initial points. The model-based incidence rate of the best model thus obtained is compared with the observed incidence for 2003-2009 in Figure 20. As shown in Figure 20, we obtained an excellent fit to the observations reported through the Belgian surveillance system, with an overall Weighted Least Squares (WLS) of 861 when w_i is estimated through the fitting (see Table 39 for complete parameter set estimation and Figure 20 for the fit) and WLS of 1161 when w_i is fixed at 1/6 years (see Table 40 for estimates of other parameters and Figure 21). The global search algorithm does not allow to directly calculate confidence intervals for the parameter estimates. This would require a computer-intensive method such as the bootstrap. Furthermore, it would be computationally infeasible to propagate the uncertainty into the model projections for all vaccination options considered.

Table 39 – Parameter estimations including waning immunity for best fitting model

Parameter		2003 /04	2004 /05	2005 /06	2006 /07	2007 /08	2008 /09	Overall
$\overline{R_0}$	Mean R0	1.768	2.491	1.929	1.716	2.494	1.626	
δ	Amplitude	0.999	0.150	0.350	0.999	0.000	0.990	
t0	Start season	20/08	31/08	06/10	17/09	10/11	28/10	
tseed	Seed date	31/10	26/12	14/01	12/01	15/12	17/11	
α	alpha							0.148
wi/wv	Waning							0.594

See also Figure 20 for corresponding fit.

In other words, by allowing the waning of immunity to vary freely in the fitting process (Table 39), we obtain a different set of parameter estimations than when we assume this parameter to be fixed (Table 40). In the former case the fit to the data is better than in the latter case (i.e. the WLS is lower).

With an average duration of immunity of 1.68 year (exponential decline at an annual rate of 1/0.59), immunity is estimated to wane much more rapidly than the assumption of 6 years made in British models for the circulating strain. However, it is closer to the assumptions used by a number of other models (around 1 year) that also model a single strain (see the review of dynamic models and waning immunity above. This duration also fits better with recent TIV effectiveness estimates from the late 2011-12 season (any strain), which suggest a substantial waning over time within the same season: e.g. in a pooled EU analysis, the adjusted IVE for those vaccinated <3 months was 46.8% (95%CI 9.0–68.9) and 10.5% (95%CI -32.5–39.5) for those vaccinated ≥3 months before onset of symptoms; in UK, similar gradient was observed.[63, 311, 312] It also corresponds better to the waning of LAIV immunity against any strain shown in LAIV clinical trials (from pooled VE at 81% in year 1 to 23% and 35% in year 2 if no revaccination).[28, 31]

Table 40 – Parameter estimations for best fitting model with fixed waning parameter

Parameter		2003 /04	2004 /05	2005 /06	2006 /07	2007 /08	2008 /09	Overall
$\overline{R_0}$	Mean R0	2.566	3.495	3.312	2.724	3.373	2.381	
δ	Amplitude	0.999	0.351	0.219	0.822	0.180	0.997	
t0	Start season	14/08	12/09	06/10	20/09	20/10	18/10	
tseed	Seed date	02/11	23/12	08/01	07/01	15/12	17/11	
α	alpha							0.421

Figure 20 – Model-based and observed ILI incidence rates in Belgium, 2003-2009 (best fitting model)

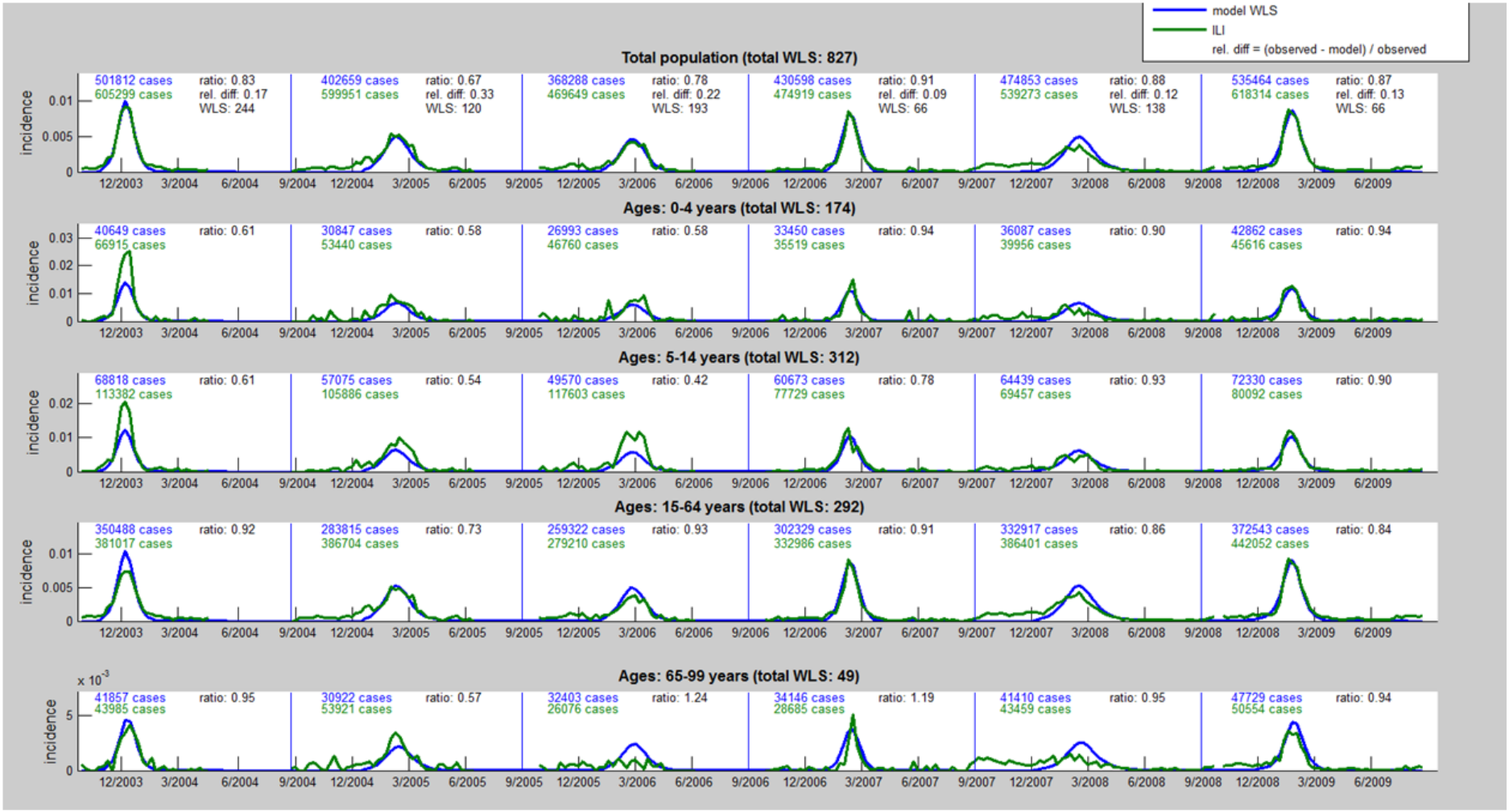
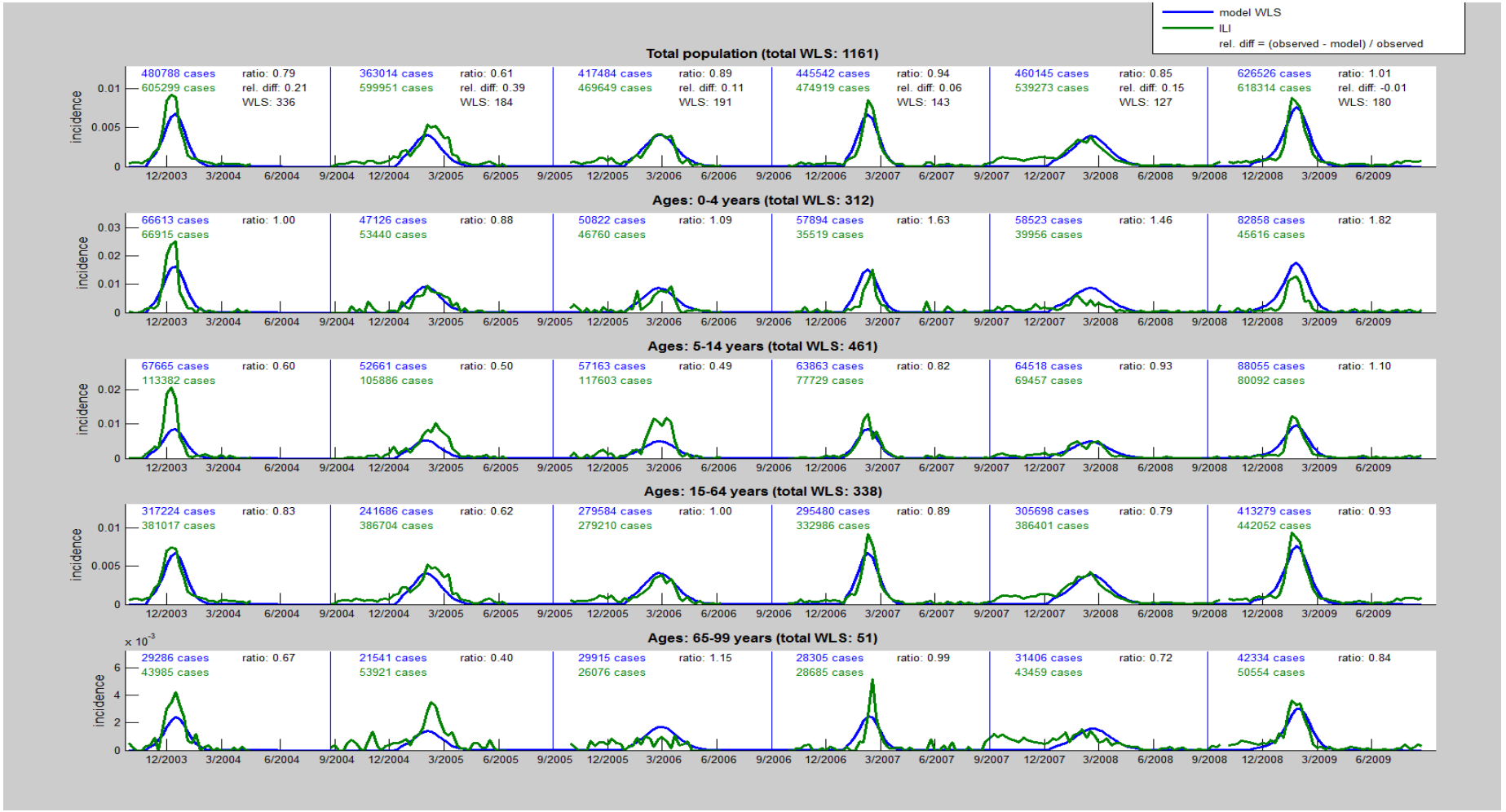


Figure 21 – Model-based and observed ILI incidence rates in Belgium, 2003-2009 (fixed waning parameter)



The main outcome of interest from the dynamic transmission model, the age-specific total number of infected individuals over time, is used as an intermediary outcome to perform economic evaluations. That is, the age-specific caseload generated by the dynamic model is further used to calculate expected number of days of illness by age, physician consultations, hospitalizations, deaths, life years and QALYs, as well as the associated health care costs under each scenario over time. This way we can estimate the impact of certain health policies and interventions by adapting our base scenario settings. These infections are also used as an input into the static models, for the specific age groups to which they apply.

In order to substantially increase computational efficiency in producing projections with the dynamic model integrated with the cost-effectiveness model, the model originally programmed in Matlab, was reprogrammed and run in C++ to produce projected estimates of cost-effectiveness. For the simulations we used the infrastructure of the VSC – Flemish Supercomputer Center, funded by the Hercules Foundation and the Flemish Government – department EWI.

5.3 Description of the static models

In order to estimate the costs and benefits of vaccination options in risk groups which do not influence the population transmission dynamics, we developed static (fixed risk) state transition models that are structured generally according to the decision tree shown in Figure 22.

These risk groups are: pregnant women, health care workers and people with comorbidities. As indicated above, healthy adult target groups will be explored by simulation with the above described dynamic transmission model (and not by static models as was hitherto the standard, see literature review), in order to account for different extents to which the transmission dynamics would be affected by vaccinating these and other age groups in the population.

Unit costs and disutility weights are given to cases requiring hospitalization, to cases not requiring hospitalization (which include cases consulting a physician and cases not consulting a physician) and to deaths (through life-years lost).

The force of infection used in the static models is an average of the force of infection projected over the seasons modeled using the dynamic transmission model. The probabilities are age-specific where appropriate, and the vaccine effectiveness and related attributable probabilities (e.g., hospitalization, death) are adjusted to the definition of what constitutes an infection.

Note that for pregnant women and health care workers we include projections of secondary effects to newborns and contacted patients, respectively. This is implemented by a “spill-over” assumption that links the infected groups in both arms (vaccinated – not vaccinated) of the main decision tree model to a nested state transition model of the newborns and contacted patients, respectively. This nested model has the same general structure as the main state transition model. Since this “spill-over” assumption is largely unknown and likely influential, the impact on the results of changing it is explored in sensitivity analysis.

In sum these secondary effects are not generated by a dynamic transmission model, but imposed in the static model framework, by attributing a proportionate decrease in the risk of infection of these secondary target groups (i.e. for every pregnant woman targeted, one newborn is modeled using the same framework as the decision tree shown in Figure 22, whereas for every health care worker targeted, a number of contacted patients, which would be context-specific (e.g. elderly in institutions) is modeled.

5.4 Analytical approach to economic evaluation

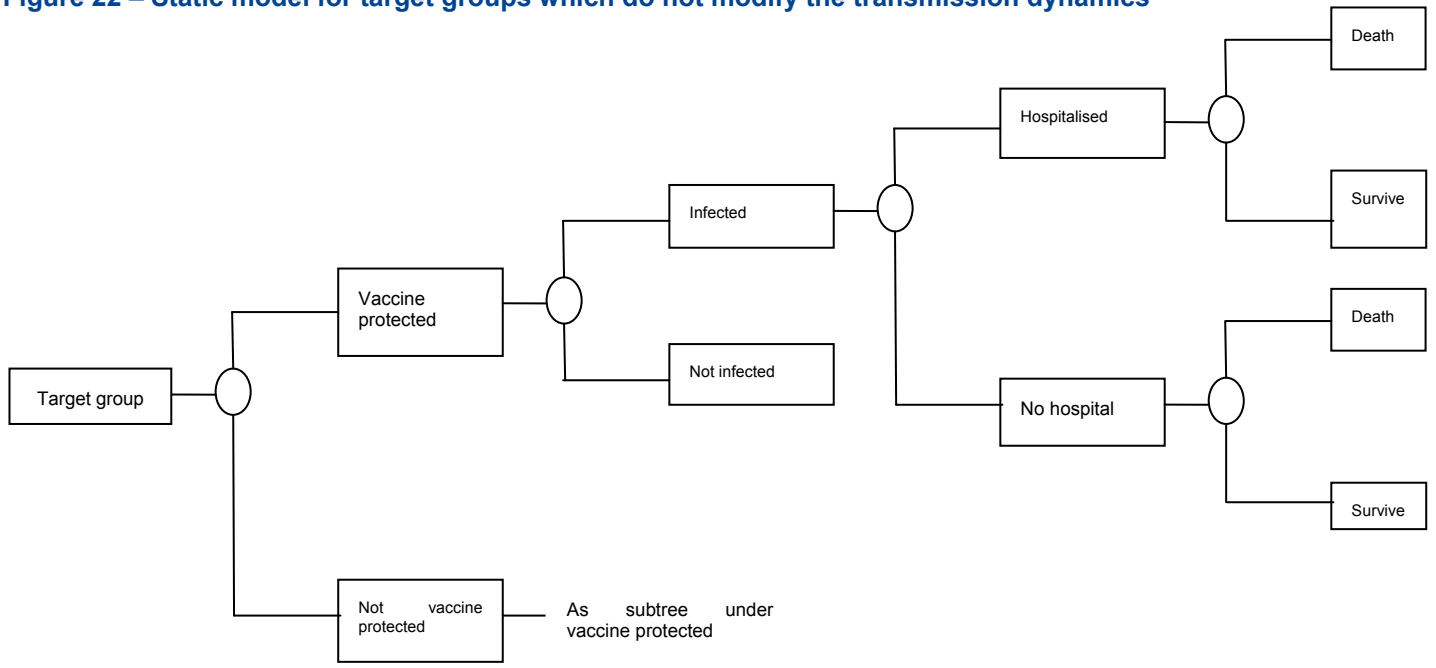
The analysis is performed from the perspective of the health care payer, in line with KCE recommendations.[114] We present the results in terms of incremental direct costs and incremental health outcomes (focusing on Quality-Adjusted Life Years (QALYs) gained) of an option for intervention under consideration versus the current situation as well as versus the next best alternative.

Probabilistic sensitivity analysis is carried out throughout the report, based on 10 000 simulations for each vaccination option considered. The considered time horizon for the simulations is 10 years. A 5-year time horizon was also investigated, however no qualitative difference was observed relative to the results with a 10-year time horizon. Parameter distributions are given in the next subsection and the median, mean and 95% uncertainty interval around the median incremental direct costs, QALYs gained and ICER are reported for all considered options in tabular

form. Furthermore Cost-Effectiveness Acceptability Curves (CEACs) are constructed where informative. CEACs have the attractive feature of summarizing parameter uncertainties in the ICERs in relation to a range of willingness to pay values. The CEACs we present in this report are constructed as follows. The costs and health outcomes of an option for vaccination are compared to another option for vaccination with a parameter value drawn from data driven distributions on most of the input parameters that determine the outputs. This process is repeated 10 000 times per comparison of two vaccination options. Thus we obtain for each comparison of two options 10 000 pairs of incremental costs and QALYs. These sets of paired comparisons can be categorised based on where they fall in the cost-effectiveness plane. Model runs are ranked at the highest (most favorable) end if they fall in the South East (SE) quadrant (i.e. they achieve cost savings and improve effectiveness (from most to least cost-saving)) and at the lowest end if they fall in the North West (NW) quadrant (i.e. cost more and are less or equally effective) as their comparator. The CEACs are constructed such that the proportion of model runs yielding a SE quadrant result (out of the 10 000 runs) cuts the Y-axis of the CEAC, and that the proportion of model runs ending up in the NW quadrant is the complement of the proportion of cost-effective runs at the maximum willingness to pay depicted.

The next best alternative for a vaccination option is identified through application of the concepts of dominance and extended dominance to the incremental direct costs and QALYs. That is, options are excluded if they cost more and prevent fewer QALYs than the current situation (i.e. “excluded by dominance”), or if they have a higher median ICER (incremental cost-effectiveness ratio, in this report defined, unless stated otherwise, as the incremental direct costs per QALY gained) and are less effective in gaining QALYs than the option in the ranked lists of options that preceeds them in terms of median ICER versus the current situation (i.e. “excluded by extended dominance”).

Figure 22 – Static model for target groups which do not modify the transmission dynamics



5.5 Parameter values and distributions

5.5.1 Parameters for dynamic transmission model-based projections

In addition to the parameter estimations for the dynamic model fit (see Table 39), which is used for projections of cost-effectiveness, a range of other parameters have been estimated from various sources described throughout this report. An overview is presented in Table 44 and the choice for specific parameters, including which parameter is included in the base case and in the sensitivity analysis, is explained below.

We described previously that the target groups explored in the dynamic model are children, healthy adults (18-64 years) and the elderly (≥65 years), to account for the extent to which the transmission dynamics of influenza would be affected by vaccinating them. Other target groups are addressed by the static model.

5.5.1.1 Influenza cases, admissions and deaths

The infected compartment in the dynamic model contains both symptomatic and asymptomatic infections. The number of infected individuals multiplied by the correction factor (alpha, see Table 39 and Table 40) represents the total number of ILI cases consulting a general practitioner (GP). We assumed that all individuals with ILI who visited a GP are symptomatic. In the fitting process we compared these total numbers of ILI cases consulting a general practitioner as predicted by the model with the ILI incidence data reported through the GP sentinel system to obtain optimal values for the unknown parameters. Using these optimal values we performed projections with the dynamic model to project for future influenza seasons the total number of ILI cases who visited a GP. However, in the economic evaluation we need the total number of ILI+ cases irrespective of GP health seeking behavior. In order to do this we therefore, as a first step in the economic evaluation, calculate the total number of ILI+ cases irrespective of GP health seeking behavior from the projected total number of ILI cases who visited a GP. First we calculate the total number of ILI cases by dividing the total number of ILIs visiting GPs (as projected by the dynamic model) by the percentage that effectively visits a GP (49.2%, Table 44). This percentage was not found to be age-specific, as shown in Figure 10 where age distributions are comparable for ambulatory persons and persons not seeking medical care. Secondly, from this total number of ILI cases in the population we calculate the total estimated number of influenza (ILI+) cases in the population by considering a fraction of the ILI cases that are truly infected with influenza A or B. This fraction is randomly sampled from a distribution, which is calculated based on the virological information available in the GP data (see Table 41). With this total number of ILI+ cases (which thus contains both individuals who visited and who did not visit a GP), we performed the economic analyses.

Table 41 – ILI+ fraction relative to ILI and distributions (irrespective of GP visits) by age based on laboratory test results

Age (years)	[0-5[	[5-15[	[15-65[	[65-100[
2003/04	58.6% Beta(41,29)	59.2% Beta(122,84)	52.5% Beta(368,333)	39.4% Beta(26,40)
2004/05	40.8% Beta(20,29)	62.4% Beta(118,71)	50.9% Beta(335,323)	62.2% Beta(46,28)
2005/06	30.6% Beta(22,50)	57.6% Beta(118,87)	39.5% Beta(180,276)	14.7% Beta(5,29)
2006/07	50.9% Beta(27,26)	66.7% Beta(124,62)	53.8% Beta(448,384)	62.3% Beta(43,26)
2007/08	28.6% Beta(10,25)	55.0% Beta(71,58)	45.5% Beta(332,398)	20.0% Beta(8,32)
2008/09	42.9% Beta(12,16)	57.4% Beta(70,52)	54.6% Beta(419,349)	41.0% Beta(25,36)

Beta distribution: Beta(number of positive cases, number of negative cases).

The number of influenza-attributable admissions and deaths by age group has been estimated by a multivariate regression analysis based on admissions and deaths coded for influenza and pneumonia from hospital discharge and death certificates datasets (see the summary under “4.1.2. Estimation of influenza related admissions and deaths through regression analyses” and full details in Supplement 2).

5.5.1.2 Effective coverage

TIV is considered for any age groups, while LAIV is only applied to the 2-17 year age group. As previously explained, we model a high number of vaccination options which also vary in vaccine coverage. More specifically, vaccination coverage in children is increased from the current level up to 90% in 10% steps. Vaccination coverage changes in adults have been advised by stakeholders, are described under Objectives and listed below in Table 42. Furthermore additional changes to adult vaccination are modeled (as explained under methods, and detailed further below).

Table 42 – Vaccine uptake change for the target groups explored in the dynamic model

Target groups	Change in vaccine uptake to consider	Vaccine uptake to reach
Children	Various (10% steps)	Various
Healthy 18-49 years	-11%	0%
Healthy 50-64 years	+10% +20%	38% 48%
Elderly 65-74 years	+25%	75%
Elderly 75+ years	+4%	75%

In children, two doses of TIV or LAIV are given for the first vaccination under age 8 years, whereas one dose is required for those aged over 8 years. In the model it is assumed that the two doses are given on the same time point, more specifically on October 10. A simple algorithm was made based on the expected proportion of vaccinated children <8 years of age in one year who would be revaccinated in the next year, and thus need only one dose, instead of two. An assumption was made that 90% of those aged less than 8 years who receive influenza vaccination in a particular year will also have received vaccination in the preceding year. For example, suppose we want a coverage of 70% for those aged less than 8 years. In the first year 70% of those aged less than 8 years receive two doses. In the second year 63% (90% of 70%) receives one dose because they are revaccinated. To complete the 70%, some individuals that were not vaccinated in the first year now receive two doses. In the third year, 90% is again considered of those individuals that were vaccinated in the second year and they receive one dose. To complete the coverage of 70%, two doses are given to some individuals that have not received a vaccine in the past years and one dose is given to some individuals that have received already a vaccine in previous years. This process is continued for the other seasons. In this algorithm we account for the fact that each year a cohort ages.

As the literature review on VE indicated that TIV efficacy estimates are highly influenced by the type of season (matching between vaccine and circulation strains and season intensity), we applied TIV estimates stratified by age and type of season to the randomly sampled sequence of seasons drawn from the past observations for each run of the model. The season- and age-specific TIV vaccine estimates used for the projections with the dynamic model are listed in Table 43 (described in the review on TIV efficacy, Section 3.1).

Conversely for LAIV, given the stability of efficacy estimates across different types of season, we used single VE estimates for all seasons. We thus use the VE of two doses in a single season (81%, see Table 44) for those who receive the vaccine for the first time as we assume they receive the two doses. For all those who receive the vaccine for the second time (immediately after the first or later after the first season), we assume the single dose vaccine efficacy (75%, see Table 44). Our model is not designed to apply the combined VE over two consecutive seasons (2 doses in season 1 and 1 dose in the next season, i.e. 81% see Influenza vaccine efficacy in children), because each season is modeled separately. Additionally, the VE of a single dose in subsequent seasons is unknown, and the difference between these parameter value choices is very limited: instead of using a VE of 81% in season 1 and 81% in season 2 (and an unknown VE in subsequent seasons), we used a VE of 81% in season 1 and 75% in all subsequent seasons.

Table 43 – Influenza VE_{SP} estimates for TIV per age group, type of intensity and vaccine match (for references see Table 37)

Age group	Intensity: high-medium Match: good-relative 04-05, 06-07, 08-09 (01-02, 02-03, 10-11)	Intensity: high-medium Match: poor 03-04
6 months-17 years	65% (single* [6])	48% (mean [3, 13, 14])
18-64y (healthy)	65% (pooled [2, 10, 11])	60% (single [5])
≥65 years	60% (mean [8, 9])	55%***
Age group	**Intensity: low Match: good-relative 07-08 (00-01, 11-12)**	**Intensity: low Match: poor 05-06**
6 months-17 years	30% (mean [4, 6])	16%**
18-64y (healthy)	45% (Part I pooled [7, 12])	22% (part I single [1])
≥65 years	42%***	20%***

** Truncated estimate according to the following biomedical premise: VE_{SP} in 6m-17y olds cannot be higher compared to healthy adults 18-64y.*
*** Averaged estimate based on the relative VE_{SP} differences estimated in healthy adults 18-64y for the two other season categories, with overlapping intensity or matching; mean of 17.6% ((22%/60%)*48% = 17.6%) and 14.7% ((22%/45%)*30% = 14.7%).*
**** Estimate obtained by multiplying the estimate for high-medium intensity and good-relative match season in elderly with the relative VE_{SP} difference estimated in healthy adults 18-64y.*

Conversely for LAIV, given the stability of efficacy estimates across different types of season, we used single VE estimates for all seasons. We thus use the VE of two doses in a single season (81%, see Table 44) for those who receive the vaccine for the first time as we assume they receive the two doses. For all those who receive the vaccine for the second time (immediately after the first or later after the first season), we assume the single dose vaccine efficacy (75%, see Table 44). Our model is not designed to apply the combined VE over two consecutive seasons (2 doses in season 1 and 1 dose in the next season, i.e. 81% see Influenza vaccine efficacy in children), because each season is modeled separately. Additionally, the VE of a single dose in subsequent seasons is unknown, and the difference between these parameter value choices is very limited: instead of using a VE of 81% in season 1 and 81% in season 2 (and an unknown VE in subsequent seasons), we used a VE of 81% in season 1 and 75% in all subsequent seasons.

5.5.1.3 Waning immunity

The waning rate of 1/1.68 year has been selected for the base case as it is the waning rate estimated by the best fitting model using Belgian data and is more in line with recent TIV and LAIV effectiveness data, which indicate a rapid waning over time, even within a single season (see section Parameter estimation). However, the sensitivity analysis also explored the impact of using the assumption of 1/6 years made for the circulating strain by Vynnycky et al.

5.5.1.4 Costs

Cost related to influenza episodes

For the cost-effectiveness analyses based on the dynamic model, we used the fitted spline function, which reflects the smoothed average hospital cost by age for hospitalized patients with influenza as primary diagnosis, or as primary and secondary diagnosis (MCD, Section 4.2.2).

Unlike for the dynamic model, in-hospital costs for the static models are computed separately and involve different age categories than those used for the dynamic model, because the analysis of these specific groups involve different age categories. This is detailed in Section 5.5.2.3.

For the out of hospital costs for hospitalized patients, we used the ILI costs (Table 29) instead of the costs for influenza confirmed ILI (ILI+), because in our survey the latter costs were based on only 4 hospitalized patients and there was no significant difference in all other ambulatory costs between ILI and ILI+.

Costs related to vaccines

Regarding administration costs of the vaccine, we assumed in the base case that the vaccines were administered by GPs, and that vaccination of children under the age of 18 years would cost exactly the same as vaccination above that age in terms of vaccine acquisition costs and administration. However, the costs of vaccinating the children would be likely lower when children receive the vaccine through the school system, Mother & Child clinics, or some other form of organized vaccination and vaccines may be purchased in large quantities following a tender procedure. The impact of this potentially lower cost is explored in the sensitivity analysis.

The cost of adverse events due to vaccination was not included explicitly in the models since it was considered to be negligible compared to the total vaccination costs, as also described in our cost-effectiveness literature review (see Section 3.3), and difficult to estimate. The main excess in adverse event compared to placebo is observed with LAIV for fever, and an excess in the use of anti-pyretics. However, the higher proportion of anti-pyretic use in LAIV compared to placebo is a few percent, there are no data on the proportion of parents who would have to buy a new package of antipyretics. This extra-cost is estimated to be of an order of magnitude of less than €0.30 per dose. In view of the large uncertainty about the vaccine price and administration costs, the addition of such adverse events costs, surrounded by a high level of uncertainty, does not seem relevant.

5.5.1.5 Quality of life

The data presented in O'Brien 2003 are used to estimate the average QALY loss for a person with ILI+ in ambulatory care.[261] O'Brien did not present the average QALY loss for the study population, but provided the average VAS score per day for 7 days (+ standard error of the average), and the average number of days with symptoms (+ 95% confidence interval). To account for sample size uncertainty, to each of these 8 data points (VAS scores for 7 days and number of days with symptoms), a normal distribution was assigned with standard deviation based on the standard error of the mean (VAS) or confidence interval (number of days). In the probabilistic sensitivity analysis, these 8 distributions were sampled independently to obtain QALY loss for a person with ILI+ in ambulatory care (=(sampled number of days with symptoms – sum of the 7 sampled VAS scores)/365), and to propagate the uncertainty into the outcome of the cost-effectiveness analysis. This way of specifying uncertainty is not ideal (for example it assumes no correlation between number of days with symptoms and VAS scores per day), but represents in our opinion the best way, given the limitations of the data available. Also with this approach, the estimated average QALY loss for an ambulatory ILI+ person is similar as presented in O'Brien (without uncertainty interval): 4.24 QALDs (cumulative utility score for 7 days in O'Brien) = 6.8 - 4.24 QALDs lost = 0.0070 QALYs lost.

To obtain the average QALY loss for a hospitalized person with ILI+, we (1) divide the average QALY loss for an ambulatory ILI+ person by the average number of days with symptoms in ambulatory persons to obtain the average QALY loss for one day with ILI+, and (2) multiply this by the average number of days with symptoms in hospitalized persons. The same approach was used to calculate the average QALY loss for a person with ILI not seeking medical care. Hence, we assume that the average QALY loss for a day with flu does not differ between persons with ambulatory, no medical care and hospitalization.

Table 44 – Parameter values, distributions and their sources for the projected cost-effectiveness estimates integrated with the two defined dynamic transmission models (see Table 39 and Table 40)

ILI or influenza*	Parameter	Estimate	Source
ILI	No medical care fraction (=no GP and not hospitalized)	0.492, Beta(1107,1143)	BE survey ILI (see Section 4.2.1)
ILI+	ILI+ fraction relative to ILI (irrespective of GP visits)	Table 41	Laboratory test results in GP sentinel surveillance (Scientific Institute of Public Health)
Influenza	If influenza, probability to die	Use a single randomization parameter for these 3 parameters, to randomize between the age-specific estimates for primary (P=0.5) and any (=primary + secondary) diagnosis (P=0.5). In a next step (only for probability to be hospitalized) randomize between 2 types of regression models (P(regr model 1)=0.5 and P(regr model 2)=0.5)	BE death certificates (ILI+ and pneumonia multiplied by fraction attributable to ILI+, scaled on ILI+ data (same as used for fitting), with Fisher correction) (see Section 4.1.2)
Influenza	If influenza probability to be hospitalized		BE MCD (ILI+ and pneumonia multiplied by the fraction attributable to ILI+, scaled on ILI+ data (same as used for fitting)) (see section 4.1.2)
Influenza	In-hospital cost for a hospitalized patient§		BE HBD-MCD (see Section 4.2.2)
We use a single randomization parameter for the following 3 cost categories, to randomize between highest (P=0.5) and lowest (P=0.5) costs.			
ILI, assumed to equal ILI+	Out-of-hospital costs for a hospitalized patient	lowest unit costs: Normal (m=€119.65, s=€17.69)	BE survey ILI (see Section 4.2.1.5, Table 29)
		highest unit costs: Normal (m=€139.94, s=€20.19)	
Influenza	Cost for an ambulatory patient (i.e. consulting GP) (no difference between ILI and influenza)	lowest unit costs: Normal (m=€51.04, s=€1.18)	BE survey ILI (see Section 4.2.1.5, Table 27)
		highest unit costs: Normal (m=€63.8, s=€1.34)	
ILI	Cost for a person with ILI not seeking medical care	lowest unit costs: Normal (m=€3.39, s=€0.21)	BE survey ILI (see Section 4.2.1.4, Table 23)
		highest unit costs: Normal (m=€7.17, s=€0.37)	
NA	Fixed marginal cost vaccination programme	€0	

ILI or influenza*	Parameter	Estimate	Source
NA	Variable vaccination costs: TIV per dose	€11.81 (altered in sensitivity analysis)	BE official price (BCFI)
NA	Variable vaccination cost: LAIV per dose	€11.81 (altered in sensitivity analysis)	Assumption (based on price parity with TIV in the baseline)
NA	Variable administration cost per dose	€23.32	BE official price of one GP visit
NA	Cost or health impact vaccine associated adverse effects	€0	Assumption
Influenza	Vaccine efficacy of LAIV after 1 dose	0.75 (95%CI 0.08–0.93) VE=1-exp(ln(RR))~Normal (m=-1.3863, s=0.6571)	Pooled estimate, based on 2 RCTs from all settings[29, 31]
Influenza	Vaccine efficacy of LAIV after 2 doses	0.81 (95%CI 0.69–0.89) VE=1-exp(ln(RR))~Normal (m=-1.6607, s=0.2643)	Pooled estimate, based on 4 RCTs from all settings[28, 29, 31, 37]
Influenza	QALY loss for an ambulatory patient	0.0070 (sampling from 8 normal distributions: 7 days for which VAS scores were measured + number of days with symptoms)	O'Brien et al 2003 (ILI+)[261]
ILI	Duration of symptoms for an ambulatory patient	Normal (m=6.43, s=0.14)	BE survey ILI (see Section 4.2.1)
ILI	Duration of symptoms for a hospitalized patient	Normal (m=8.5, s=1.04)	BE survey ILI (see Section 4.2.1)
ILI	Duration of symptoms for a person not seeking medical care	Normal (m=5.51, s=0.14)	BE survey ILI (see Section 4.2.1)
ILI	QALY loss for a hospitalized patient	= QALY loss ambulatory * duration symptoms hosp/duration of symptoms ambulatory	Assuming average QALY loss for a day with flu does not differ between persons with ambulatory/no medical care and hospitalization, based on O'Brien et al 2003 (ILI+)[261] and BE survey ILI
ILI	QALY loss for a no medical care patient	= QALY loss ambulatory * ratio duration symptoms nomed/duration of symptoms ambulatory	
NA	Baseline age-specific utilities	As a function of age (1-inflated beta-regression)	BE survey general population (unpublished data; n=2204)

ILI or influenza*	Parameter	Estimate	Source
NA	Life expectancy	As a function of age	BE, Eurostat, see http://epp.eurostat.ec.europa.eu/portal/page/portal/statistics/themes
NA	Discount rate for costs	0.03	BE, Belgian guidelines[114]
NA	Discount rate for health effects	0.015	BE, Belgian guidelines[114]

** ILI+ = influenza laboratory-confirmed ILI.*
§ Direct costs for a deceased person are implicitly accounted for in the costs for nomed/GP/hosp, as the sum of these 3 relates to the total number of ILI+ cases (including those who die from influenza).
BE: Specific source for Belgium; P: proportion; Beta distribution: Beta(number of positive cases, number of negative cases).

Table 45 (replicated from Table 39) shows the dynamic model parameters estimated by the best fit of the model to past observations. After fitting, these parameters were fixed to be used for projections with the dynamic model.

Table 45 – Parameter estimations including waning immunity for best fitting model

Parameter		2003 /04	2004 /05	2005 /06	2006 /07	2007 /08	2008 /09	Overall
$\overline{R_0}$	Mean R0	1.768	2.491	1.929	1.716	2.494	1.626	
δ	Amplitude	0.999	0.150	0.350	0.999	0.000	0.990	
t0	Start season	20/08	31/08	06/10	17/09	10/11	28/10	
tseed	Seed date	31/10	26/12	14/01	12/01	15/12	17/11	
α	alpha							0.148
wi/wv	Waning							0.594

5.5.2 Parameters for static model-based projections

The following sections list the tables of parameter values, and their distributions and sources, used for static model-based projections. An overview is presented in Table 48, Table 49 and Table 50. The choice of parameters for the base case and for sensitivity analysis, when differing from those described for the dynamic model, is explained below.

As explained under Section 5.3, the target groups that are explored by the static models are pregnant women, persons with comorbidities and health care workers (Table 47).

5.5.2.1 Influenza cases, admissions and deaths

There are no data available on the true numbers of influenza admissions and deaths in these target groups in Belgium. We thus used the age-specific influenza admission and death rates found by the multivariate regression analyses by age groups, adjusted them for increased risk of these groups when relevant and applied them to the corresponding denominator and age groups. To account for the uncertainty, we used high and low estimates from the regression analysis.

More specifically:

- For HCW, we assume no increased risk compared to the general population and we applied the rates from the 15-64 years to the total number of 239 740 HCW active in health care (2008 estimates, see Part I report). For both outcomes, a low case corresponded to the influenza attributable rates estimated by regression models involving P+I outcomes coded as principal diagnosis. For admissions, the high case involved rates estimated by regressing on any respiratory and circulatory admissions as principal diagnosis; for deaths, the high case was based on death rates estimated by regression models involving any P+I deaths (see Supplement 2).
- For persons with co-morbidities, we applied the age-specific proportion of all influenza coded admissions and deaths in which at least one comorbidity was coded (MCD data, see Part I report) to the total numbers of influenza-attributable outcomes estimated by the regression analyses in the corresponding age group. We conducted a parallel estimation by applying the fraction attributable to influenza from the regression analysis to the P+I outcomes estimated in Part I for these target groups (using the same datasets). As the two methods yielded very similar estimates, we selected the first option as it involved similar influenza seasons.
- For pregnant women, we used two assumptions:
  - A base case where pregnant women are assumed to have no increased risk of influenza admissions compared to non-pregnant women. We thus applied the rates estimated in the 15-49 year age group to the denominator of pregnant women. We used estimates based on the rates estimated by regression models involving P+I admissions coded as principal diagnosis and as any P+I diagnosis. For the admissions, we also based parameters on the rate estimated by regressing any respiratory and circulatory admissions as principal diagnosis (see Supplement 2).
  - In the sensitivity analysis, we assumed that pregnant women experience the same increased risk of admission and deaths as during the H1N1 2009 pandemic influenza, by applying the estimates of relative risk retrieved from a systematic review on admissions and deaths involving similar settings.[313] For the admissions, we applied a relative risk of 7.2 compared to rates among women of same age.[314] For the deaths, we applied two measures of increased risk: one based on the high relative risk from this systematic review (RR=10.2 compared to women of reproductive age), and one based on the pooling of all studies retrieved by this review (pregnant amount to 5.7% of all H1N1 influenza deaths).[313]

The results from these estimates are described in Table 46 below, and how these estimates are integrated in the models is described in Table 48, Table 49 and Table 50.

Table 46 - Estimates of influenza admissions and deaths per season in the three target groups for the static models

Target Group	Admissions	Deaths
HCW, low case	18	0.6
HCW, high case	55	1.3
Pregnant, base case, P+I main	7	0.1
Pregnant, base case, P+I any	11	0.2
Pregnant, base case, R+C main	15	NA
Pregnant, high case, H1N1	54	2 or 20
Co-morbidities 0-14 years	76	2
Co-morbidities 15-49 years	127	8
Co-morbidities 50-64 years	160	30

P+I: Pneumonia and/or influenza coded outcomes.
Main: ICD coded as principal diagnosis or cause of death.
Any: ICD coded as any diagnosis or cause of death.
R+C: Respiratory and circulatory admissions.

5.5.2.2 Effective coverage

The scenarios selected for vaccine uptake of these specific groups are discussed in the Objectives, and the values are listed below. As the force of infection in the static models is based on an average of the force of infection projected over the seasons modeled in the dynamic model, we

used the pooled vaccine efficacy over several seasons provided by the Osterholm review.[42] Vaccine protection is assumed to be provided on average 4 weeks after vaccine administration.

Table 47 – Vaccine uptake changes for the target groups explored in the static models

Target groups	2008 vaccine coverage[a]	Change in vaccine uptake	Vaccine coverage to reach
Persons 1-64 years with co-morbidities	20%	+ 20%	40%
Pregnant women	NA (~0%)	+ 50%	50%
Health care workers	35%	+15%	50%

a: Based on the Health Interview Survey (HIS) conducted by the Scientific Institute of Public Health in 2008.

5.5.2.3 Costs

Cost related to influenza episodes

Unlike for the dynamic model, in-hospital costs for the static models are computed separately, because the analysis of these specific groups involve different age categories than those used for the dynamic model.

In-hospital costs for hospitalized patients have been calculated directly from the raw cost data to be used as inputs for the static models (i.e. these cost inputs are not explicitly separately shown in Section 4.2 on intermediary data analyses for hospitalization costs).

For pregnant women (Table 48), we randomized between two scenarios. In the first scenario (€1838.16), we calculated the weighted average of primary influenza hospitalization costs, for women with a primary diagnosis of influenza. In order to do this, we grouped the raw data into 1-year age groups and then took the weighted average of the age distribution of women giving birth in 2011 in Belgium (minimum age 15 years, maximum age 49 years; Eurostat data 2011). In the second scenario (€1480.81), we calculated the costs as an unweighted mean of all identified women with a primary diagnosis of influenza combined with a secondary diagnosis of any pregnancy complication. The cost of women with pregnancy complications appears to be lower than the estimated cost of admission for influenza as primary diagnosis. The reasons for this observation are unknown.

- For health care workers we calculated the mean cost per age category directly as an average from the raw data of people falling in the category (Table 49). Costs for both the elderly and health care workers were extracted from admissions with a primary diagnosis of influenza.
- For people with comorbidities we calculated, as for the other age groups, a direct average by age group from the raw data (Table 50). We used the data from admissions with a primary diagnosis of influenza combined with a diagnosis indicating a comorbidity.

Costs related to vaccines

TIV in pregnant women is assumed to be administered during regular prenatal visits at no extra-cost for administration (but the alternative, with administration costs equal to a GP visit is also investigated). In HCW, we also explored two main scenarios: no marginal cost for vaccine administration (i.e. TIV administered through regular occupational health visits) and the cost of a GP visit. In persons with co-morbidity, we assumed for administration costs that TIV administration would require an additional GP visit in the base case (but here too this assumption was explored in sensitivity and threshold analysis).

As for children, the cost of adverse events due to vaccination was not included explicitly in the models as safety reviews show that TIV is well tolerated and that these adverse events, mainly consisting of pain and inflammation at the injection site, would involve marginal costs which are negligible compared to the other vaccination costs (purchase and administration).

We perform sensitivity and threshold analysis on vaccination costs (and the reader could easily add to a vaccination cost in a given threshold scenario a very small amount for adverse events, e.g. €0.3 per dose).

5.5.2.4 *Quality of life and life expectancy*

The same methods for estimating QALYs have been used as for the dynamic model projections (see above).

Life expectancy is expected to be shorter in persons with comorbidities but no data are available for Belgium. In the base case, we assumed that persons with comorbidities have the same age-specific life expectancy as the overall population. In the sensitivity analysis, we explored reducing life expectancy of people with comorbidities by multiplying these life expectancies by a factor of 0.5 and 0.3.

5.5.2.5 *Indirect protection*

The analysis involving vaccination of HCWs investigates the potential impact of preventing both primary infections in the HCWs and secondary infections in patients contacted by the HCWs. In the absence of data, the definition of these secondary infections has been limited to an overall age specification and is not linked to specific comorbidities or to a specific health care setting.

For the analyses conducted on vaccinating pregnant women, we assumed the fetus dies if the mother dies. After birth, for the remainder of the influenza season, baby and mother have a different clinical attack rate. They are separately at risk of acquiring influenza. We make the analyses assuming that children born from vaccinated mothers remain 6 months protected with the same vaccine efficacy as the mother. We investigated the impact of the latter assumption, by varying the extent to which vaccine efficacy is transferred from mother to neonate from 100% over 50% to 0%.

Table 48 – Parameter values and distributions used in the static model for pregnant women

ILI or influenza*	Parameter	Estimate	Source
ILI	No medical care fraction (=no GP and not hospitalized)	0.492, Beta(1107, 1143)	BE survey ILI (see Section 4.2.1)
ILI/ILI+	Scaling factor ILI to ILI+, we take the reference category 15-65 for pregnant women, and 0-5 reference category for newborns, overall observed seasons	0.499, Beta(2069.54, 2075.46) for pregnant women 0.431, Beta(132.17, 2075.46) for newborns	Dynamic model
Influenza	If influenza, probability to die	For pregnant women we randomize between two scenarios: • Beta(0.1, DENOM-0.1) (low CFR) • Beta(0.2, DENOM-0.2) (medium CFR) DENOM (95% range 12 825.44–13 631.71) refers to the denominator, which is the number of symptomatic influenza cases sampled from a run of the static model with the no program assumption (0% vaccination coverage), we vary this fraction in sensitivity analysis.	See Table 46

ILI or influenza*	Parameter	Estimate	Source
		In sensitivity analysis we also investigate the H1N1 scenario with: • Beta(2, DENOM-2) (low CFR) • Beta(20, DENOM-20) (medium CFR) For neonates we randomize between models age for the reference category 0 to 5.	
Influenza	If influenza, probability to be hospitalized	For pregnant women, randomize between 3 scenarios: • Beta(7, DENOM-7) • Beta(11, DENOM-11) • Beta(15, DENOM-15) DENOM refers to the denominator, which is the number of symptomatic influenza cases sampled from a run of the static model with the no program assumption (0% vaccination coverage), we vary this fraction in sensitivity analysis. In sensitivity analysis we also investigate the H1N1 scenario with: • Beta(54, DENOM-54) For neonates we used the reference category 0-5 and randomized between models. Women just after giving birth are assumed to have the same hospitalization rate as pregnant women.	Pregnant women: Table 46 Newborns: BE MCD (Influenza and pneumonia multiplied by the fraction attributable to influenza, scaled on ILI+ data - same as used for fitting, see Section 4.1.2)
Influenza	In-hospital cost for a hospitalized patient§	For pregnant women, we randomize between two options: • weighted average of primary influenza hospitalization costs, based on age distribution of women giving birth (age 15-49 years with primary diagnosis influenza: €1838.16) • hospitalization costs for women with primary diagnosis influenza and secondary diagnosis pregnancy complication (€1480.81) For newborns we use the average hospitalization cost of primary diagnosis influenza for newborns (€2571.69)	BE HBD-MCD (see Section 5.5.2.3)
We use a single randomization parameter for the following 3 cost categories, to randomize between highest (P=0.5) and lowest (P=0.5) costs.			
ILI assumed = to ILI+	Out-of-hospital costs for a hospitalized patient	lowest unit costs: Normal (m=€119.65, s=€17.69) highest unit costs: Normal (m=€139.94, s=€20.19)	BE survey ILI (see Section 4.2.1.5, Table 29)

ILI or influenza*	Parameter	Estimate	Source
ILI+	Cost for an ambulatory patient (i.e. consulting GP) (no difference between ILI and influenza)	lowest unit costs: Normal (m=€51.04, s=€1.18) highest unit costs: Normal (m=€63.8, s=€1.34)	BE survey ILI (see Section 4.2.1.5)
ILI	Cost for a person with ILI not seeking medical care	lowest unit costs: Normal (m=€3.39, s=€0.21) highest unit costs: Normal (m=€7.17, s=€0.37)	BE survey ILI (see Section 4.2.1.4)
NA	Fixed marginal cost vaccination programme	€0	
NA	Variable vaccination costs: TIV per dose	€11.81	BE official price (BCFI)[22]
NA	Variable administration cost per dose	€0	Assumption
ILI+	QALY loss for an ambulatory patient	0.0070 (sampling from 8 normal distributions: 7 days for which VAS scores were measured + number of days with symptoms)	O'Brien et al 2003 (ILI+)[261]
ILI	Duration of symptoms for an ambulatory patient	Normal (m=6.43, s=0.14)	BE survey ILI (see Section 4.2.1)
ILI	Duration of symptoms for a hospitalized patient	Normal (m=8.5, s=1.04)	BE survey ILI (see Section 4.2.1)
ILI	Duration of symptoms for a person not seeking medical care	Normal (m=5.51, s=0.14)	BE survey ILI (see Section 4.2.1)
ILI	QALY loss for a hospitalized patient	= QALY loss amb * duration symptoms hosp/duration of symptoms amb	Assuming average QALY loss for a day with flu does not differ between persons with ambulatory/no medical care and hospitalization,
ILI	QALY loss for a no medical care patient	= QALY loss amb * ratio duration symptoms nomed/duration of symptoms amb	

ILI or influenza*	Parameter	Estimate	Source
			based on O'Brien et al 2003 (ILI+)[261] and BE survey ILI
NA	Baseline age-specific utilities	As a function of age (1-inflated beta-regression)	BE survey general population (unpublished data; n=2204)
NA	Life expectancy	As a function of age	BE, Eurostat, see http://epp.eurostat.ec.europa.eu/portal/page/portal/statistics/themes
NA	Discount rate for costs	0.03	BE, Belgian guidelines[114]
NA	Discount rate for health effects	0.015	BE, Belgian guidelines[114]
ILI	Proportion of attack rate exposure during pregnancy and during the period of vaccine protection for the cohort giving birth, on average, on 15th February. This period is defined as week 51-week 25	0.84	Dynamic model, weighted average of cases per age by age distribution of pregnant women
Influenza	In mothers who acquire influenza and die during pregnancy, the proportion of neonates who are not yet born (cases week 51-week 7 of the mother / cases week 51-25 for women)	0.58	Dynamic model weighted average of cases per age by age distribution of pregnant women

ILI or influenza*	Parameter	Estimate	Source
Influenza	Proportion of the attack rate applicable to neonates after they are born (week 8-25)	0.33	Dynamic model
Influenza	Vaccine efficacy (TIV)	Normal(mean=0.59, s=0.04081633)	Osterholm et al[42]
NA	Vaccine uptake program	0.50	Assuming half of women who deliver in a year will be targeted in their second or third trimester in the period 1st October-31st December
NA	Vaccine uptake no program	0	See Table 47
NA	Size target group	121 363	BE, source KCE report part I[23]
ILI	Attack rate	Age dependent, averaged over seasons	Dynamic model

** ILI+ = influenza laboratory-confirmed ILI.*
§ Direct costs for a deceased person are implicitly accounted for in the costs for nomed/GP/hosp, as the sum of these 3 relates to the total number of ILI+ cases (including those who die from influenza).
BE: specific source for Belgium; CFR: case-fatality ratio; P: proportion; Beta distribution: Beta(number of positive cases, number of negative cases).

Table 49 – Parameter values and distributions used in the static model for health care workers

ILI or influenza *	Parameter	Estimate	Source
ILI	No medical care fraction (=no GP and not hospitalized)	0.492, Beta(1107,1143)	BE survey ILI (see Section 4.2.1)
ILI/ILI+	Scaling factor ILI to ILI+, by age category of the health care workers, assumed to be the same fraction as the general population reference age 15-64	0.499, Beta(2069.54, 2075.46)	Dynamic model
Influenza	If influenza, probability to die	For HCW, we randomize between 2 scenarios: • Beta(0.6, DENOM-0.6) • Beta(1.3, DENOM-1.3) DENOM (95% range 17 757.95–19 501.40) refers to the denominator, i.e. the number of symptomatic influenza cases sampled from a run of the static model with the no program assumption (35% vaccination coverage) over the whole population of HCW: 239 740 people We randomized between models for the elderly (hospitalized) population (see Table 44)	For HCW: see Table 46 For the elderly: BE MCD (Influenza and pneumonia multiplied by the fraction attributable to influenza, scaled on ILI+ data - same as used for fitting, see Section 4.1.2)
Influenza	If influenza, probability to be hospitalized	For HCW we randomize between 2 scenarios: • Beta(18, DENOM-18) • Beta(55, DENOM-1.3) DENOM (95% range 17 757.95–19 501.40) refers to the denominator, which is the number of symptomatic influenza cases sampled from a run of the static model with the no program assumption (35% vaccination coverage) over the whole population of HCW: 239 740 people We randomized between models for the elderly (hospitalized) population (see Table 44)	For HCW: see Table 46 For the elderly hospitalized patients: BE MCD (Influenza and pneumonia multiplied by the fraction attributable to influenza, scaled on ILI+ data - same as used for fitting, see Section 4.1.2)

ILI or influenza *	Parameter	Estimate	Source
Influenza	In-hospital cost for a hospitalized patient	Depending on the age group: • 20-29, HCW: €1653.40 • 30-49, HCW: €2300.21 • 50-64, HCW: €3659.81 • 50-64, elderly: €3659.81 • 65-74, elderly: €4824.72 • 75+, elderly: €5664.49	BE HBD-MCD (see Section 5.5.2.3)
We use a single randomization parameter for the following 3 cost categories, to randomize between highest (P=0.5) and lowest (P=0.5) costs.			
ILI assumed = to ILI+	Out-of-hospital costs for a hospitalized patient	lowest unit costs: Normal (m=€119.65, s=€17.69) highest unit costs: Normal (m=€139.94, s=€20.19)	BE survey ILI (see Section 4.2.1.5, Table 29)
ILI+	Cost for an ambulatory patient (i.e. consulting GP) (no difference between ILI and influenza)	lowest unit costs: Normal (m=€51.04, s=€1.18) highest unit costs: Normal (m=€63.8, s=€1.34)	BE survey ILI (see Section 4.2.1.5)
ILI	Cost for a person with ILI not seeking medical care	lowest unit costs: Normal (m=€3.39, s=€0.21) highest unit costs: Normal (m=€7.17, s=€0.37)	BE survey ILI (see Section 4.2.1.4)
NA	Fixed marginal cost vaccination programme	€0	Assumption
NA	Variable vaccination costs: TIV per dose	€11.81 (altered in sensitivity analysis)	BE official price (BCFI)[22]
NA	Variable administration cost per dose	€0 or €23.32	BE official price of one GP visit
ILI+	QALY loss for an ambulatory patient	0.0070 (sampling from 8 normal distributions: 7 days for which VAS scores were measured + number of days with symptoms)	O'Brien et al 2003 (ILI+)[261]
ILI	Duration of symptoms for an ambulatory patient	Normal (m=6.43, s=0.14)	BE survey ILI (see Section 4.2.1)

ILI or influenza *	Parameter	Estimate	Source
ILI	Duration of symptoms for a hospitalized patient	Normal (m=8.5, s=1.04)	BE survey ILI (see Section 4.2.1)
ILI	Duration of symptoms for a person not seeking medical care	Normal (m=5.51, s=0.14)	BE survey ILI (see Section 4.2.1)
ILI	QALY loss for a hospitalized patient	= QALY loss amb * duration symptoms hosp/duration of symptoms amb	Assuming average QALY loss for a day with flu does not differ between persons with ambulatory/no medical care and hospitalization, based on O'Brien et al 2003 (ILI+)[261] and BE survey ILI
ILI	QALY loss for a no medical care patient	= QALY loss amb * ratio duration symptoms nomed/duration of symptoms amb	
NA	Baseline age-specific utilities	As a function of age (1-inflated beta-regression)	BE survey general population (unpublished data; n=2204)
NA	Life expectancy	As a function of age	BE, Eurostat, see http://epp.eurostat.ec.europa.eu/portal/page/portal/statistics/themes
NA	Discount rate for costs	0.03	BE, Belgian guidelines[114]
NA	Discount rate for health effects	0.015	BE, Belgian guidelines[114]
Influenza	Vaccine efficacy (TIV)	Normal(mean=0.59, s=0.04081633)	Osterholm et al[42]
NA	Vaccine uptake program	0.50	See Table 47
NA	Vaccine uptake no program	0.35	See Table 47
NA	Size target group	239 740 HCWs aged 20-65 years 10 000 assumed as hypothetical cohort size when analyzing specific age groups (since age distribution HCWs remained unknown to us)	KCE report part I, Table 37
ILI	Attack rate	Age dependent, averaged over seasons	Dynamic model

** ILI+ = influenza laboratory-confirmed ILI; BE: specific source for Belgium; CFR: case-fatality ratio; HCW: health care worker; P: proportion; Beta distribution: Beta(number of positive cases, number of negative cases).*

Table 50 – Parameter values and distributions used in the static model for people with comorbidities

ILI or influenza *	Parameter	Estimate	Source
ILI	No medical care fraction (=no GP and not hospitalized)	0.492, Beta(1107,1143)	BE survey ILI (see Section 4.2.1)
ILI/ILI+	Scaling factor ILI to ILI+, we use the proportions of the general population from an average season, depended on age group	• Beta(751.2257; 592.7743) (0-14 years) • Beta(2069.5438; 2075.4562) (15-49 years) • Beta(2069.5438; 2075.4562) (50-64 years) • Beta(142.1336; 201.8664) (65+ years)	Dynamic model
Influenza	If influenza, probability to die	• Beta(2, DENOM-2) (0-14 years) • Beta(8, DENOM-8) (15-49 years) • Beta(30, DENOM-30) (50-64 years) DENOM refers to the denominator, which is the number of symptomatic influenza cases sampled from a run of the static model with the no program assumption (20% vaccination coverage) over the whole age group of comorbidities For the 65+ group we randomize from the case fatality ratios of the general population of that age	See Table 46
Influenza	If influenza, probability to be hospitalized	• Beta(76, DENOM-76) (0-14 years) • Beta(127, DENOM-127) (15-49 years) • Beta(160, DENOM-160) (50-64 years) DENOM refers to the denominator, which is the number of symptomatic influenza cases sampled from a run of the static model with the no program assumption (20% vaccination coverage) over the whole age group of comorbidities For the 65+ group we randomize from the hospitalization rates of the general population of that age	See Table 46
Influenza	In-hospital cost for a hospitalized patient	We calculated the cost per age of admission for persons with comorbidities:	BE HBD-MCD (see Section 5.5.2.3)

		• €3436.69 (0-14 years) • €4575.99 (15-49 years) • €6293.41 (50-64 years) • €7506.74 (65+ years)	
We use a single randomization parameter for the following 3 cost categories, to randomize between highest (P=0.5) and lowest (P=0.5) costs.			
ILI assumed = to ILI+	Out-of-hospital costs for a hospitalized patient	lowest unit costs: Normal (m=€119.65, s=€17.69) highest unit costs: Normal (m=€139.94, s=€20.19)	BE survey ILI (see Section 4.2.1.5, Table 29)
ILI+	Cost for an ambulatory patient (i.e. consulting GP) (no difference between ILI and influenza)	lowest unit costs: Normal (m=€51.04, s=€1.18) highest unit costs: Normal (m=€63.8, s=€1.34)	BE survey ILI (see Section 4.2.1.5)
ILI	Cost for a person with ILI not seeking medical care	lowest unit costs: Normal (m=€3.39, s=€0.21) highest unit costs: Normal (m=€7.17, s=€0.37)	BE survey ILI (see Section 4.2.1.4)
NA	Fixed marginal cost vaccination programme	€0	
NA	Variable vaccination costs: TIV per dose	€11.81	BE official prices (BCFI)[22]
NA	Variable administration cost per dose	€23.32	BE Official price of one GP visit
ILI+	QALY loss for an ambulatory patient	0.0070 (sampling from 8 normal distributions: 7 days for which VAS scores were measured + number of days with symptoms)	O'Brien et al 2003 (ILI+)[261]
ILI	Duration of symptoms for an ambulatory patient	Normal (m=6.43, s=0.14)	BE survey ILI (see Section 4.2.1)
ILI	Duration of symptoms for a hospitalized patient	Normal (m=8.5, s=1.04)	BE survey ILI (see Section 4.2.1)
ILI	Duration of symptoms for a person not seeking medical care	Normal (m=5.51, s=0.14)	BE survey ILI (see Section 4.2.1)
ILI	QALY loss for a hospitalized patient	= QALY loss amb * duration symptoms hosp/duration of symptoms amb	Assuming average QALY loss for a day with flu does not differ between persons with

ILI	QALY loss for a no medical care patient	= QALY loss amb * ratio duration symptoms nomed/duration of symptoms amb	ambulatory/no medical care and hospitalization, based on O'Brien et al 2003 (ILI+)[261] and BE survey ILI
NA	Baseline age-specific utilities	As a function of age (1-inflated beta-regression)	BE survey general population (unpublished data; n=2204)
NA	Life expectancy	As a function of age multiplied with a factor 1 or 0.5 or 0.3 to investigate the influence of shorter life expectancy due to comorbidities	BE, Eurostat, see http://epp.eurostat.ec.europa.eu/portal/page/portal/statistics/themes
NA	Discount rate for costs	0.03	BE, Belgian guidelines[114]
NA	Discount rate for health effects	0.015	BE, Belgian guidelines[114]
Influenza	Vaccine efficacy (TIV)	Normal(mean=0.59, s=0.04081633)	Osterholm et al[42]
NA	Vaccine uptake program	0.40	See Table 47
NA	Vaccine uptake no program	0.20	See Table 47
NA	Size target group	117 473 (0-14 years) 407 613 (15-49 years) 320 672 (50-64 years) 559 788 (65+ years)	BE, Health Interview Survey 2008
ILI	Attack rate	Age dependent, averaged over seasons	Dynamic model

** ILI+ = influenza laboratory-confirmed ILI; BE: specific source for Belgium; CFR: case-fatality ratio; Beta distribution: Beta(number of positive cases, number of negative cases).*

6 RESULTS

6.1 Options considered with the dynamic transmission model

6.1.1 Modified children options + current adult vaccination

The options considered here are shown in Table 51. All results assume a waning immunity rate of 1/1.68 year, unless specified.

Table 51 – Options for expanded childhood vaccination by age group (in years)

Vaccination option		[0.5-2[	[2-5[	[5-12[	[12-18[
Current situation		TIV current	TIV current	TIV current	TIV current
c1	TIV 0.5-2	TIV change	TIV current	TIV current	TIV current
c2	TIV 2-5	TIV current	TIV change	TIV current	TIV current
c3	TIV 5-12	TIV current	TIV current	TIV change	TIV current
c4	TIV 12-18	TIV current	TIV current	TIV current	TIV change
c5	TIV 0.5-5	TIV change	TIV change	TIV current	TIV current
c6	TIV 0.5-12	TIV change	TIV change	TIV change	TIV current
c7	TIV 0.5-18	TIV change	TIV change	TIV change	TIV change
c8	TIV 2-18	TIV current	TIV change	TIV change	TIV change
c9	TIV 5-18	TIV current	TIV current	TIV change	TIV change
c10	TIV 2-12	TIV current	TIV change	TIV change	TIV current
c11	LAIV 2-5	TIV current	LAIV	TIV current	TIV current
c12	LAIV 5-12	TIV current	TIV current	LAIV	TIV current
c13	LAIV 12-18	TIV current	TIV current	TIV current	LAIV
c14	TIV 0.5-2+LAIV 2-5	TIV change	LAIV	TIV current	TIV current
c15	TIV 0.5-2+LAIV 2-12	TIV change	LAIV	LAIV	TIV current
c16	TIV 0.5-2+LAIV 2-18	TIV change	LAIV	LAIV	LAIV
c17	LAIV 2-18	TIV current	LAIV	LAIV	LAIV
c18	LAIV 5-18	TIV current	TIV current	LAIV	LAIV
c19	LAIV 2-12	TIV current	LAIV	LAIV	TIV current

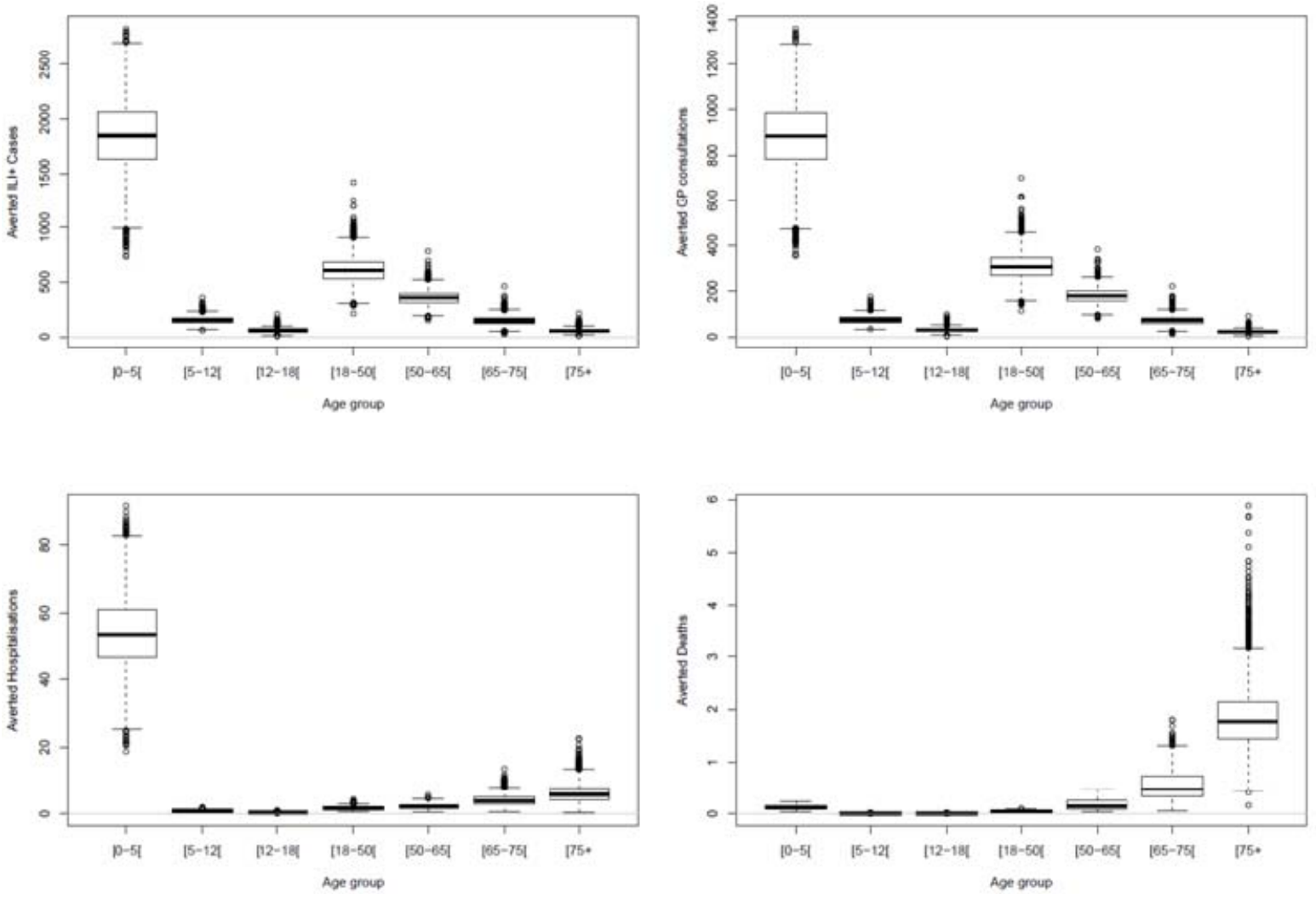
In Table 51, the "TIV current" cells indicate that in the given age group vaccination coverage remains as is currently the case (i.e. estimated at 0.066%, Table 35). The "TIV change" cells indicate that vaccination coverage is increased from the current level up to 90% in 10% steps. "LAIV" indicates the replacement of TIV by LAIV, again at coverage levels ranging from 10% to 90%.

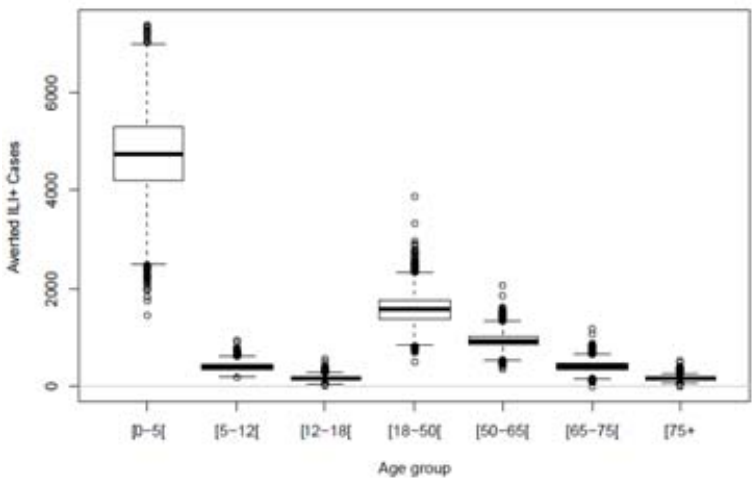
Assuming all adult vaccination coverage levels remain as is currently the case, we can estimate the incremental cost-effectiveness of these 19 child options at different levels of coverage.

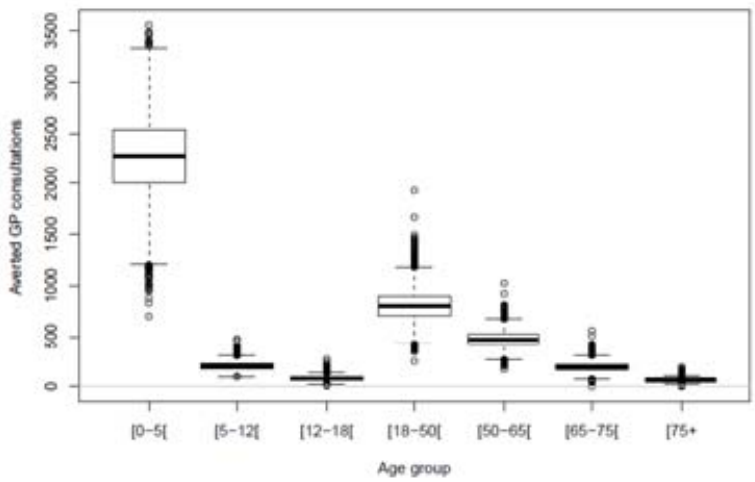
6.1.1.1 Effectiveness versus current situation

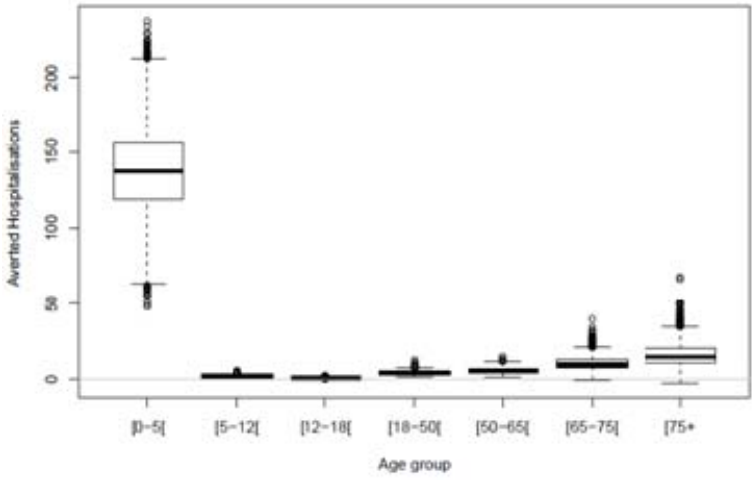
The most effective option in terms of QALYs gained amongst all the child options from Table 51 at any level of coverage versus the current situation is the vaccination of all children <18 years, using LAIV in the 2-18 age group for which it is indicated and TIV in the 0.5-2 age group (option c16). The least effective option compared to the current situation is the option where vaccination remains unchanged in the 2 to <18 year old children, while those aged 0.5-2 years are vaccinated with TIV (option c1). Figure 23 and Figure 24 show the per-season averaged averted numbers of cases of ILI+ (i.e. influenza), GP consultations, hospitalisations and deaths for these two options at two plausible vaccine coverage levels (30% and 80%).

Figure 23 – Box plots of the per-season averaged averted numbers of cases of ILI+ (i.e. influenza), GP consultations, hospitalisations and deaths for the least effective option c1 (in terms of QALYs gained) amongst all the child options in Table 51 at 30% (top) and 80% (bottom) coverage




Averted ILI+ Cases
0
2000
4000
6000
[0-5[
[5-12[
[12-18[
[18-50[
[50-65[
[65-75[
[75+
Age group


Averted GP consultations
0
500
1000
1500
2000
2500
3000
3500
[0-5[
[5-12[
[12-18[
[18-50[
[50-65[
[65-75[
[75+
Age group


Averted Hospitalisations
0
50
100
150
200
[0-5[
[5-12[
[12-18[
[18-50[
[50-65[
[65-75[
[75+
Age group

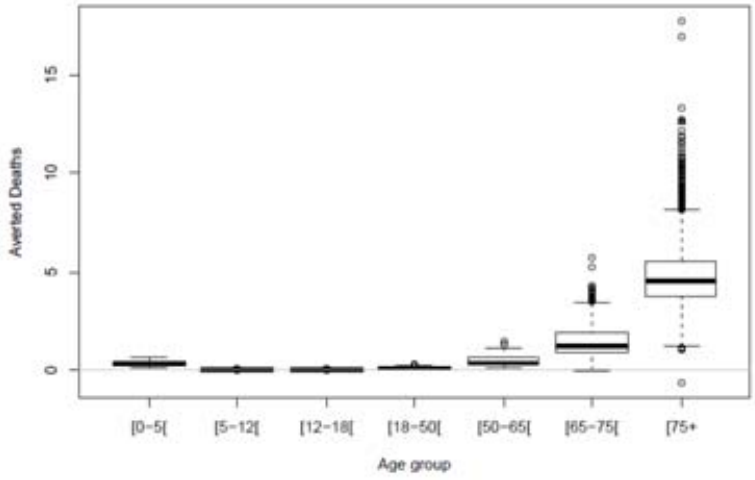
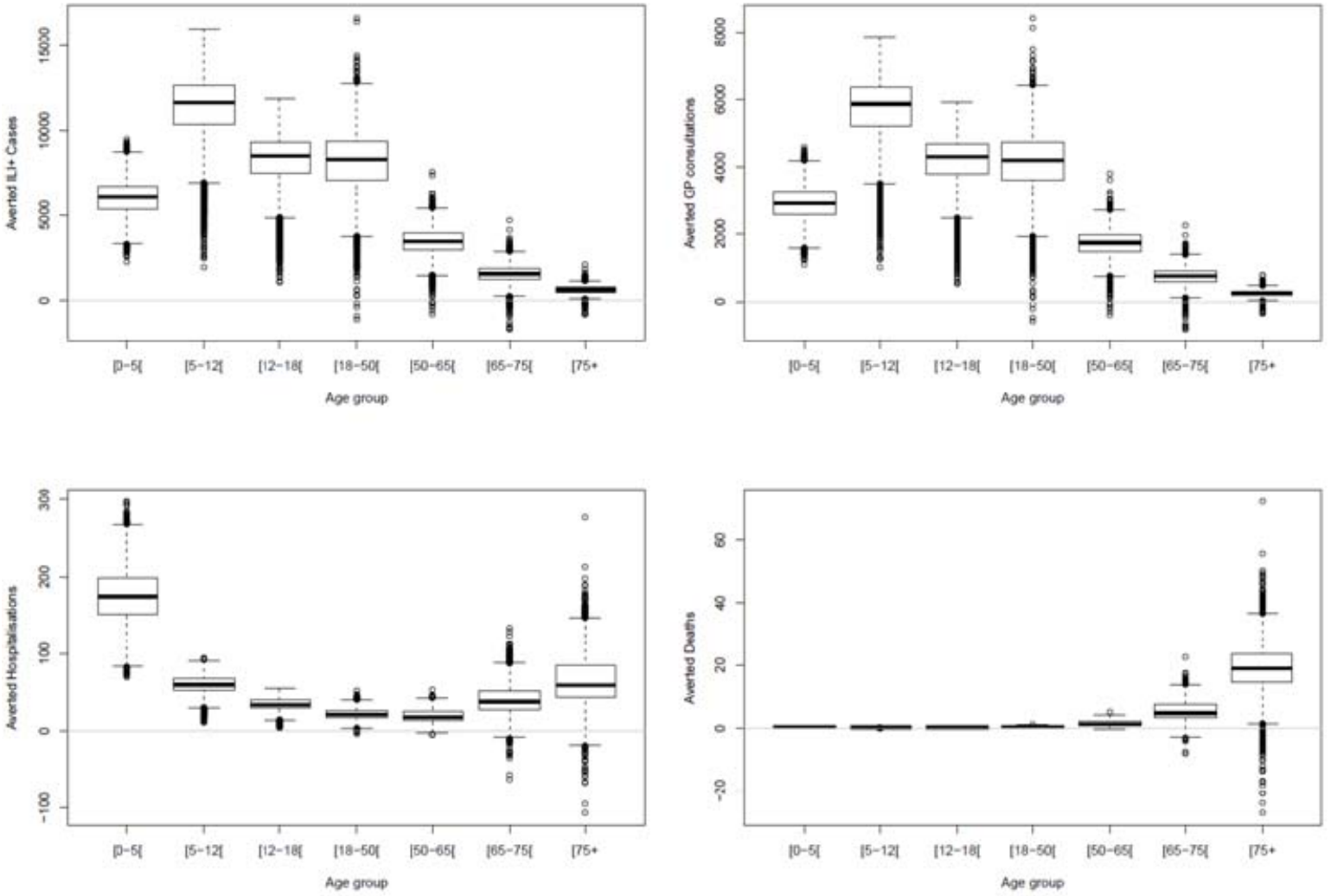
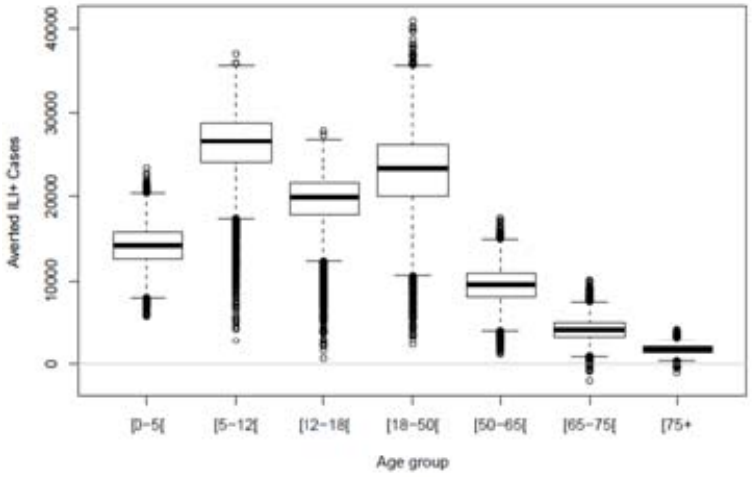
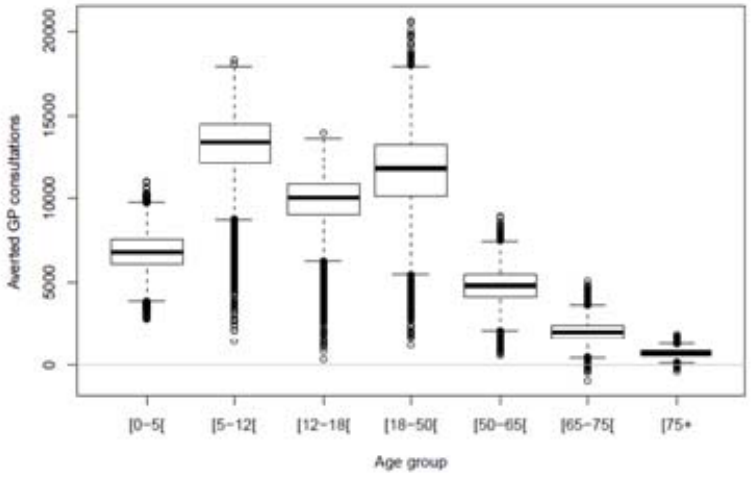
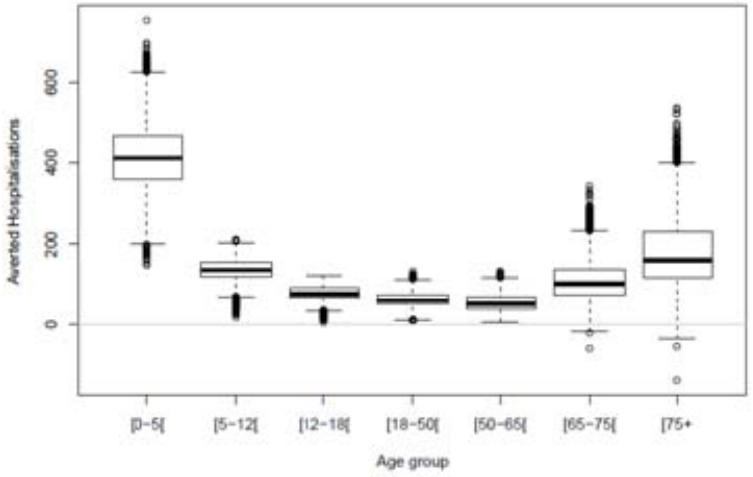

Averted Deaths
0
5
10
15
[0-5[
[5-12[
[12-18[
[18-50[
[50-65[
[65-75[
[75+
Age group

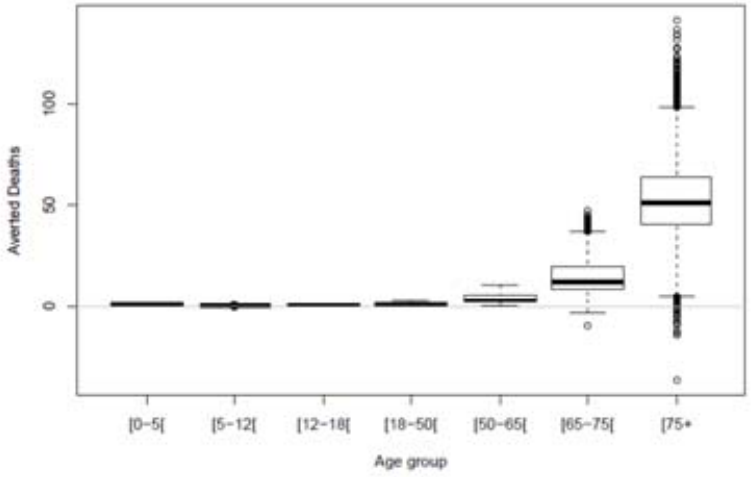
Figure 24 – Box plots of the per-season averaged averted numbers of cases of ILI+ (i.e. influenza), GP consultations, hospitalisations and deaths for the most effective option c16 (in terms of QALYs gained) amongst all the child options in Table 51 at 30% (top) and 80% (bottom) coverage




Averted ILI+ Cases
0
10000
20000
30000
40000
[0-5[
[5-12[
[12-18[
[18-50[
[50-65[
[65-75[
[75+
Age group


Averted GP consultations
0
5000
10000
15000
20000
[0-5[
[5-12[
[12-18[
[18-50[
[50-65[
[65-75[
[75+
Age group

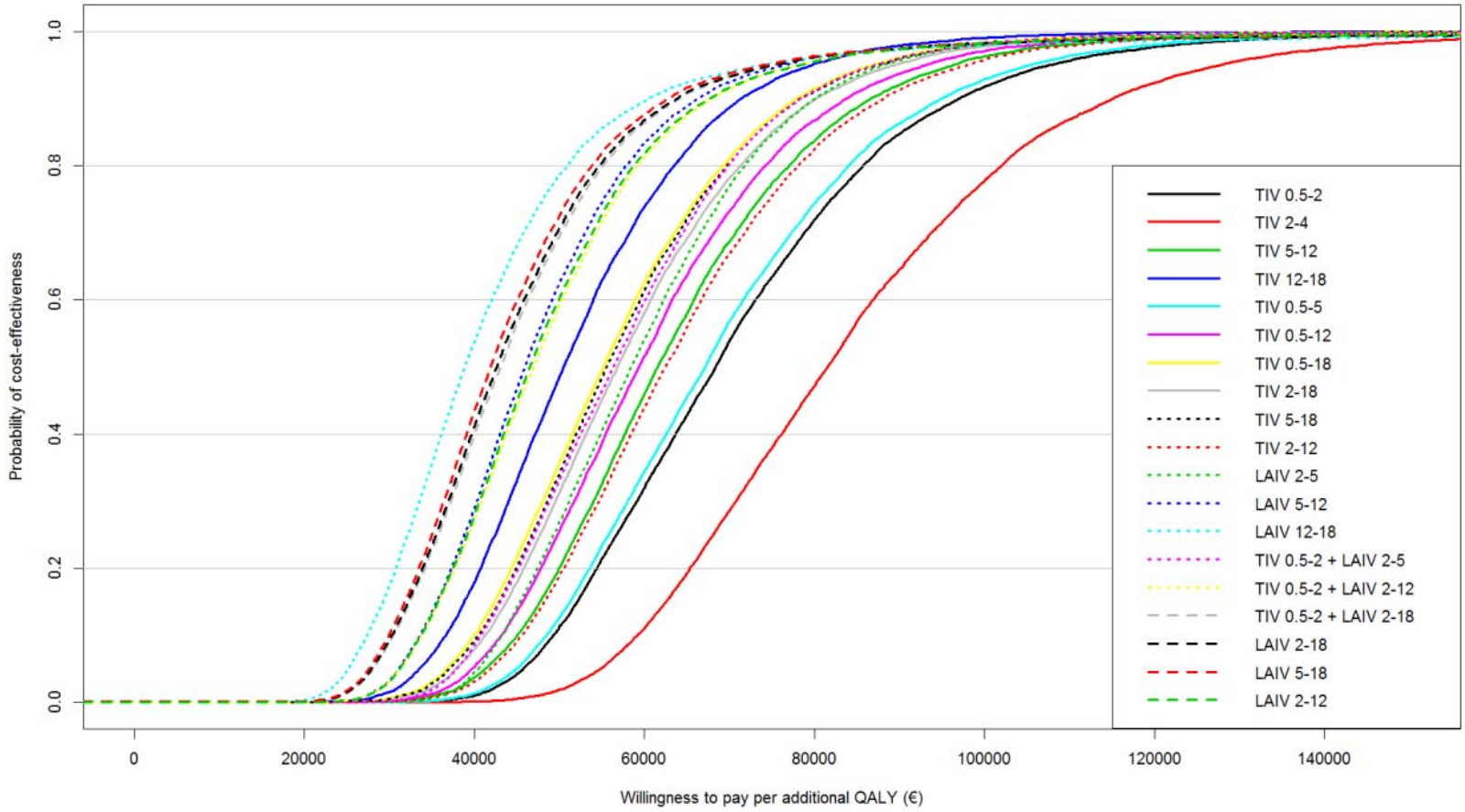

Averted Hospitalisations
0
200
400
600
[0-5[
[5-12[
[12-18[
[18-50[
[50-65[
[65-75[
[75+
Age group

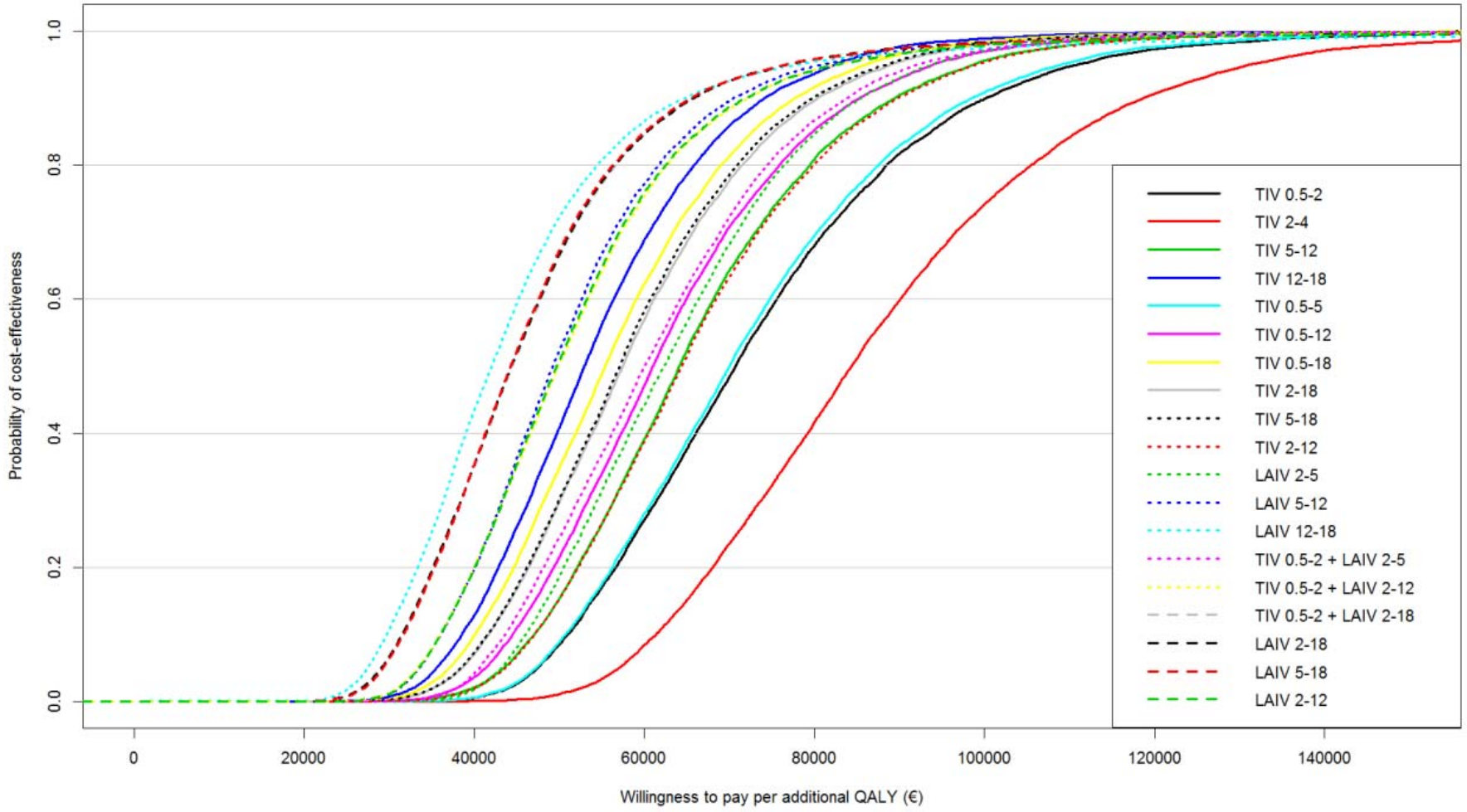

Averted Deaths
0
50
100
[0-5[
[5-12[
[12-18[
[18-50[
[50-65[
[65-75[
[75+
Age group

6.1.1.2 Cost-effectiveness versus current situation

Figure 25 shows the CEACs for selected levels of coverage for all 19 options versus the current situation.

Figure 25 – CEACs for 19 childhood vaccination options at 30% (top) and 80% (bottom) vaccination coverage versus the current situation

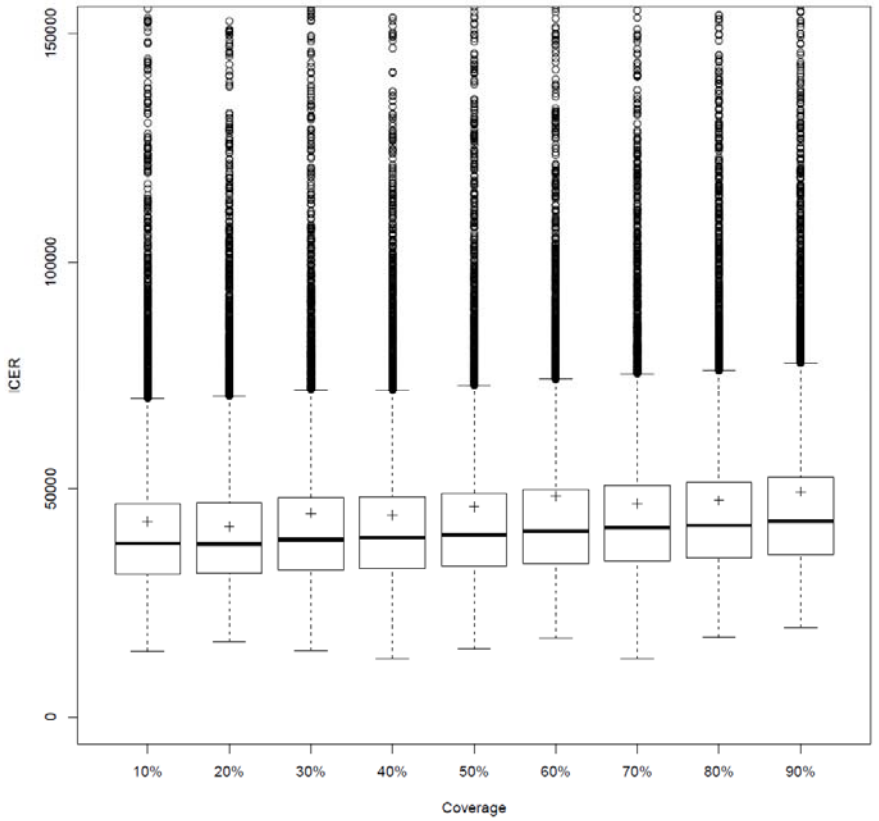


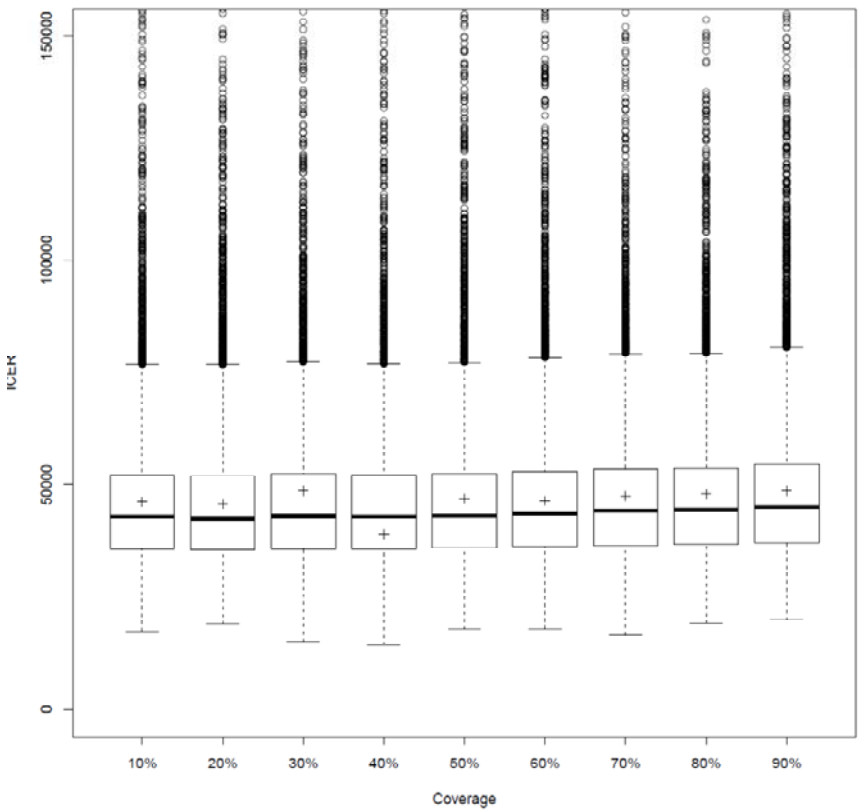


For details on the legend, see Table 51.

Figure 26shows the relationship between the ICERs and the vaccination coverage levels for the child option with the lowest median ICER versus the current situation (child option c13: LAIV12-18), and the child option with the largest effectiveness (child option c16: TIV 0.5-2 + LAIV 2-18). There is a slight increasing trend in ICER with increasing coverage. These figures show that there is relatively little impact in variations in coverage levels, mainly because the recurring vaccination costs (which are assumed to require high administration costs, equivalent to a GP consultation per dose) dominate the potential savings in treatment costs and gains in QALYs per increment in vaccination coverage.

Figure 26 – Boxplots of the distribution of the ICERs by 10% increases in vaccination coverage when vaccinating children aged 12 to 18 years (option c13: LAIV 12-18, top) and when vaccinating all children <18 years (option c16: TIV 0.5-2 + LAIV 2-18, bottom) versus the current situation





6.1.1.3 Incremental analyses

The sequence of options in Table 52 shows the efficiency frontier (using the ICER compared to the next best option, i.e. each incremental analysis uses as reference strategy the previous listed option) along the expansion path of increased vaccination coverages for the child vaccination options, whilst assuming adult vaccination remains constant. The direct costs per life year gained remained equally stable along the sequence of child options. The median ICERs range between €38 000 and €45 000 per QALY gained. Child options c13 (LAIV 12-18) and c18 (LAIV 5-18) are frequently selected. The sequence thus suggests that it is more efficient to vaccinate first older age groups in the age range under 18 years, and then progressively younger age groups. The shorter duration of vaccine induced and natural immunity limits the herd immunity effects and hence also the relative advantage of vaccinating younger children over older ones. Child options c16 (TIV<2 and LAIV 2-18) and c17 (LAIV 2-18), targeting most or all children <18 years, are also frequently selected.

Options using TIV are not selected in these options (except in <2 years as LAIV is not indicated), indicating that LAIV dominates TIV in the age groups for which either vaccine can be considered. This is not surprising given our baseline assumption of price parity between LAIV and TIV, and the observed efficacy estimates we used for both.

Table 52 – Incremental costs, life-years gained, QALYs gained and ICERs (€) along the expansion path of increased vaccination coverage for 19 child vaccination options with 9 different coverage levels each, whilst assuming adult vaccination remains constant over a 10 year time span, and with immunity lasting an average of 1.68 years (i.e. exponential waning rate of 1/1.68 per year)

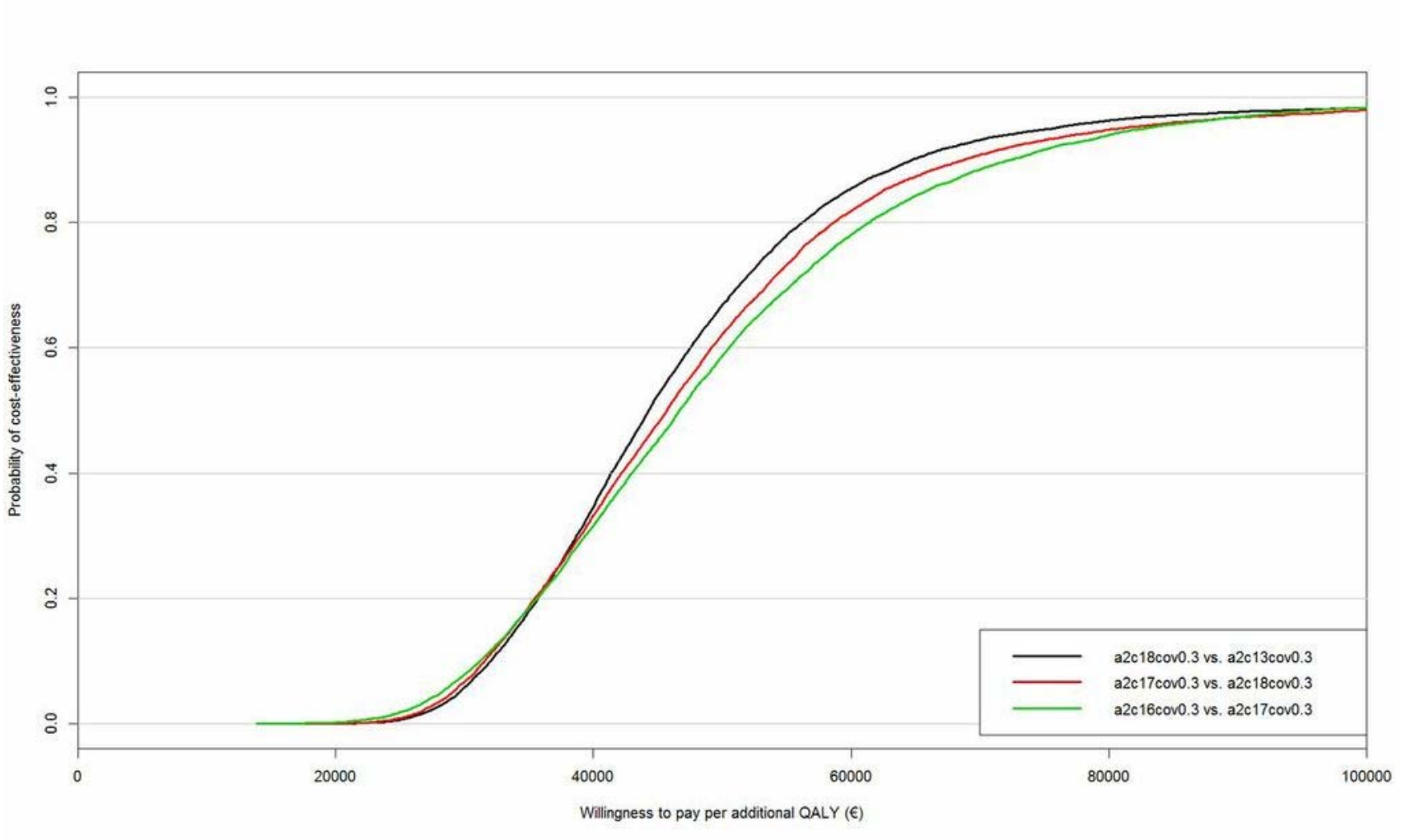
Vaccination option * (Compared to the previous listed option)	Median incremental cost	Median QALYs gained	Median life-years gained	Incremental direct costs per QALY gained			Incremental direct costs per life-year gained		
				Median	2.50%	97.50%	Median	2.50%	97.50%
a2c13cov0.2[a]	37 266 893	978	417	38 008	22 987	92 743	88 818	42 177	281 850
a2c13cov0.3	56 079 505	1 441	611	38 856	23 510	92 403	91 237	43 386	268 767
a2c13cov0.4	74 894 914	1 903	815	39 345	23 849	93 804	91 408	44 001	279 805
a2c13cov0.5	93 806 148	2 347	1 005	39 959	24 394	97 346	92 910	45 019	287 618
a2c13cov0.6	112 827 320	2 768	1 181	40 740	24 785	100 429	94 969	45 366	299 753
a2c13cov0.7	131 892 722	3 175	1 355	41 515	25 231	97 806	96 739	46 426	279 732
a2c18cov0.3	136 550 303	3 256	1 353	41 895	25 859	90 103	100 555	48 463	273 852
a2c13cov0.8	150 972 404	3 589	1 532	42 046	25 678	101 085	97 975	47 826	294 138
a2c18cov0.4	182 264 356	4 327	1 819	42 083	26 003	88 861	99 924	48 716	277 325
a2c18cov0.5	228 155 980	5 361	2 267	42 504	26 467	92 833	100 342	49 533	290 421
a2c17cov0.4	229 766 284	5 389	2 326	42 649	26 105	90 369	98 682	48 323	267 476
a2c16cov0.4	254 067 739	5 913	2 599	42 944	26 137	88 831	97 759	47 997	252 307
a2c17cov0.5	287 372 713	6 681	2 899	42 965	26 534	93 099	98 777	48 877	268 206
a2c16cov0.5	317 619 998	7 343	3 246	43 198	26 566	91 659	97 960	48 330	256 633
a2c17cov0.6	344 825 475	7 928	3 452	43 479	26 550	92 903	99 900	48 124	262 754
a2c16cov0.6	380 786 903	8 720	3 873	43 631	26 469	91 326	98 413	47 724	251 241
a2c17cov0.7	402 070 299	9 118	3 987	44 068	26 715	90 227	100 772	48 961	255 624
a2c16cov0.7	443 807 688	10 036	4 467	44 238	26 692	89 204	99 331	48 237	242 704

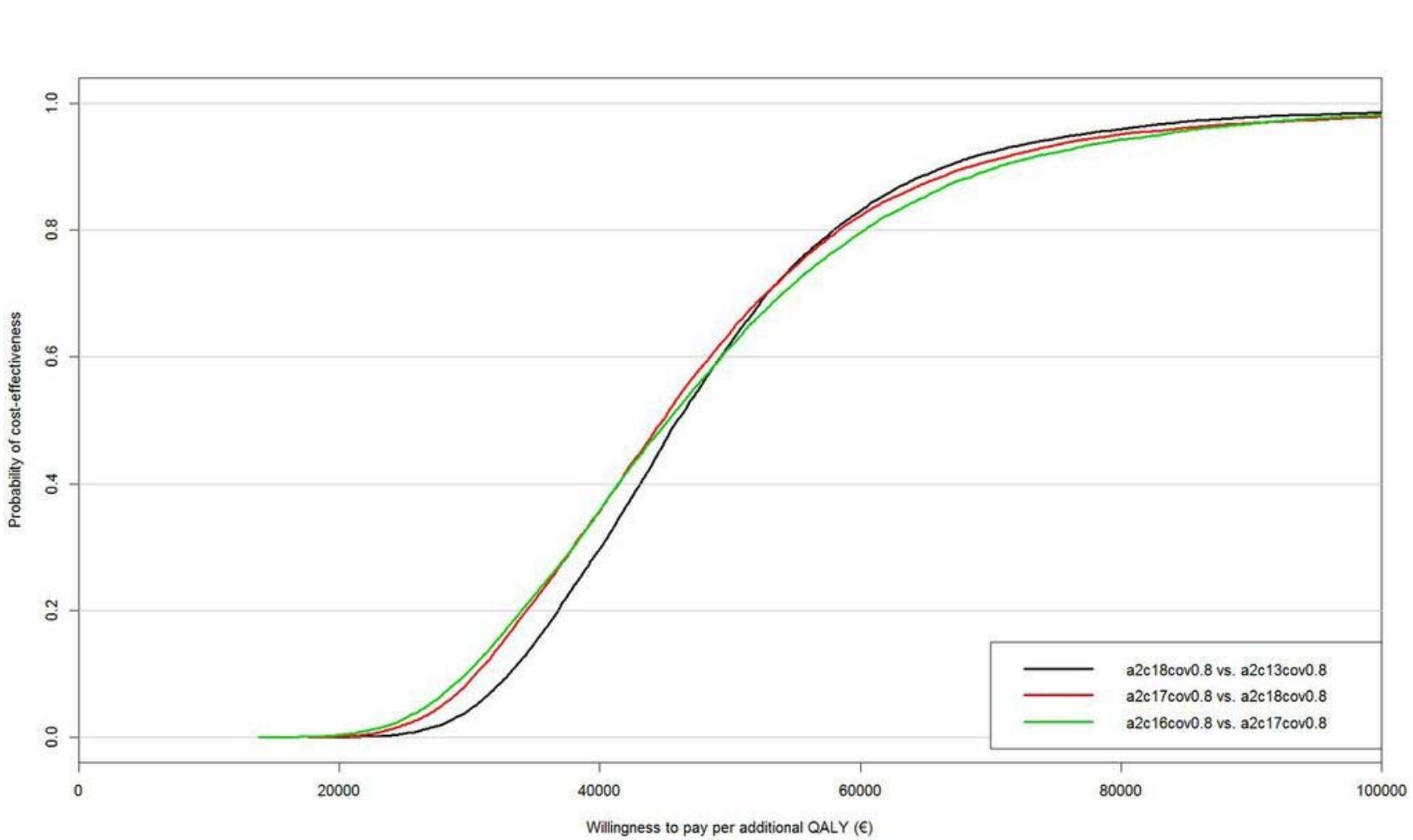
Vaccination option * (Compared to the previous listed option)	Median incremental cost	Median QALYs gained	Median life-years gained	Incremental direct costs per QALY gained			Incremental direct costs per life-year gained		
				Median	2.50%	97.50%	Median	2.50%	97.50%
a2c17cov0.8	458 330 418	10 336	4 557	44 280	27 273	90 670	100 831	49 695	253 854
a2c16cov0.8	505 420 856	11 381	5 098	44 415	27 105	90 006	99 215	49 000	242 438
a2c17cov0.9	513 113 575	11 426	5 083	44 909	27 544	96 477	100 906	50 172	263 236
a2c16cov0.9	565 526 028	12 571	5 693	44 990	27 481	95 228	99 280	49 339	250 945

** The options should be read as follows: a2 stands for current adult vaccination (see also Table 53); c# stands for a particular child option (see Table 51), covp stands for modeled vaccination coverage p for the child option c#. E.g.: a2c16cov0.4 : current adult vaccination supplemented with vaccination at 40% coverage in children aged 0.5-2 years using TIV, and in children aged 2-18 years using LAIV.*
c13: LAIV 12-18; c16: TIV 0.5-2 + LAIV 2-18; c17: LAIV 2-18; c18: LAIV 5-18.
a: Compared to the current situation.

We also performed incremental analyses for each level of coverage separately, and obtained identical expansion paths for coverage levels between 10% and 80%. Namely c13 → c18 → c17 → c16. For vaccination coverage of 90%, c18 was excluded by extended dominance, such that the optimal path ran as c13 → c17 → c16. This signifies that it is preferable to vaccinate the older children first, before starting to vaccinate younger children at the same coverage rate. In each case the ICER and 95% uncertainty interval were of similar magnitude as the ICERs depicted in Table 52. Figure 27 shows the CEACs of the incremental analyses along the paths for separate coverage levels of 30% and 80%.

Figure 27 – Incremental CEACs for remaining childhood vaccination options at 30% (top) and 80% (bottom) vaccination coverage after exclusion of dominated options, whilst assuming adult vaccination remains constant over a 10 year time span, and with immunity lasting an average of 1.68 years (i.e. exponential waning rate of 1/1.68 per year)





The options should be read as follows: a2 stands for current adult vaccination (see also Table 53); c# stands for a particular child option (see Table 51), covp stands for modeled vaccination coverage p for the child option c#. E.g.: a2c16cov0.4 : current adult vaccination supplemented with vaccination at 40% coverage in children aged 0.5-2 years using TIV, and in children aged 2-18 years using LAIV. c13: LAIV 12-18; c16: TIV 0.5-2 + LAIV 2-18; c17: LAIV 2-18; c18: LAIV 5-18.

6.1.2 *Current children vaccination + modified adult vaccination targets*

The options considered here are shown in Table 53. These correspond to the options described in Table 35 of the current report.

Table 53 – Options for adult TIV vaccination coverage targets by age group (in years)

Vaccination options		[18-50[	[50-65[	[65-75[	75+
Current		**11%**	**28%**	**50%**	**71%**
At1	I 75+	11%	28%	50%	75%
At2	I 65-74	11%	28%	75%	71%
At3	I 65-75+	11%	28%	75%	75%
At4	I 50-64	11%	38%	50%	71%
At5	I 50-64 + I 75+	11%	38%	50%	75%
At6	I 50-74	11%	38%	75%	71%
At7	I 50-75+	11%	38%	75%	75%
At8	II 50-64	11%	48%	50%	71%
At9	II 50-64 + I 75+	11%	48%	50%	75%
At10	II 50-64 + I 65-74	11%	48%	75%	71%
At11	II 50-64 + I 65-75+	11%	48%	75%	75%
At12	D 18-49	0%	28%	50%	71%
At13	D 18-49 + I 75+	0%	28%	50%	75%
At14	D18-49 + I 65-74	0%	28%	75%	71%
At15	D18-49 + I 65-75+	0%	28%	75%	75%
At16	D18-49 + I 50-64	0%	38%	50%	71%
At17	D18-49 + I 50-64 + I 75+	0%	38%	50%	75%
At18	D18-49 + I 50-74	0%	38%	75%	71%
At19	D18-49 + I 50-75+	0%	38%	75%	75%
At20	D18-49 + II 50-64	0%	48%	50%	71%
At21	D18-49 + II 50-64 + I 75+	0%	48%	50%	75%
At22	D18-49 + II 50-64 + I 65-74	0%	48%	75%	71%
At23	D18-49 + II 50-64 + I 65-75+	0%	48%	75%	75%

I: increase vaccination coverage; II: larger increase vaccination coverage (50-64 years only); D: decrease vaccination coverage; At: adult target.

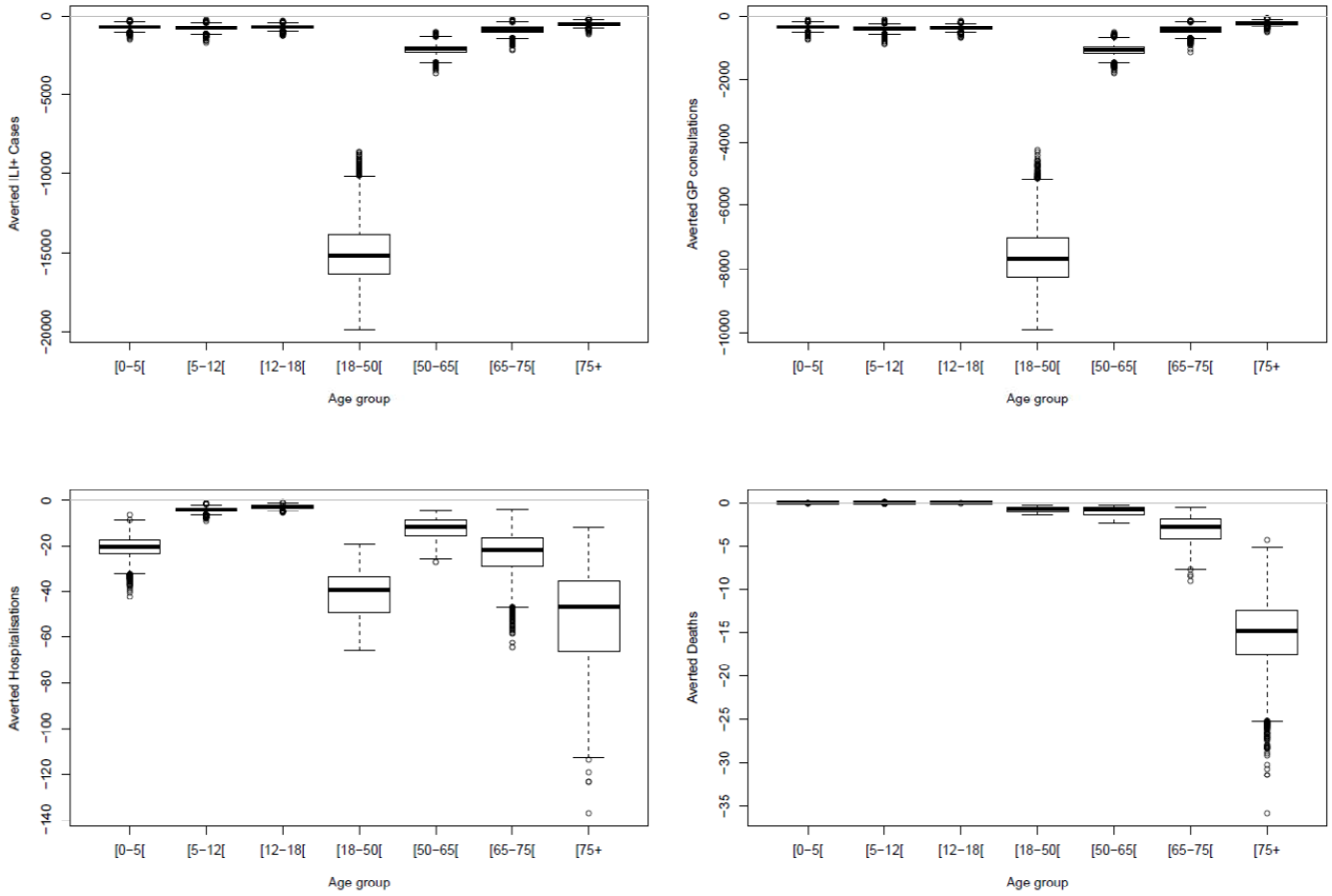
Assuming all child vaccination coverage levels remain as they are currently, we can estimate the incremental effectiveness and cost-effectiveness of these 23 adult target options.

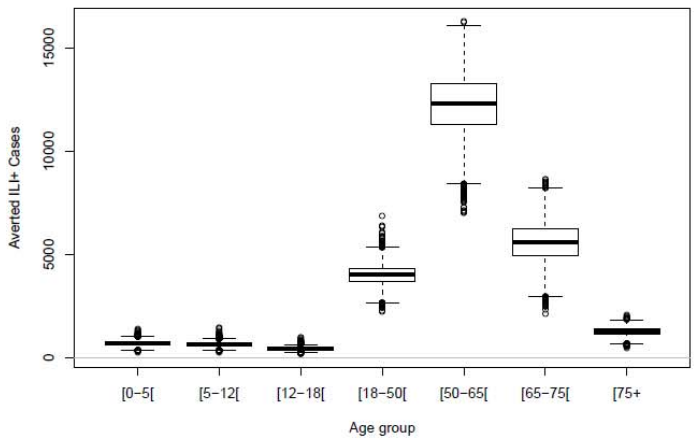
6.1.2.1 *Effectiveness versus current situation*

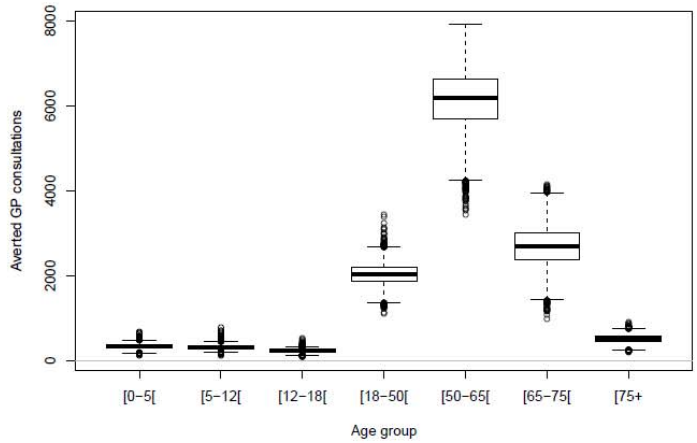
The most effective option (in terms of QALYs gained) amongst all adult options is the largest increase in vaccination coverage with no decrease in the 18-49 years of age (At11 in Table 53). The least effective option is the theoretical option of no longer vaccinating the 18-50 years of age (At12), thus decreasing the current coverage from 11% to 0%. In Figure 28, box plots show the per-season averaged averted numbers of cases of ILI+ (i.e. influenza), GP consultations, hospitalisations and deaths for the most effective and the least effective option (in terms of QALYs gained) amongst all the adult options versus the current situation.

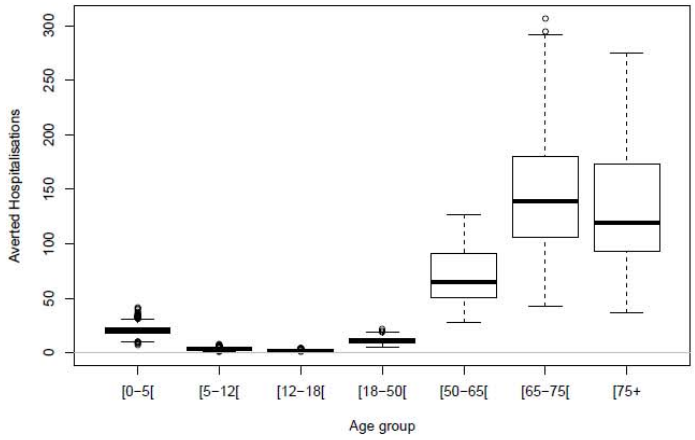
Figure 28 shows that the least effective option (i.e. reductions in vaccination coverage in the age group 18-49 years) would adversely impact all the health effects described, whereas the most effective option (improve coverage in all >50 years and keep current coverage in the 18-49 years of age) naturally would substantially reduce the disease burden in all age groups.

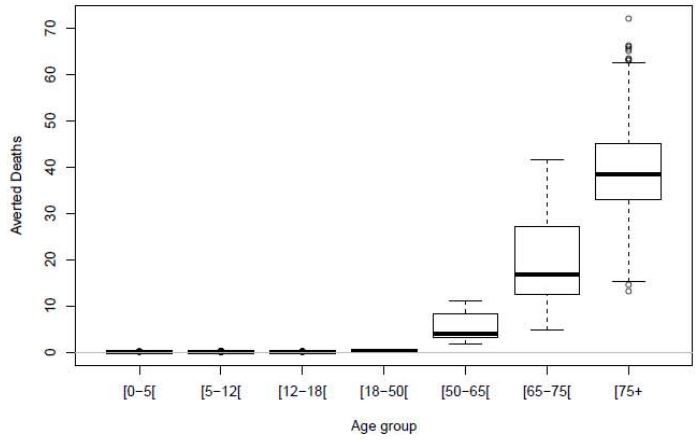
Figure 28 – Box plots of the per-season averaged averted numbers of cases of ILI+ (i.e. influenza), GP consultations, hospitalisations and deaths for the least (option At12: D 18-49, top) and the most (option At11: II 50-64 + I 65-75+, bottom) effective option (in terms of QALYs gained) amongst all the adult options in Table 53




Averted ILI+ Cases
0
5000
10000
15000
[0−5[
[5−12[
[12−18[
[18−50[
[50−65[
[65−75[
[75+
Age group


Averted GP consultations
0
2000
4000
6000
8000
[0−5[
[5−12[
[12−18[
[18−50[
[50−65[
[65−75[
[75+
Age group

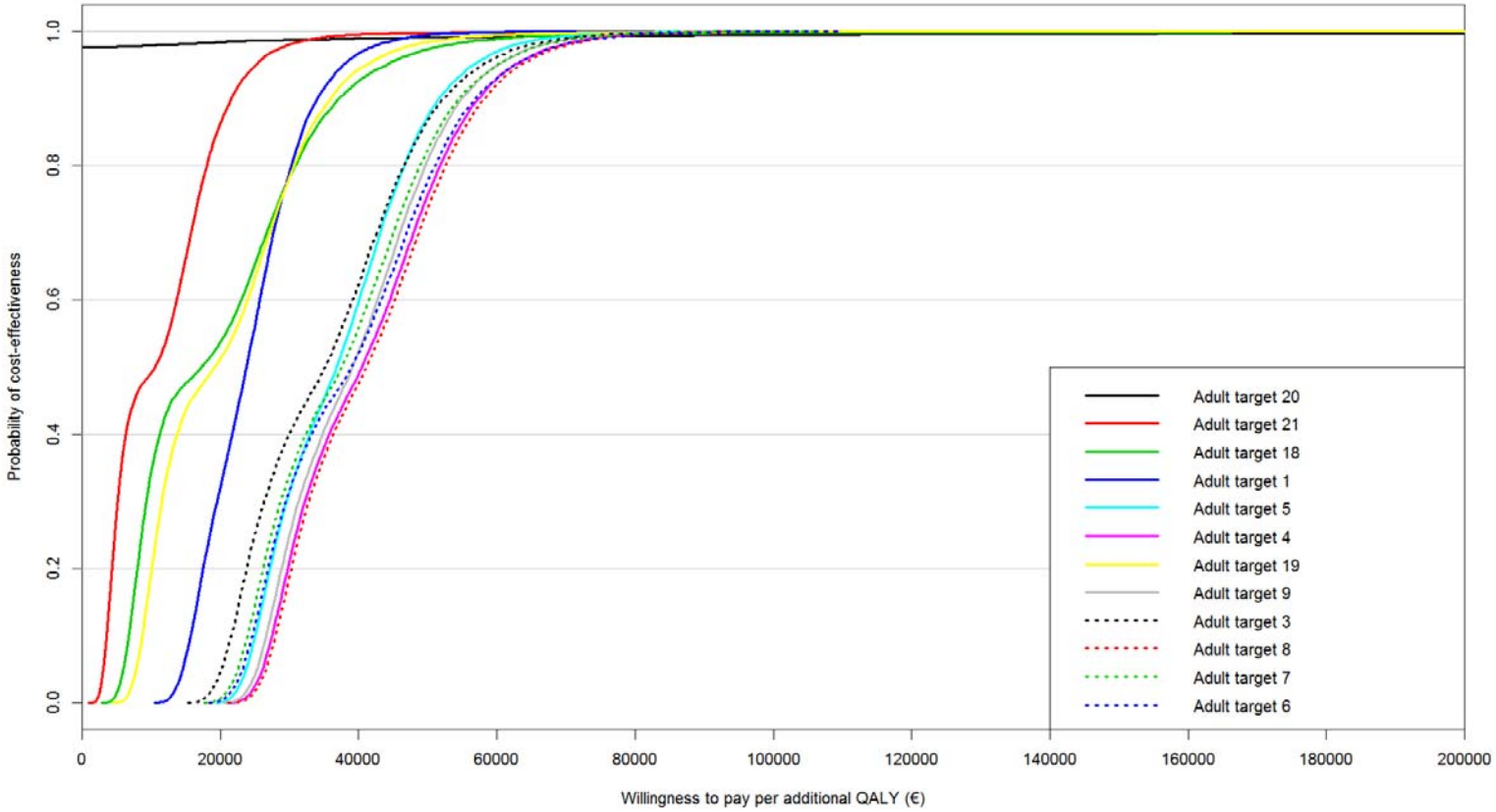

Averted Hospitalisations
0
50
100
150
200
250
300
[0−5[
[5−12[
[12−18[
[18−50[
[50−65[
[65−75[
[75+
Age group

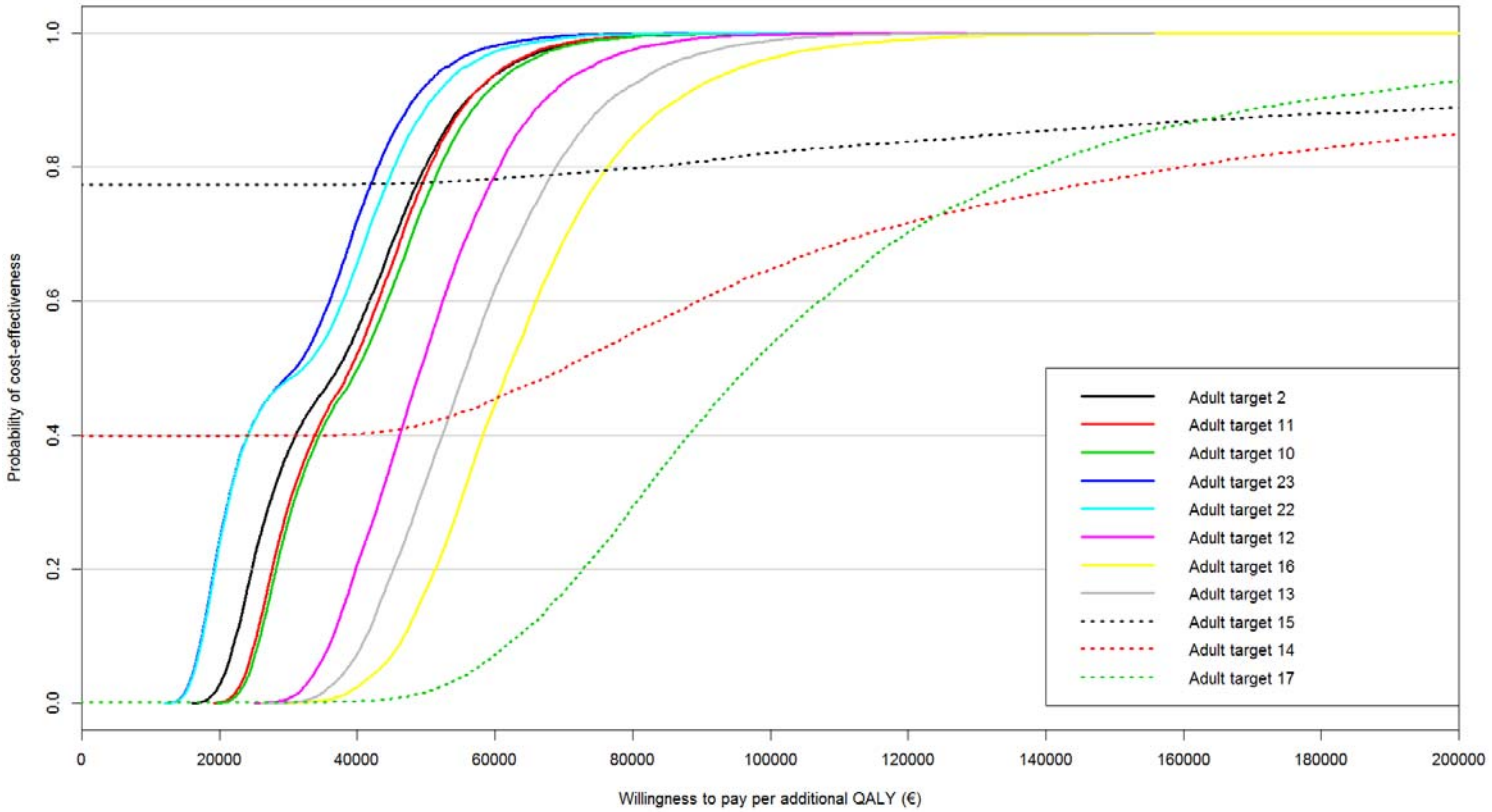

Averted Deaths
0
10
20
30
40
50
60
70
[0−5[
[5−12[
[12−18[
[18−50[
[50−65[
[65−75[
[75+
Age group

6.1.2.2 Cost-effectiveness versus current situation

Figure 29 shows the CEACs for the 23 adult target options versus the current situation. The cost-effectiveness of the 23 adult target options ranges from cost-saving to a median of almost €100 000 per QALY gained versus the current situation. Cost saving options, which cut the Y axis > 0, tend to show a much more uncertain (less steep) CEACs.

Figure 29 – CEACs for the 23 adult target options versus the current situation (split in two panels for clarity)





Vaccination options by age group (at=adult target):

At1: I 75+	*At7: I 50-75+*	*At13: D 18-49 + I 75+*	*At19: D18-49 + I 50-75+*
At2: I 65-74	*At8: II 50-64*	*At14: D18-49 + I 65-74*	*At20: D18-49 + II 50-64*
At3: I 65-75+	*At9: II 50-64 + I 75+*	*At15: D18-49 + I 65-75+*	*At21: D18-49 + II 50-64 + I 75+*
At4: I 50-64	*At10: II 50-64 + I 65-74*	*At16: D18-49 + I 50-64*	*At22: D18-49 + II 50-64 + I 65-74*
At5: I 50-64 + I 75+	*At11: II 50-64 + I 65-75+*	*At17: D18-49 + I 50-64 + I 75+*	*At23: D18-49 + II 50-64 + I 65-75+*
At6: I 50-74	*At12: D 18-59*	*At18: D18-49 + I 50-74*	

I: increase vaccination coverage; II: larger increase vaccination coverage (50-64 years only); D: decrease vaccination coverage.

6.1.2.3 Incremental analyses

None of the 23 strategies for adults were excluded by dominance, but 16 were excluded by extended dominance. The sequence of options in Table 54 shows the efficiency frontier (using the ICER compared to the next best option) for adult vaccination, whilst assuming child vaccination remains constant at very low levels of coverage. It shows that the sequence of optimal options is: At15→At20→At21→At18→At19→At23→At7→At11. The most attractive option (At15) in terms of net health care savings consists of reducing vaccination in the youngest adult group (18-50y) and increasing it in all elderly ≥65 years. In almost 80% of the simulations, these net health care savings are accompanied by a net gain in QALYs. In about 90% of the simulations this approach would yield an acceptable ICER at any level of willingness to pay (see Figure 30). It is followed by the reduction of vaccination in the 18-49 years old and increasing it in the 50-64 year olds (At20: D 18-49 + II 50-64), while vaccination in the other age groups remains constant (see Table 53). However, the incremental cost-effectiveness of At20 versus At15 is high at the median and highly uncertain. A small increase in coverage in those aged over 75 years would be the next most efficient option (At21: D 18-49 + II 50-64 + I 75+). This is followed in sequence by increasing vaccine uptake considerably in those aged 65-74 years (by 25%), but this at the expense of those aged 50-64y and 75+, who should at the same time receive fewer vaccines (At18: D 18-49 + I 50-74). The information in Table 54 with regard to the ICER is also shown in Figure 30, which presents the incremental CEACs of these strategies. Note that in Table 54 the incremental ICERs are not monotonously increasing along the expansion path. This seems mainly due to the small differences occurring in the denominator of the ratio, for some comparisons along the path. Since the incremental effectiveness can be very small (even changing signs between runs), and the results are not forced into some preconceived base case setting, but expressing joint parameter uncertainty at each paired comparison, the median ICER does not necessarily increase monotonously.

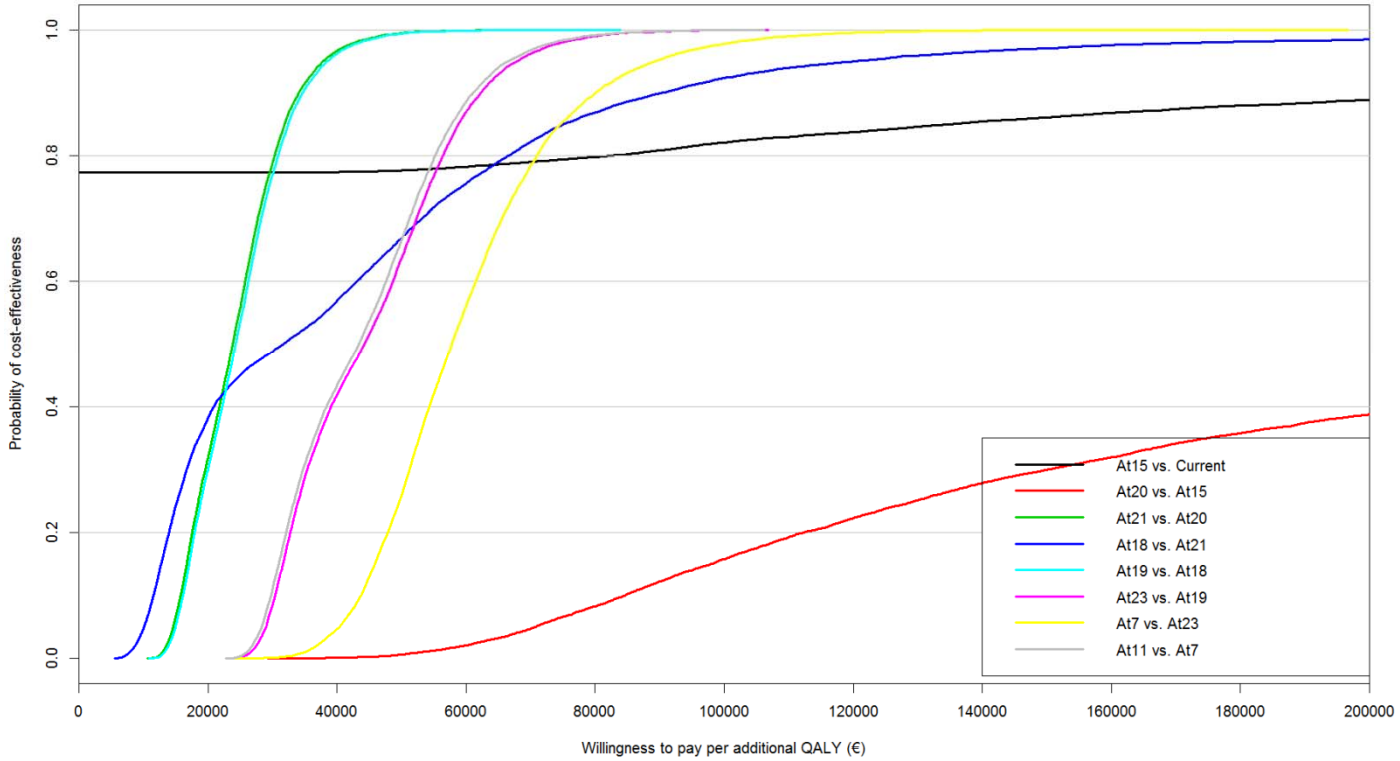
Table 54 – Incremental costs, life-years gained, QALYs gained and ICERs for adult vaccination options, whilst assuming child vaccination remains constant over a 10 year time span, and with immunity waning completely at a over an average period of 1.68 years

Vaccination option *	Median incremental cost	Median QALYs gained	Median life-years gained	Incremental direct costs per QALY gained			Incremental direct costs per life-year gained		
				Median	2.50%	97.50%	Median	2.50%	97.50%
Immunity lasts on average 1.68 years									
At15 vs. current	-29 694 662	314	1103	-44 036	-1 103 829	1 046 098	-26 791	-51 829	-16 081
At20 vs. At15	26 874 908	76	-514	96 141	-1 672 476	1 819 206	-52 131	-123 555	-30 012
At21 vs. At20	11 493 092	477	448	23 826	13 763	41 509	25 370	14 471	44 429
At18 vs. At21	12 806 913	406	505	31 392	8895	154 356	25 278	8307	63 394
At19 vs. At18	11 519 052	469	441	24 298	14 128	42 203	25 868	14 819	45 150
At23 vs. At19	62 567 580	1416	844	44 233	27 815	72 975	74 138	39 256	129 989
At7 vs. At23	64 871 488	1122	344	57 787	37 468	98 162	188 484	92 125	483 140
At11 vs. At7	62 440 424	1441	865	43 384	27 114	71 853	72 366	38 380	127 520

** Vaccination options by age group (at=adult target, I: increase vaccination coverage; II: larger increase vaccination coverage (50-64 years only); D: decrease vaccination coverage):*

At1: I 75+
At2: I 65-74
At3: I 65-75+
At4: I 50-64
At5: I 50-64 + I 75+
At6: I 50-74
At7: I 50-75+
At8: II 50-64
At9: II 50-64 + I 75+
At10: II 50-64 + I 65-74
At11: II 50-64 + I 65-75+
At12: D 18-49
At13: D 18-49 + I 75+
At14: D18-49 + I 65-74
At15: D18-49 + I 65-75+
At16: D18-49 + I 50-64
At17: D18-49 + I 50-64 + I 75+
At18: D18-49 + I 50-74
At19: D18-49 + I 50-75+
At20: D18-49 + II 50-64
At21: D18-49 + II 50-64 + I 75+
At22: D18-49 + II 50-64 + I 65-74
At23: D18-49 + II 50-64 + I 65-75+

Figure 30 – Incremental CEACs for remaining adult vaccination options after exclusion of dominated options, whilst assuming child vaccination remains constant over a 10 year time span, and with immunity waning completely over an average period of 1.68 years



Vaccination options by age group (at=adult target):

At1: I 75+	*At7: I 50-75+*	*At13: D 18-49 + I 75+*	*At19: D18-49 + I 50-75+*
At2: I 65-74	*At8: II 50-64*	*At14: D18-49 + I 65-74*	*At20: D18-49 + II 50-64*
At3: I 65-75+	*At9: II 50-64 + I 75+*	*At15: D18-49 + I 65-75+*	*At21: D18-49 + II 50-64 + I 75+*
At4: I 50-64	*At10: II 50-64 + I 65-74*	*At16: D18-49 + I 50-64*	*At22: D18-49 + II 50-64 + I 65-74*
At5: I 50-64 + I 75+	*At11: II 50-64 + I 65-75+*	*At17: D18-49 + I 50-64 + I 75+*	*At23: D18-49 + II 50-64 + I 65-75+*
At6: I 50-74	*At12: D 18-59*	*At18: D18-49 + I 50-74*	

I: increase vaccination coverage; II: larger increase vaccination coverage (50-64 years only); D: decrease vaccination coverage.

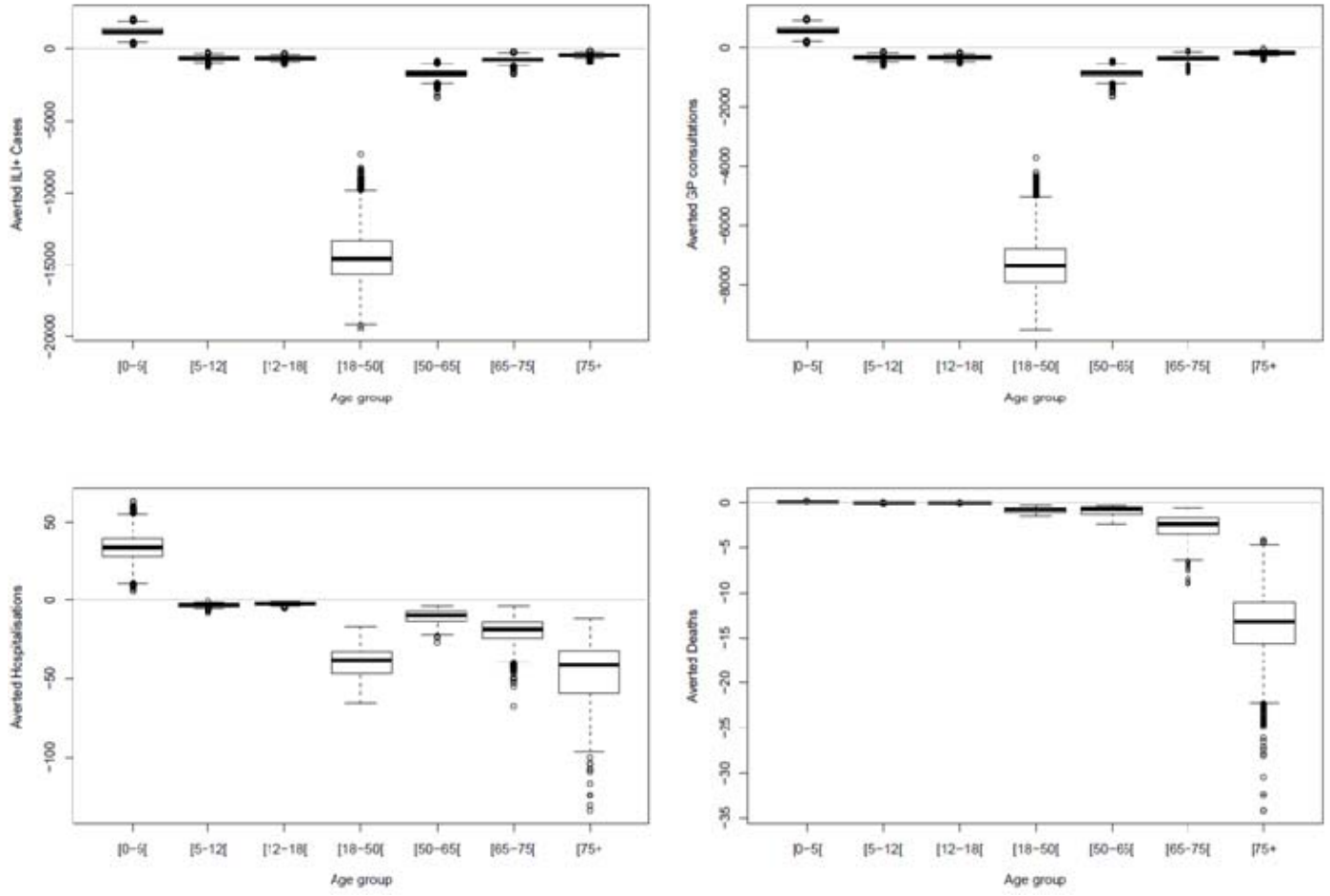
6.1.3 Modified children options + modified adult vaccination targets

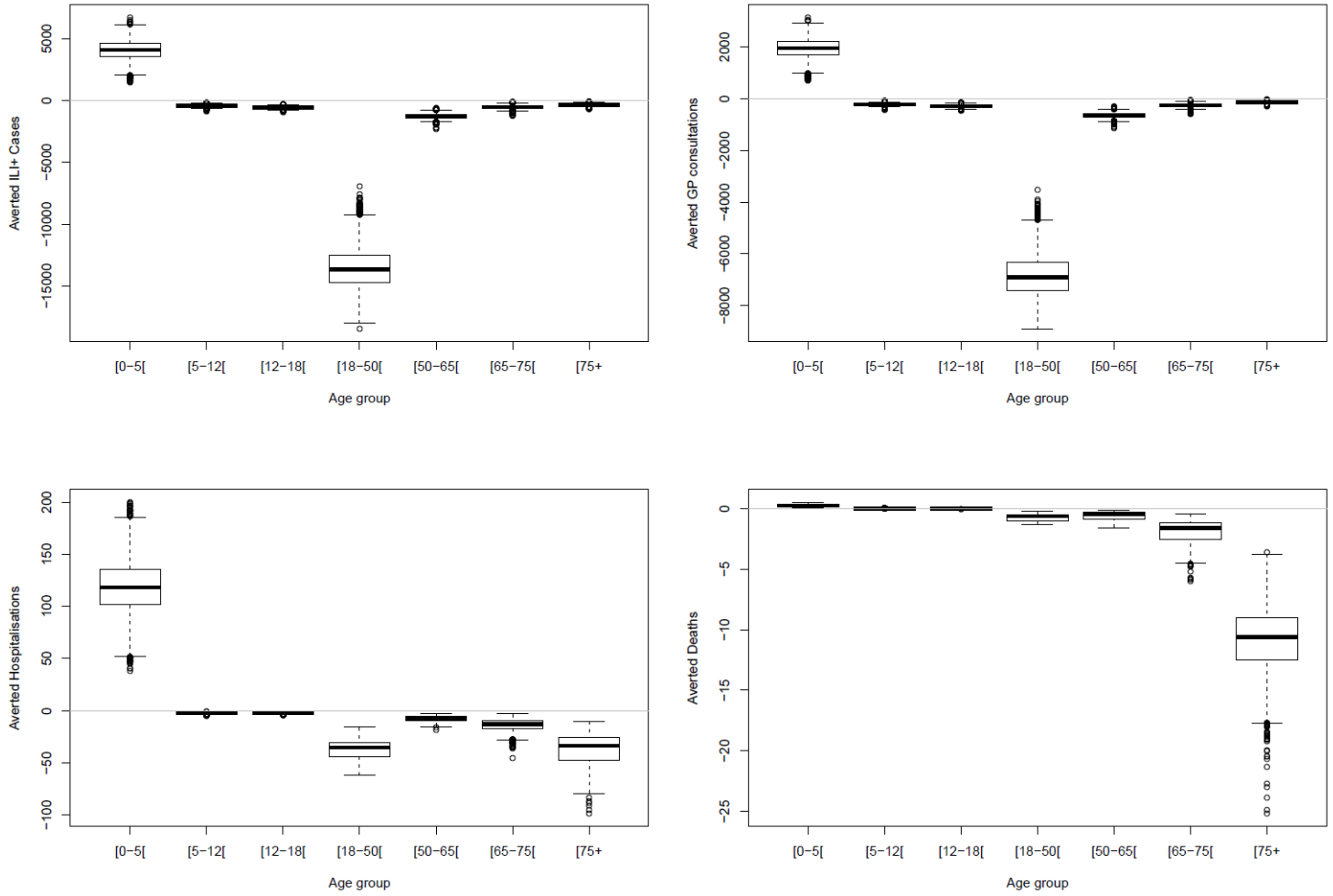
The options considered here combine the modified options considered in the previous two sections. That is, the 23 adult target options (Table 53), are combined with the 19 child options (Table 51) to yield 437 combined options, which are in a first step each compared to the current situation, and in a second step – after exclusion of (extended) dominated options – the subject of an incremental analysis.

6.1.3.1 Effectiveness versus current situation

In Figure 31 and Figure 32, box plots show the per-season averaged averted numbers of cases of ILI+ (i.e. influenza), GP consultations, hospitalisations and deaths for the most effective and the least effective option (in terms of QALYs gained) amongst all the combined child-adult options at 2 plausible vaccine coverage levels (30 and 80%) versus the current situation. A selection of these results can be found in Section 4 of Supplement 1.

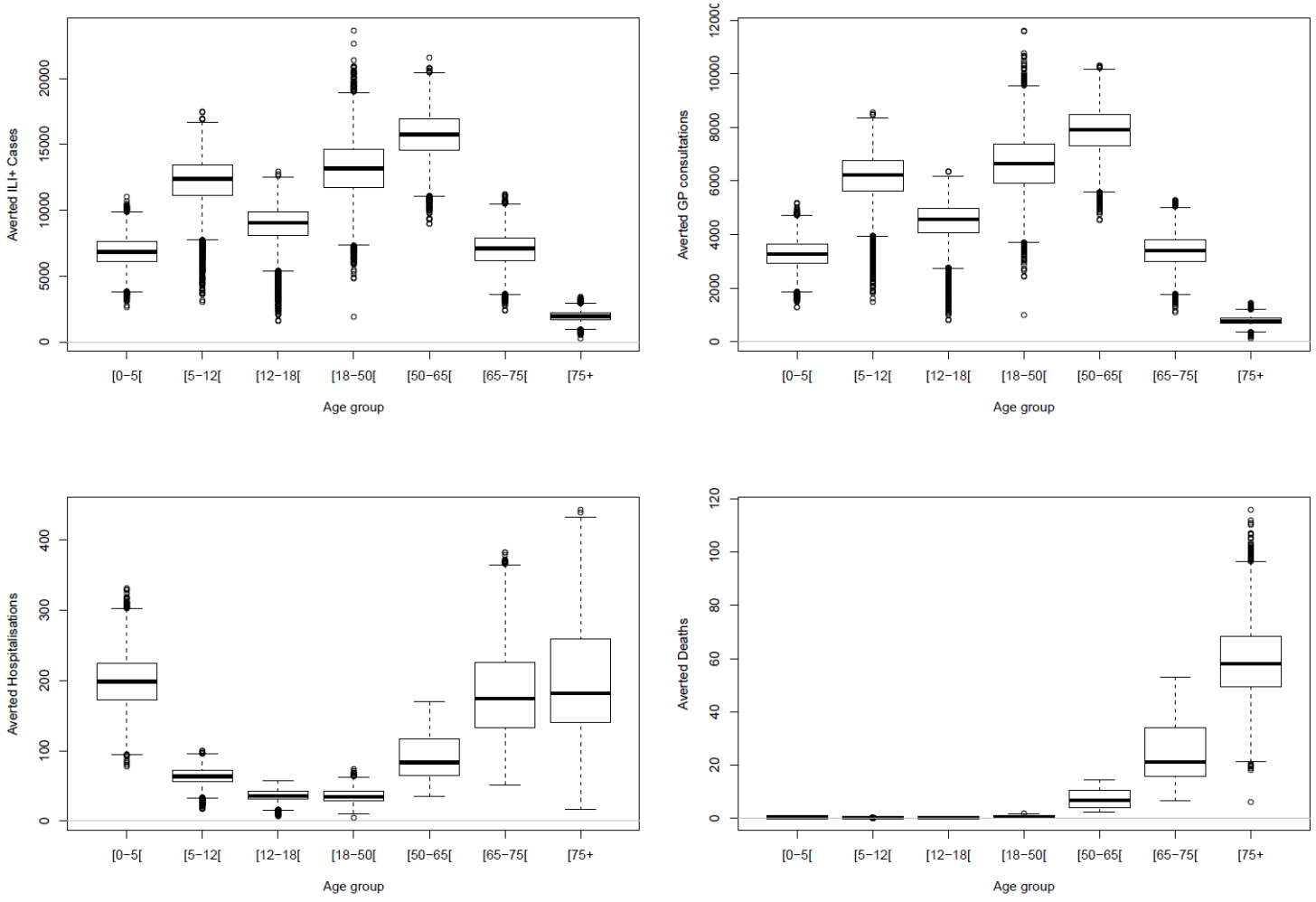
Figure 31 – Box plots of the per-season averaged averted numbers of cases of ILI+ (i.e. influenza), GP consultations, hospitalisations and deaths for the least effective option amongst 437 combined child-adult options at 30% (option At12c1, top) and 80% (option At12c2, bottom) coverage for the child components of the option

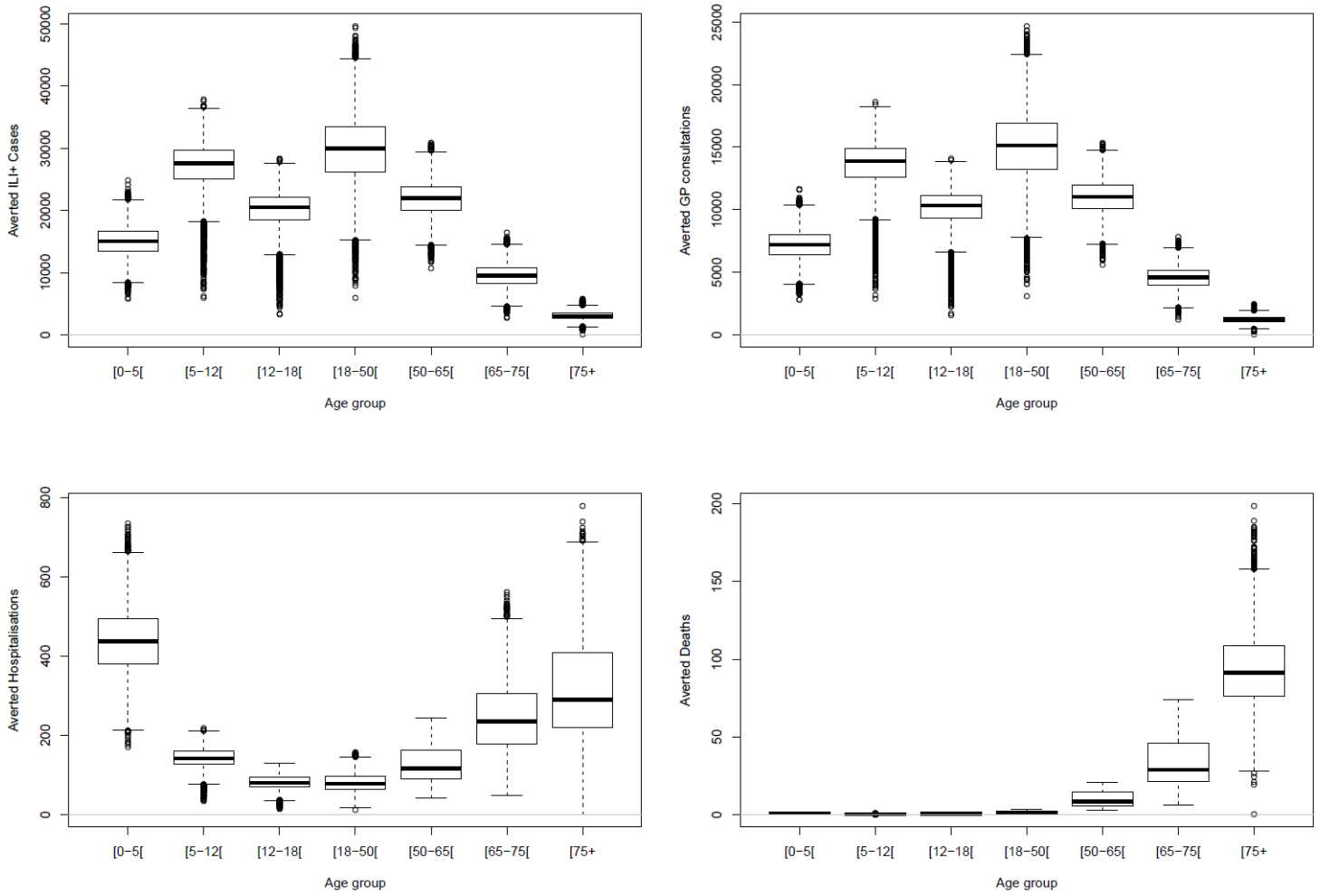




At12: D 18-49; c1: TIV 0.5-2; c2: TIV 2-5.

Figure 32 – Box plots of the per-season averaged averted numbers of cases of ILI+ (i.e. influenza), GP consultations, hospitalisations and deaths for the most effective option (At11c16) amongst 437 combined child-adult options at 30% (top) and 80% (bottom) coverage for the child components of the option



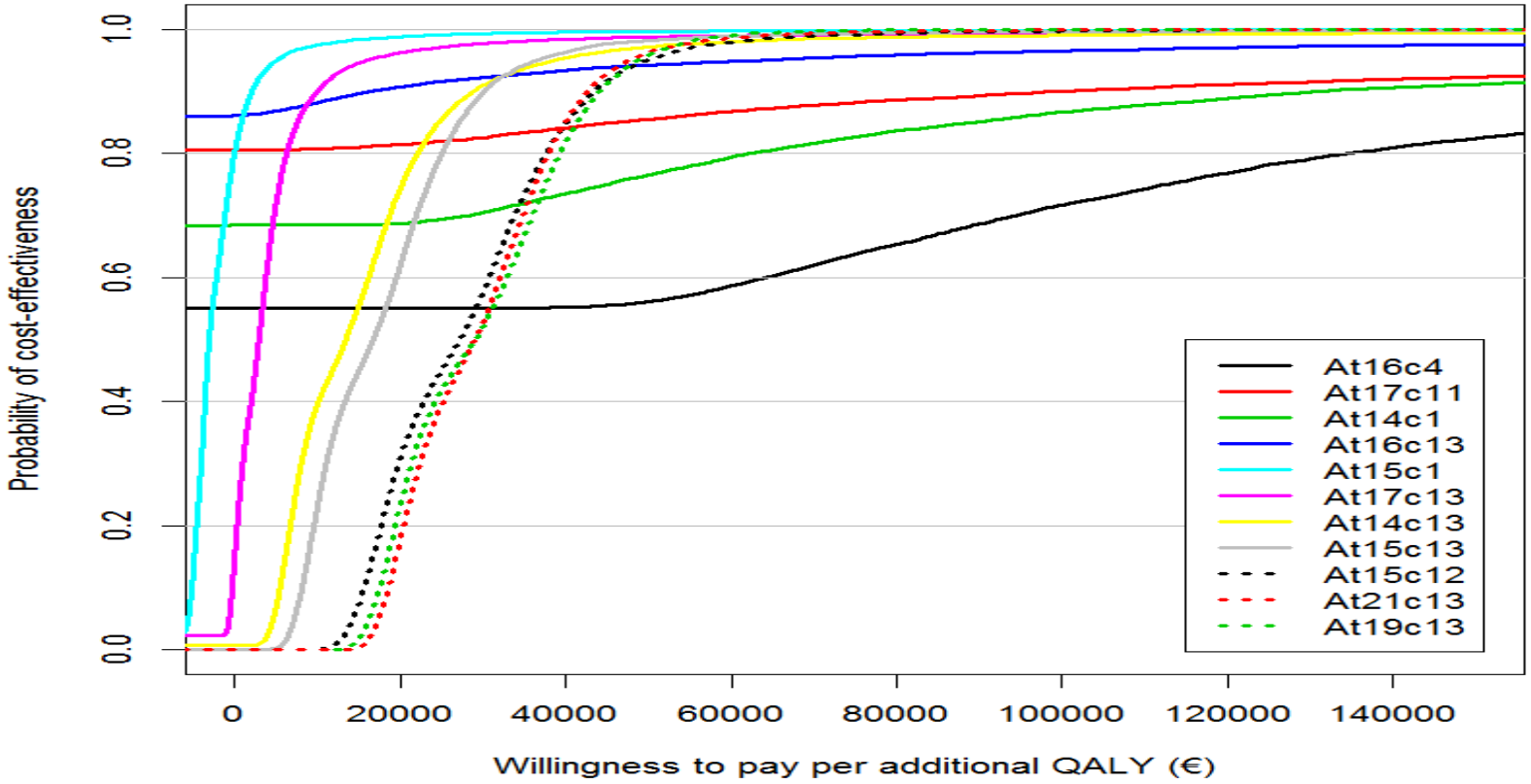


At11: II 50-64 + I 65-75+; c16: TIV 0.5-2 + LAIV 2-18.

6.1.3.2 Cost-effectiveness versus current situation

The figures below show that compared to the current situation many of these strategies can be considered cost-effective, while many of these CEACs indicate relatively little uncertainty (i.e. many CEACs are steep). Furthermore many options are very close to each other in the distribution of their ICERs, which implies that the comparison between them will be much more subject to uncertainty.

Figure 33 – CEACs for a selection of options versus the current situation at a coverage rate of 30% (2 panels)



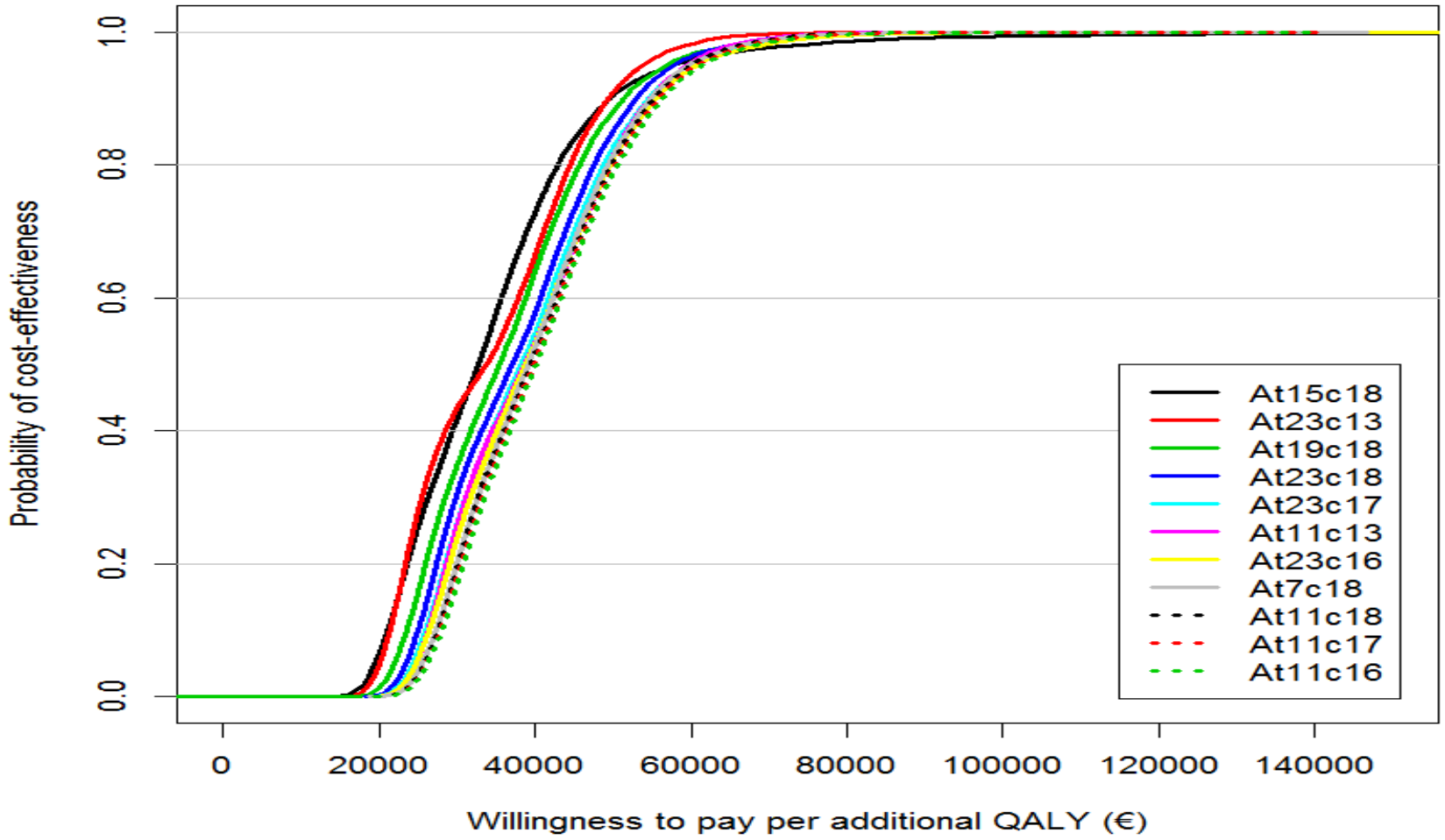
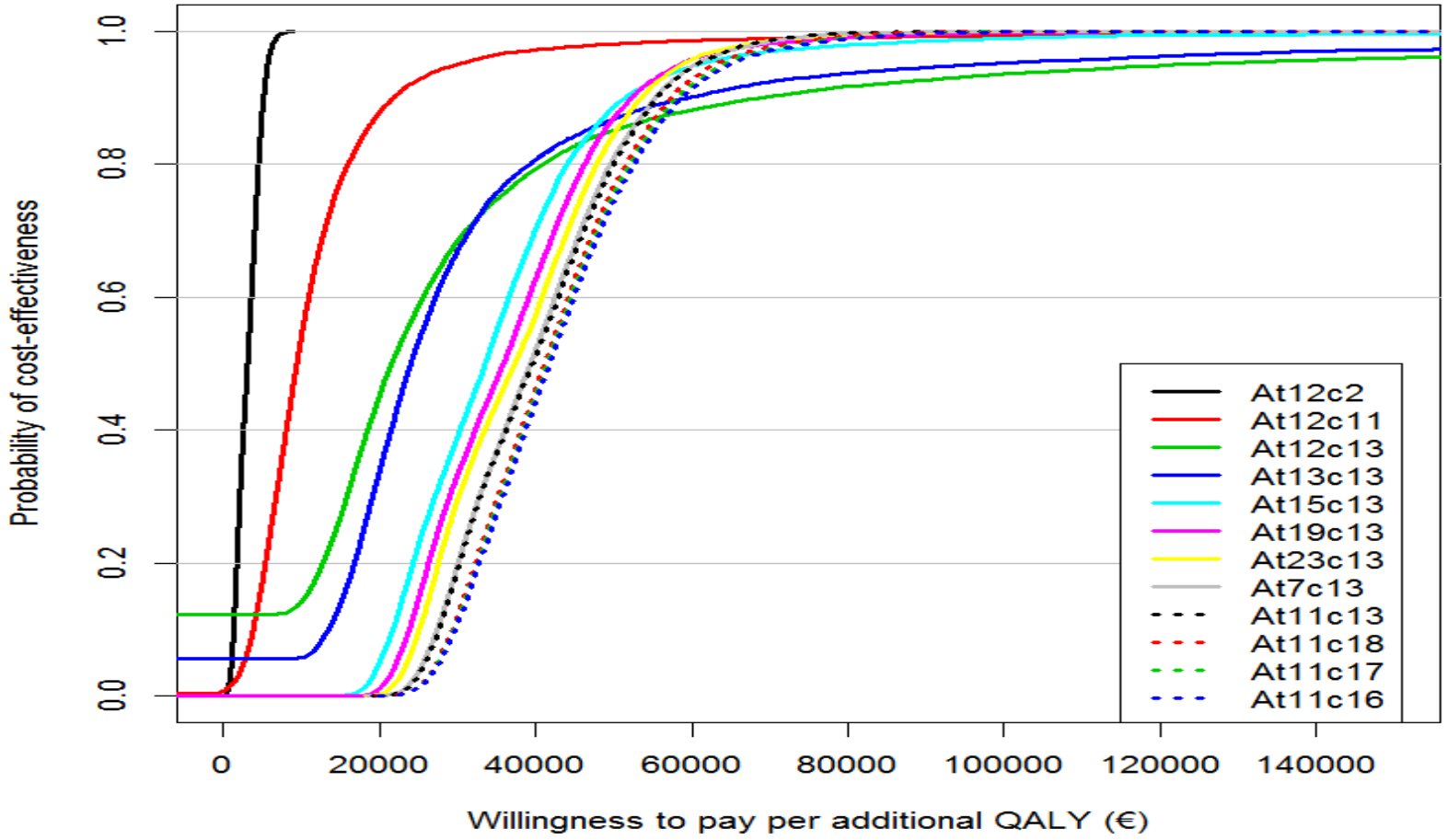

Probability of cost-effectiveness
0.0
0.2
0.4
0.6
0.8
1.0
0
20000
40000
60000
80000
100000
120000
140000
Willingness to pay per additional QALY (€)
At15c18
At23c13
At19c18
At23c18
At23c17
At11c13
At23c16
At7c18
At11c18
At11c17
At11c16

Figure 34 – CEACs for a selection of options versus the current situation at a coverage rate of 80%



6.1.3.3 Incremental cost-effectiveness analysis

At each of 9 levels of coverage at least 17 and a maximum of 24 options were selected out of 437 possible options. All in all 187 vaccination scenarios were selected out of a total of 3933 (437 x 9) considered in this part of the analyses. The sequence of options in Table 55 shows the efficiency frontier (using the ICER compared to the next best option) at a given level of coverage. The first option in the list (At17c12cov0.1) is per definition the most cost-effective option versus the current situation.

Figure 35 shows the CEACs associated with the analyses listed in Table 55. These analyses show that option At17c12 (adult: D 18-49 + I 50-64 + I 75+; child: LAIV 5-12) with 10% vaccination coverage leads to the greatest cost-effectiveness versus the current situation. The ICER for these incremental analyses is generally less favorable compared to the analyses using a waning immunity at 1/6 years (Table 61). The preference in the selection of the most clinically effective At11 (II 50-64 + I 65-75+) adult vaccination option occurs at a low coverage for vaccination in children, and without all children <18 years being included in the programme (and the sequence of including children runs from the oldest to the youngest).

Table 55 – Incremental costs, life-years gained, QALYs gained and ICERs (€) for non-dominated options among 3933 child-adult vaccination scenarios over a 10 year time span, and with immunity lasting on average 1.68 years (results based on 10 000 simulations for each vaccination scenario)

Vaccination option *	Median incremental cost	Median QALYs gained	Median life-years gained	Incremental direct costs per QALY gained			Incremental direct costs per life-year gained		
				Median	2.50%	97.50%	Median	2.50%	97.50%
At17c12cov0.1 vs. current	-271 031 133	7	355	-74 006	-2 232 729	2 393 621	-75 392	-215 784	- 41 560
At17c4cov0.2 vs. At17c12cov0.1	11 605 056	152	104	65 639	-568 455	775 179	108 026	21 193	646 156
At17c19cov0.1 vs. At17c4cov0.2	287 468	98	9	-703	-55 470	49 988	-6 916	-99 278	84 603
At17c13cov0.2 vs. At17c19cov0.1	-1 309 555	122	61	-10 324	-41 633	23 255	-19 925	-100 678	42 313
At15c1cov0.1 vs. At17c13cov0.2	-4 154 869	106	643	-10 033	-178 751	165 027	-6 434	-9 813	-4 142
At15c11cov0.1 vs. At15c1cov0.1	5 750 165	119	46	48 153	29 227	134 048	122 362	56 522	445 988
At15c1cov0.2 vs. At15c11cov0.1	3 488 345	5	10	45 049	-1 730 675	1 815 413	146 002	-2 985 154	3 355 969
At15c4cov0.1 vs. At15c1cov0.2	778 583	100	37	7 811	2 895	17 786	21 188	5 987	74 739
At15c13cov0.1 vs. At15c4cov0.1	-524 982	114	37	-4 628	-7 169	-2 733	-11 547	-53 867	29 689
At15c12cov0.1 vs. At15c13cov0.1	8 192 502	96	21	85 043	58 295	137 961	382 810	153 238	1 455 175
At15c13cov0.2 vs. At15c12cov0.1	10 677 693	353	161	30 092	16 118	99 880	65 393	27 963	253 621
At15c18cov0.1 vs. At15c13cov0.2	7 999 605	109	27	73 574	50 922	117 099	297 547	140 986	893 419

At15c13cov0.3 vs. At15c18cov0.1	10 914 904	330	152	32 820	17 908	106 666	70 790	31 015	263 557
At15c16cov0.1 vs. At15c13cov0.3	7 162 199	22	5	125 904	-2 761 271	2 845 438	155 030	-6 127 195	5 614 961
At15c13cov0.4 vs. At15c16cov0.1	11 783 040	405	169	28 663	15 158	113 557	67 554	-76 864	312 230
At19c13cov0.1 vs. At15c13cov0.4	5 535 411	153	374	8 880	-324 736	346 028	14 627	1 174	93 207
At15c13cov0.5 vs. At19c13cov0.1	13 426 650	273	-193	26 099	-413 060	433 428	-51 005	-787 792	605 366
At19c13cov0.2 vs. At15c13cov0.5	5 344 897	195	393	10 090	-317 674	304 802	13 518	1 174	73 864
At19c18cov0.1 vs. At19c13cov0.2	7 989 719	110	28	72 256	49 934	114 798	286 571	135 624	834 452
At19c13cov0.3 vs. At19c18cov0.1	10 888 095	337	156	32 087	17 523	104 668	68 897	30 251	250 747
At19c13cov0.4 vs. At19c13cov0.3	18 937 799	436	180	43 395	26 994	100 916	104 891	51 817	299 149
At19c13cov0.5 vs. At19c13cov0.4	18 990 392	424	176	44 686	27 914	102 856	107 702	53 774	308 812
At23c13cov0.2 vs. At19c13cov0.5	5 648 119	124	349	8 783	-343 610	334 135	15 977	1 451	104 305
At19c13cov0.6 vs. At23c13cov0.2	13 332 107	297	-167	26 654	-360 040	394 826	-53 333	-971 293	704 407
At23c13cov0.3 vs. At19c13cov0.6	5 449 766	169	369	10 394	-360 508	317 222	14 649	1 505	81 369
At23c13cov0.4 vs. At23c13cov0.3	18 900 905	443	185	42 574	26 389	98 607	102 046	50 389	289 825
At23c13cov0.5 vs. At23c13cov0.4	18 953 539	432	180	43 870	27 405	100 512	104 712	52 363	302 960
At23c13cov0.6 vs. At23c13cov0.5	19 012 496	419	176	45 310	28 514	102 039	107 954	54 565	310 938
At23c13cov0.7 vs. At23c13cov0.6	19 071 421	406	171	46 902	29 742	103 892	111 491	56 603	314 211
At23c18cov0.3 vs. At23c13cov0.7	4 892 435	35	-35	53 418	-1 101 698	1 177 535	-93 087	-1 228 652	1 086 196
At23c13cov0.8 vs. At23c18cov0.3	14 245 824	358	199	39 025	18 225	167 003	69 911	28 473	287 653
At23c13cov0.9 vs. At23c13cov0.8	19 196 324	379	160	50 655	32 614	107 907	119 664	62 234	322 690
At23c18cov0.4 vs. At23c13cov0.9	12 492 119	278	57	44 823	21 935	105 140	189 249	-1 338 920	2 123 714
At11c13cov0.4 vs. At23c18cov0.4	18 983 038	354	386	36 439	-498 059	653 593	48 323	10 601	257 018
At11c13cov0.5 vs. At11c13cov0.4	18 842 896	457	197	41 121	25 476	93 836	95 576	47 514	265 292
At11c13cov0.6 vs. At11c13cov0.5	18 906 563	443	191	42 597	26 555	95 210	98 679	49 364	272 130
At11c13cov0.7 vs. At11c13cov0.6	18 969 666	428	185	44 274	27 853	96 985	102 176	51 744	278 788

At11c18cov0.3 vs. At11c13cov0.7	4 734 012	68	-17	49 600	-654 329	790 618	-89 341	-1 629 658	1 268 082
At11c13cov0.8 vs. At11c18cov0.3	14 315 196	344	193	40 699	17 787	178 953	72 044	28 003	315 038
At11c18cov0.4 vs. At11c13cov0.8	31 269 094	739	272	42 297	24 133	73 487	114 785	48 636	278 601
At11c18cov0.5 vs. At11c18cov0.4	45 671 604	1 067	464	42 799	26 314	87 565	98 441	48 313	247 365
At11c17cov0.4 vs. At11c18cov0.5	1 731 597	15	47	15 353	-657 199	573 995	35 901	5 086	277 801
At11c18cov0.6 vs. At11c17cov0.4	44 022 472	1 024	409	43 013	27 107	85 359	107 471	52 924	286 628
At11c17cov0.5 vs. At11c18cov0.6	13 263 080	315	192	42 071	19 920	118 705	69 321	30 035	177 322
At11c16cov0.5 vs. At11c17cov0.5	30 251 143	660	338	45 835	25 423	94 549	89 705	42 076	205 829
At11c18cov0.7 vs. At11c16cov0.5	2 324 628	23	-80	7 010	-373 176	359 925	-25 762	-160 269	50 320
At11c17cov0.6 vs. At11c18cov0.7	24 635 249	612	338	40 150	20 945	98 109	72 975	33 425	183 945
At11c16cov0.6 vs. At11c17cov0.6	36 087 381	789	406	45 712	25 447	94 654	88 842	42 036	205 666
At11c17cov0.7 vs. At11c16cov0.6	20 835 499	468	169	44 302	27 444	109 556	120 921	53 041	446 607
At11c16cov0.7 vs. At11c17cov0.7	41 758 456	910	471	45 871	25 947	95 438	88 759	42 556	207 486
At11c17cov0.8 vs. At11c16cov0.7	14 515 713	281	82	51 010	25 279	166 653	163 117	-558 787	1 095 880
At11c16cov0.8 vs. At11c17cov0.8	47 222 017	1 021	527	46 184	26 410	96 794	89 513	43 226	208 913
At11c17cov0.9 vs. At11c16cov0.8	7 551 129	97	-8	55 326	-668 471	721 196	-84 755	-2 736 975	2 701 633
At11c16cov0.9 vs. At11c17cov0.9	52 571 071	1 122	580	46 810	26 902	98 263	90 434	44 327	211 738

** The options should be read as follows: at# stands for a particular adult vaccination option (see also Table 53); c# stands for a particular child option (see Table 51), covp stands for modelled vaccination coverage p for the child option c#.*

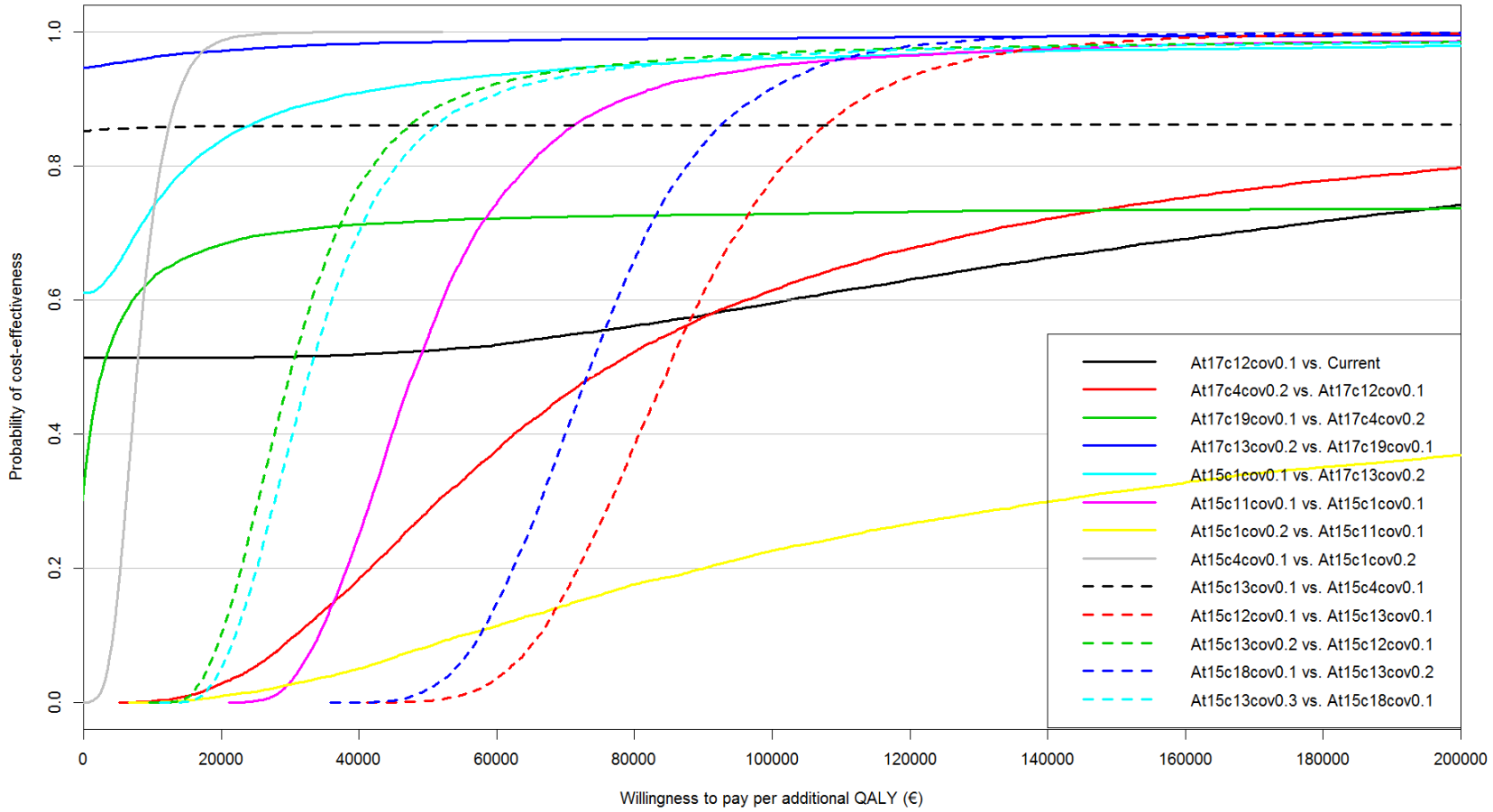
Adults vaccination options by age group (at=adult target, I= increase vaccination coverage; II: larger increase vaccination coverage (50-64 years only); D= decrease vaccination coverage):

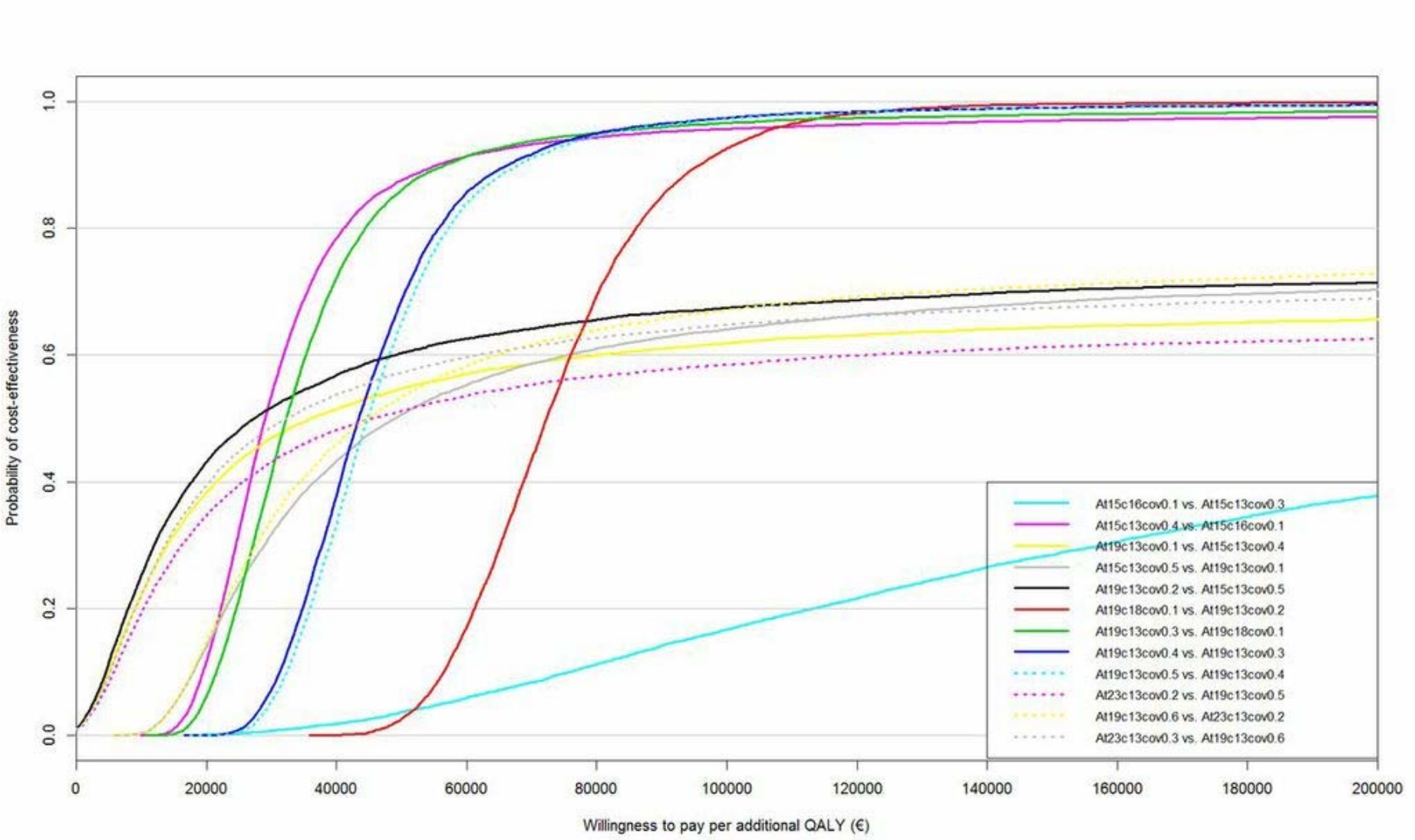
At1: I 75+	*At5: I 50-64 + I 75+*	*At9: II 50-64 + I 75+*	*At13: D 18-49 + I 75+*	*At17: D18-49 + I 50-64 + I 75+*	*At21: D18-49 + II 50-64 + I 75+*
At2: I 65-74	*At6: I 50-74*	*At10: II 50-64 + I 65-74*	*At14: D18-49 + I 65-74*	*At18: D18-49 + I 50-74*	*At22: D18-49 + II 50-64 + I 65-74*
At3: I 65-75+	*At7: I 50-75+*	*At11: II 50-64 + I 65-75+*	*At15: D18-49 + I 65-75+*	*At19: D18-49 + I 50-75+*	*At23: D18-49 + II 50-64 + I 65-75+*
At4: I 50-64	*At8: II 50-64*	*At12: D 18-49*	*At16: D18-49 + I 50-64*	*At20: D18-49 + II 50-64*	

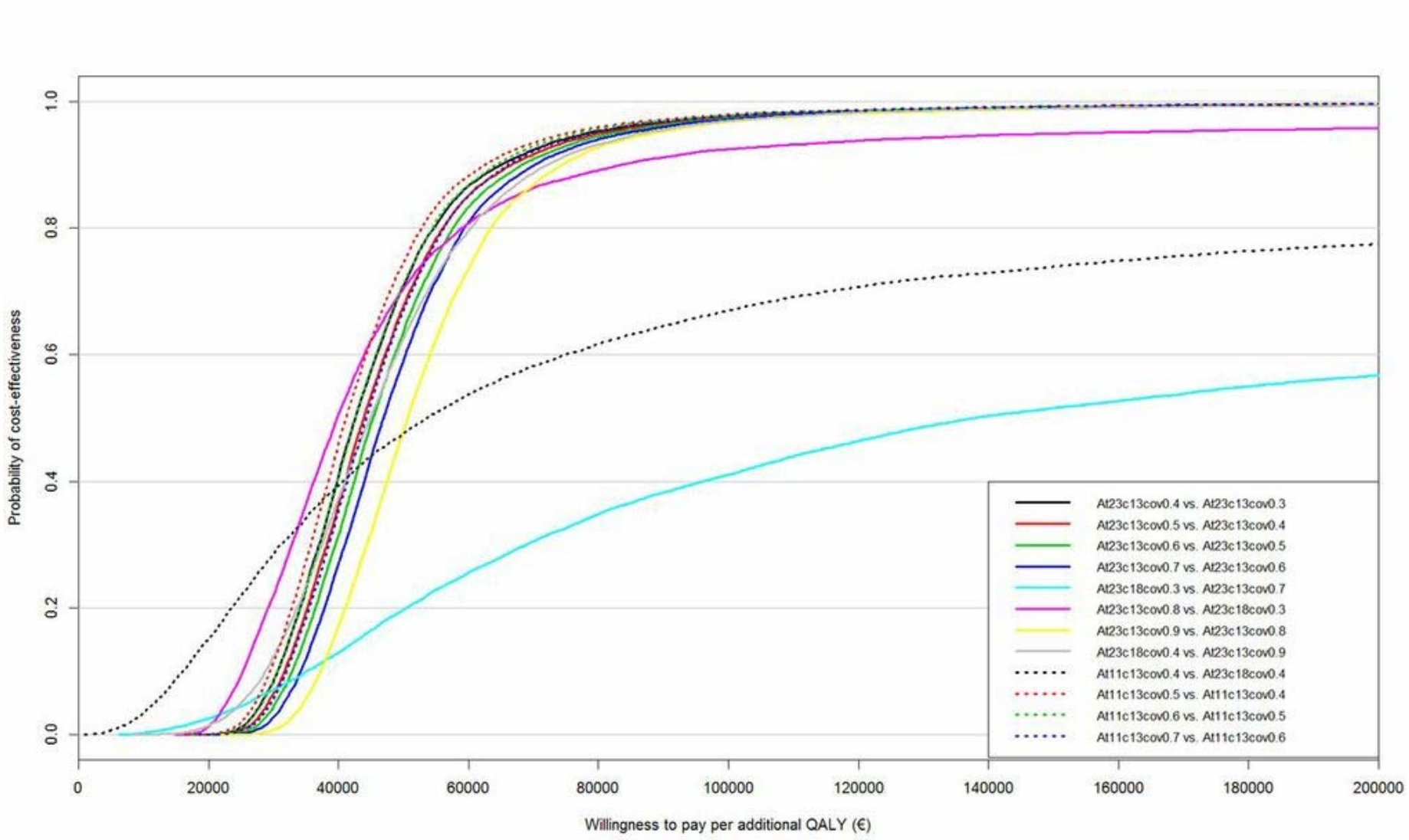
Child vaccination options by age group (c=child option):

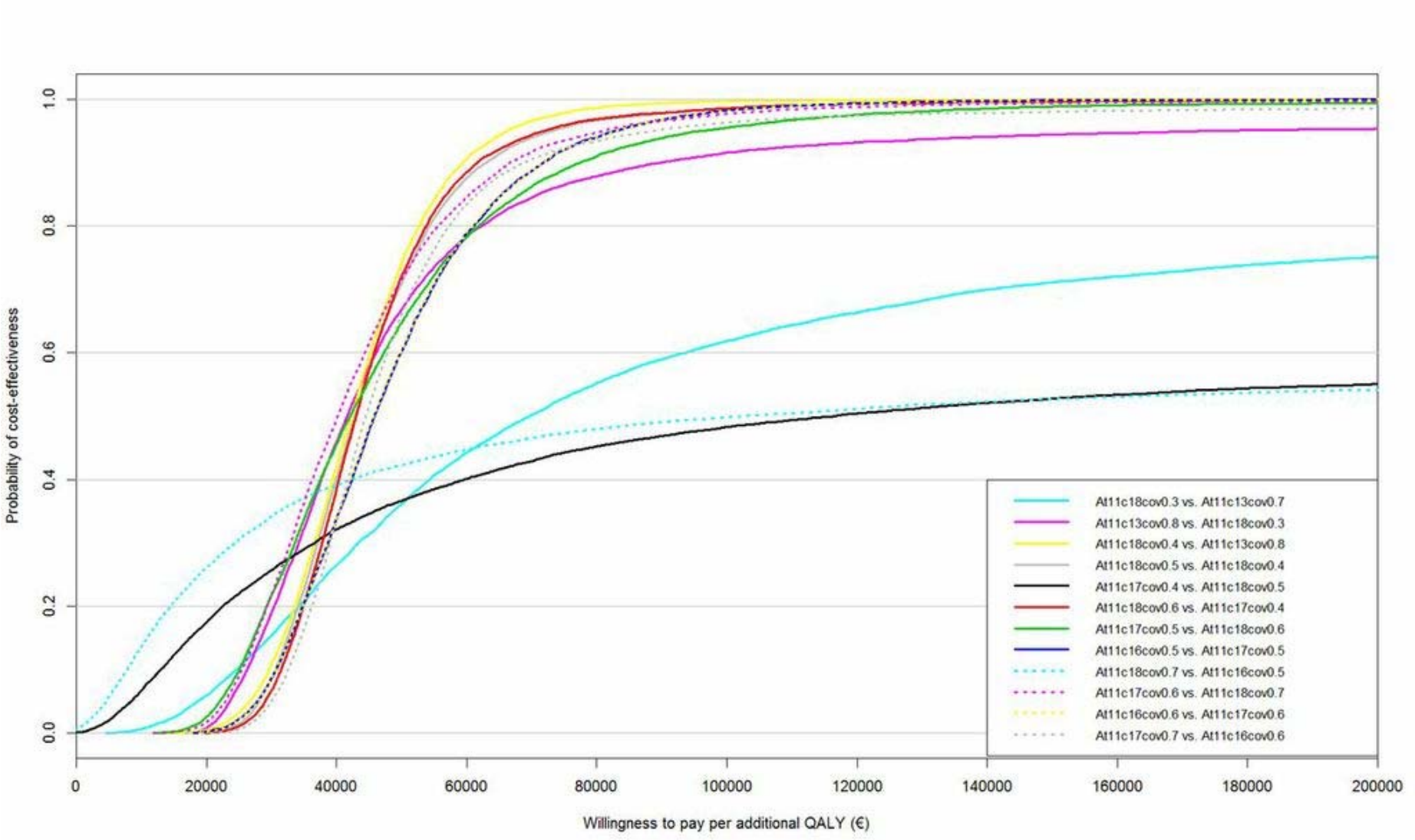
c1: TIV 0.5-2	*c5: IV 0.5-5*	*c8: TIV 2-18*	*c11: LAIV 2-5*	*c14: TIV 0.5-2 + LAIV 2-5*	*c17: LAIV 2-18*
c2: TIV 2-4	*c6: TIV 0.5-12*	*c9:TIV 5-18*	*c12: LAIV 5-12*	*c15: TIV 0.5-2+ LAIV 2-12*	*c18: LAIV 5-18*
c3: TIV 5-12	*c7: TIV 0.5-18*	*c10: TIV 2-12*	*c13: LAIV 12-18*	*c16: TIV 0.5-2 + LAIV 2-18*	*c19: LAIV 2-12*
c4: TIV 12-18					

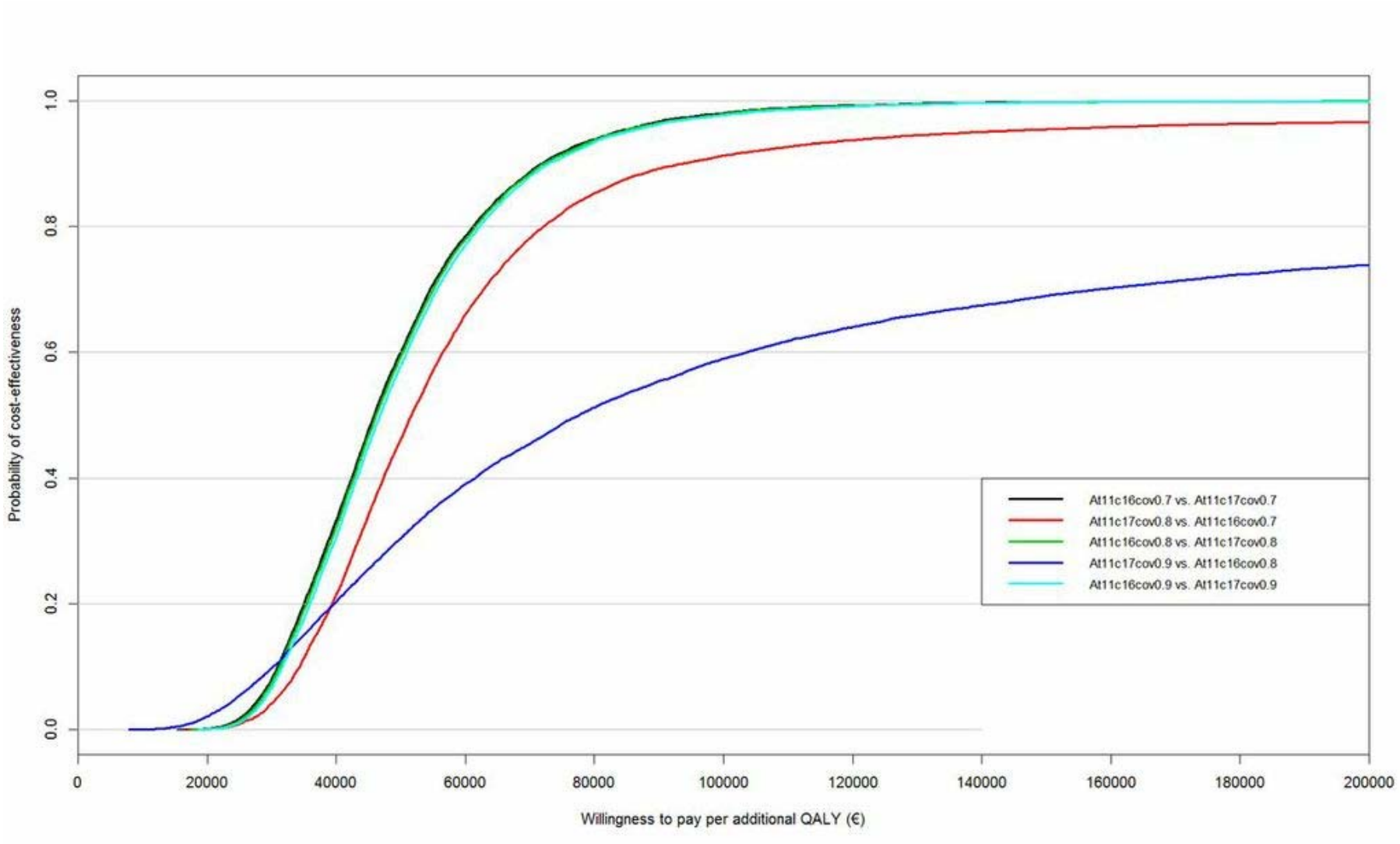
Figure 35 – CEACs of the incremental analyses on child-adult combined vaccination options after elimination of dominated options for all coverage levels of the child components of the options combined (immunity lasting on average 1.68 years) (5 panels)




Probability of cost-effectiveness
0.0
0.2
0.4
0.6
0.8
1.0
0
20000
40000
60000
80000
100000
120000
140000
160000
180000
200000
Willingness to pay per additional QALY (€)
At15c16cov0.1 vs. At15c13cov0.3
At15c13cov0.4 vs. At15c16cov0.1
At19c13cov0.1 vs. At15c13cov0.4
At15c13cov0.5 vs. At19c13cov0.1
At19c13cov0.2 vs. At15c13cov0.5
At19c18cov0.1 vs. At19c13cov0.2
At19c13cov0.3 vs. At19c18cov0.1
At19c13cov0.4 vs. At19c13cov0.3
At19c13cov0.5 vs. At19c13cov0.4
At23c13cov0.2 vs. At19c13cov0.5
At19c13cov0.6 vs. At23c13cov0.2
At23c13cov0.3 vs. At19c13cov0.6


Probability of cost-effectiveness
0.0
0.2
0.4
0.6
0.8
1.0
0
20000
40000
60000
80000
100000
120000
140000
160000
180000
200000
Willingness to pay per additional QALY (€)
At23c13cov0.4 vs. At23c13cov0.3
At23c13cov0.5 vs. At23c13cov0.4
At23c13cov0.6 vs. At23c13cov0.5
At23c13cov0.7 vs. At23c13cov0.6
At23c18cov0.3 vs. At23c13cov0.7
At23c13cov0.8 vs. At23c18cov0.3
At23c13cov0.9 vs. At23c13cov0.8
At23c18cov0.4 vs. At23c13cov0.9
At11c13cov0.4 vs. At23c18cov0.4
At11c13cov0.5 vs. At11c13cov0.4
At11c13cov0.6 vs. At11c13cov0.5
At11c13cov0.7 vs. At11c13cov0.6


Probability of cost-effectiveness
0.0
0.2
0.4
0.6
0.8
1.0
0
20000
40000
60000
80000
100000
120000
140000
160000
180000
200000
Willingness to pay per additional QALY (€)
At11c18cov0.3 vs. At11c13cov0.7
At11c13cov0.8 vs. At11c18cov0.3
At11c18cov0.4 vs. At11c13cov0.8
At11c18cov0.5 vs. At11c18cov0.4
At11c17cov0.4 vs. At11c18cov0.5
At11c18cov0.6 vs. At11c17cov0.4
At11c17cov0.5 vs. At11c18cov0.6
At11c16cov0.5 vs. At11c17cov0.5
At11c18cov0.7 vs. At11c16cov0.5
At11c17cov0.6 vs. At11c18cov0.7
At11c16cov0.6 vs. At11c17cov0.6
At11c17cov0.7 vs. At11c16cov0.6


Probability of cost-effectiveness
0.0
0.2
0.4
0.6
0.8
1.0
0
20000
40000
60000
80000
100000
120000
140000
160000
180000
200000
Willingness to pay per additional QALY (€)
At11c16cov0.7 vs. At11c17cov0.7
At11c17cov0.8 vs. At11c16cov0.7
At11c16cov0.8 vs. At11c17cov0.8
At11c17cov0.9 vs. At11c16cov0.8
At11c16cov0.9 vs. At11c17cov0.9

6.1.4 *Modified children options + modified adult vaccination reduction*

The modified adult options in this section differ from the adult targets in the previous sections, in that here the focus is on reducing vaccinations in the various adult age groups. The main question we address here is: can we afford to relax the adult vaccination when we start vaccinating children, and what would be the cost-effectiveness of such adaptations to the existing adult vaccination? Therefore we combine here the 9 adult options in Table 56 with the 19 child options in Table 51 (i.e. to explore 171 combined options).

Table 56 – Adult vaccination options to explore potential decreases in adult vaccination in the presence of expanded children vaccination (i.e. to be combined with the child options in Table 51)

Option	[18-50[	[50-65[	[65-75[	[75-85[	[85-95[	[95+
a1	-	-	-	-	-	-
a2	TIV current	TIV current	TIV current	TIV current	TIV current	TIV current
a3	-	TIV current	TIV current	TIV current	TIV current	TIV current
a4	-	-	TIV current	TIV current	TIV current	TIV current
a5	-	-	-	TIV current	TIV current	TIV current
a6	-	-	TIV current	TIV current	TIV current	-
a7	-	-	TIV current	TIV current	-	-
a8	-	TIV current	TIV current	TIV current	TIV current	-
a9	-	TIV current	TIV current	TIV current	-	-

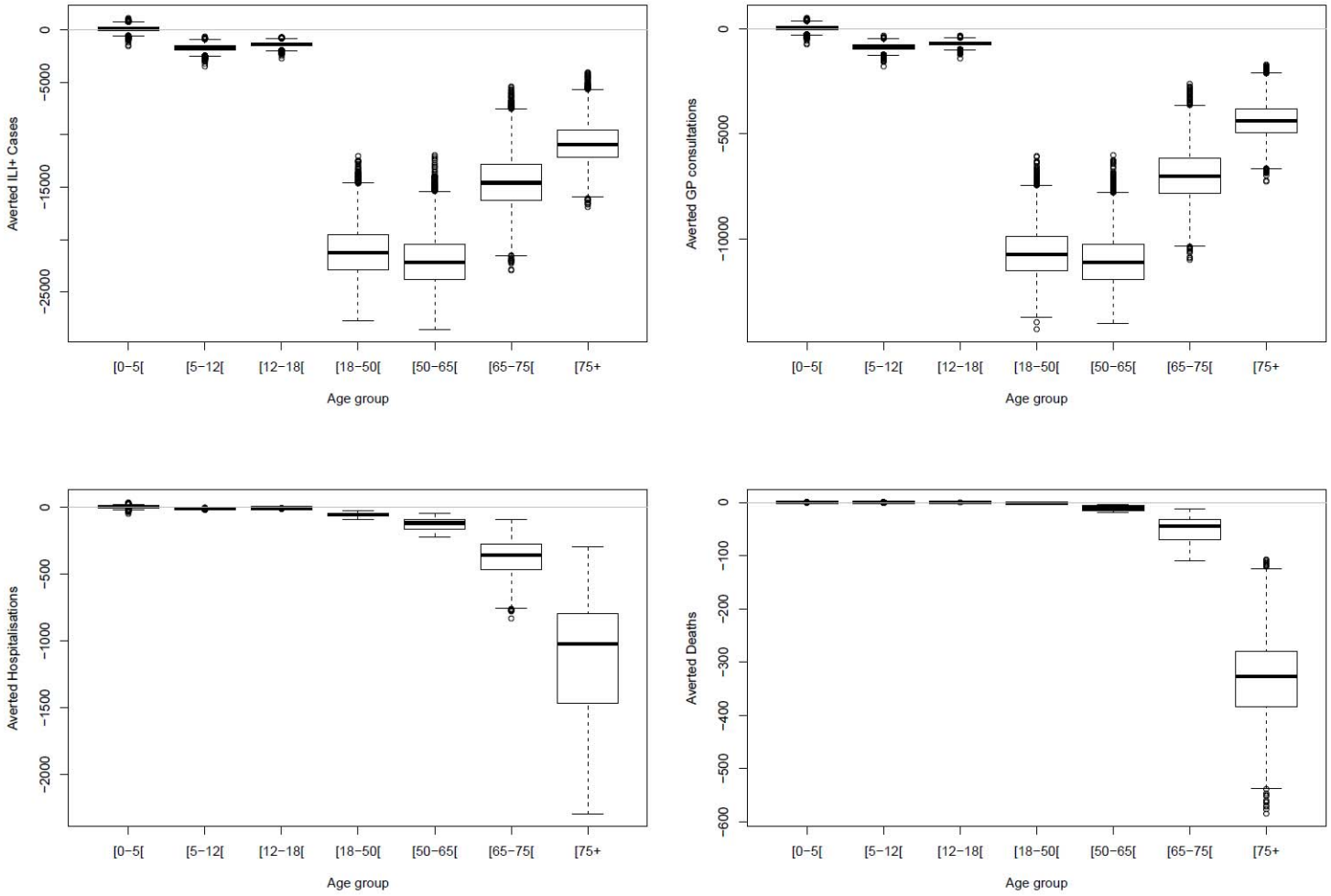
- : no vaccination

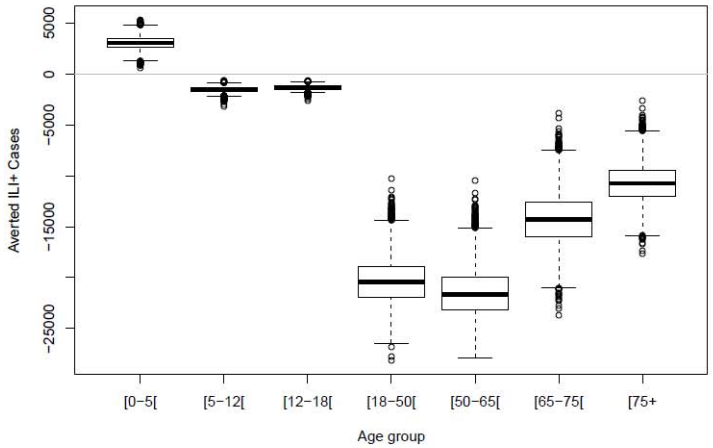
6.1.4.1 *Effectiveness versus current situation*

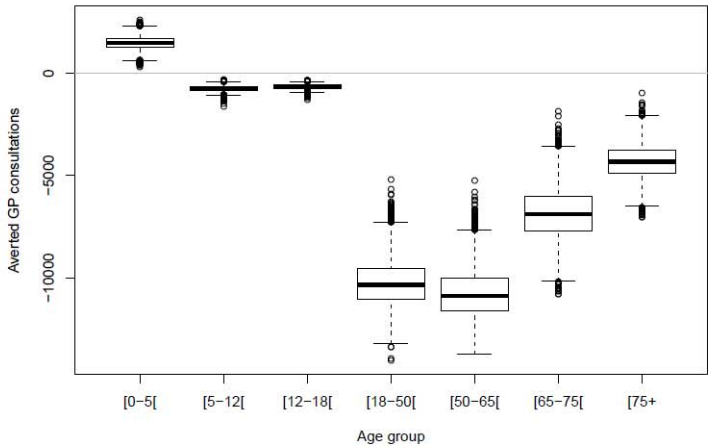
In Figure 36, the least effective scenario correspond to the theoretical situation in which no adult would be vaccinated and coverage would only change among children <2 years (a1c1) at the respective coverage (30 and 80%). The figures indicate a reduction in the number of GP consultations and admissions among children but a large increase in all outcomes among the adults that would no longer be vaccinated.

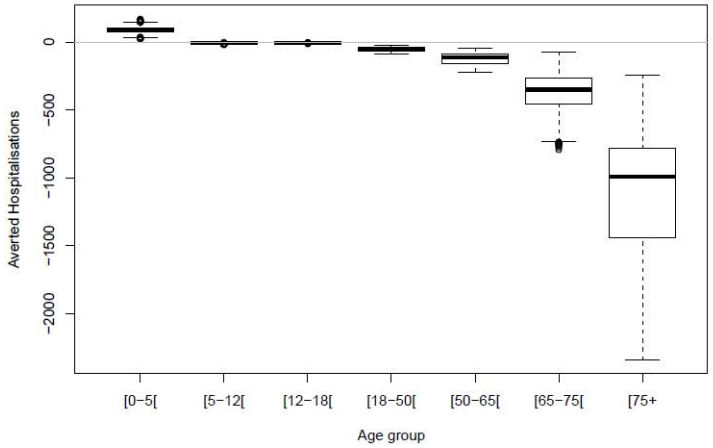
In Figure 37, the most effective scenario (a2c16) correspond to the increase in coverage among all children and keeping current coverage among adults (as no increase is simulated among the options considered in this analysis).

Figure 36 – Box plots of the per-season averaged averted numbers of cases of ILI+ (i.e. influenza), GP consultations, hospitalisations and deaths for the least effective option amongst 171 combined child-adult options (option a1c1) at 30% (top) and 80% (bottom) coverage for the child components of the option, assuming a average waning of 1.68 years




Averted ILI+ Cases
5000
0
−5000
−15000
−25000
[0−5[
[5−12[
[12−18[
[18−50[
[50−65[
[65−75[
[75+
Age group


Averted GP consultations
0
−5000
−10000
[0−5[
[5−12[
[12−18[
[18−50[
[50−65[
[65−75[
[75+
Age group


Averted Hospitalisations
0
−500
−1000
−1500
−2000
[0−5[
[5−12[
[12−18[
[18−50[
[50−65[
[65−75[
[75+
Age group

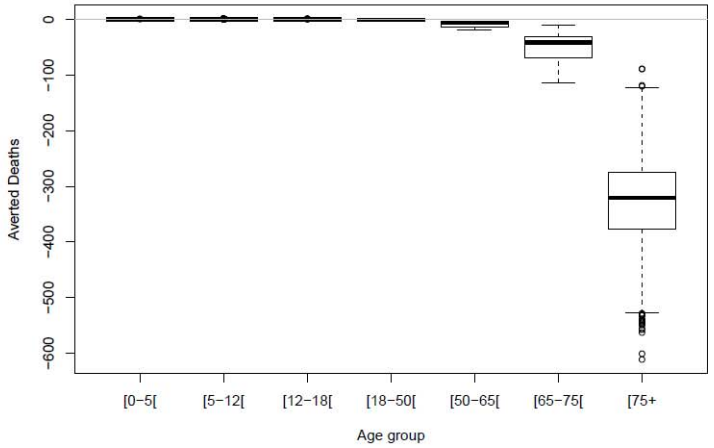
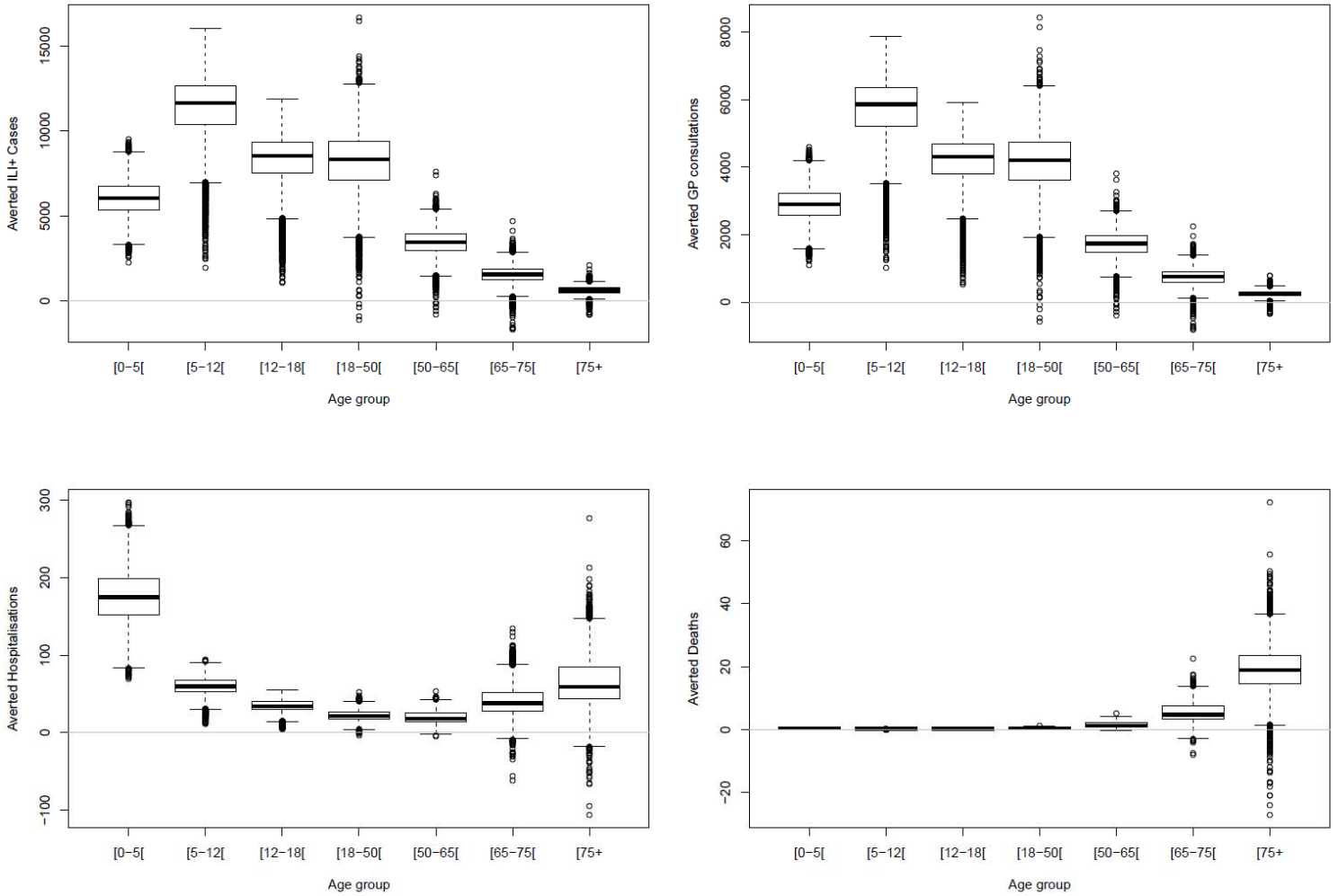
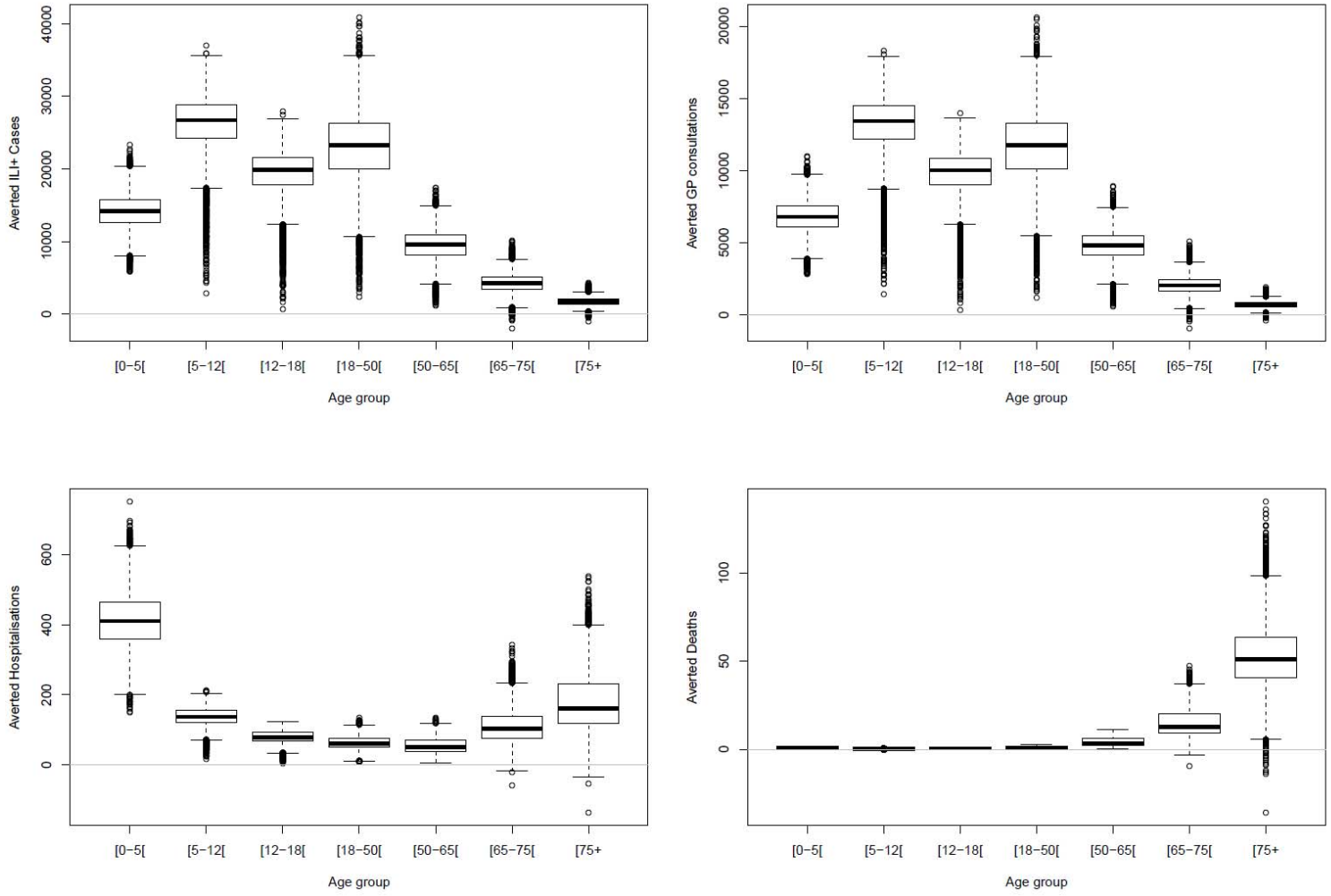

Averted Deaths
0
−100
−200
−300
−400
−500
−600
[0−5[
[5−12[
[12−18[
[18−50[
[50−65[
[65−75[
[75+
Age group

Figure 37 – Box plots of the per-season averaged averted numbers of cases of ILI+ (i.e. influenza), GP consultations, hospitalisations and deaths for the most effective option amongst 171 combined child-adult options (a2c16) at 30% (top) and 80% (bottom) coverage for the child components of the option, assuming a average waning of 1.68 years





c16: TIV 0.5-2 + LAIV 2-18.

6.1.4.2 Cost-effectiveness curves versus current situation

Figure 38 – CEACs for selected options versus the current situation at coverage rate of 30%

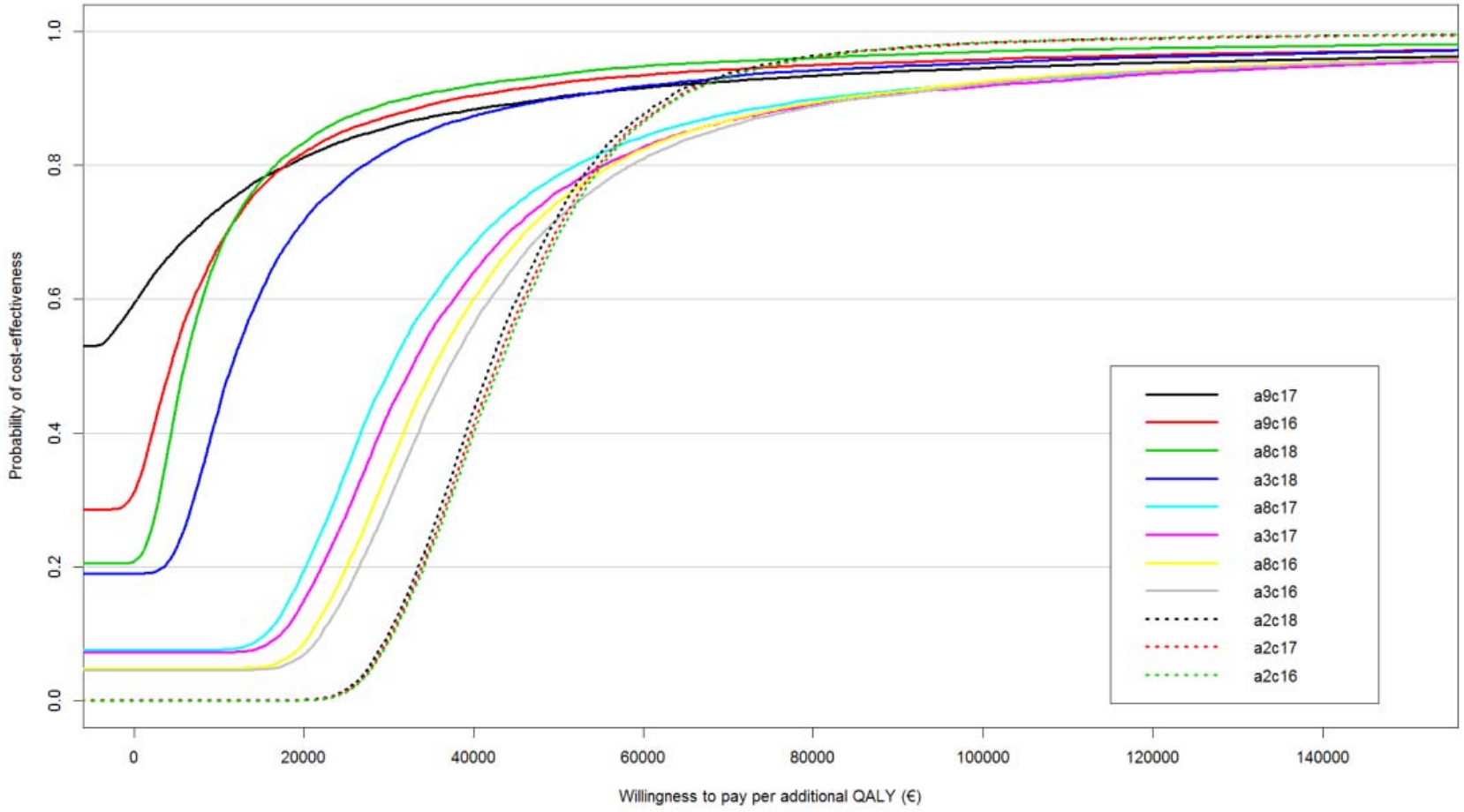
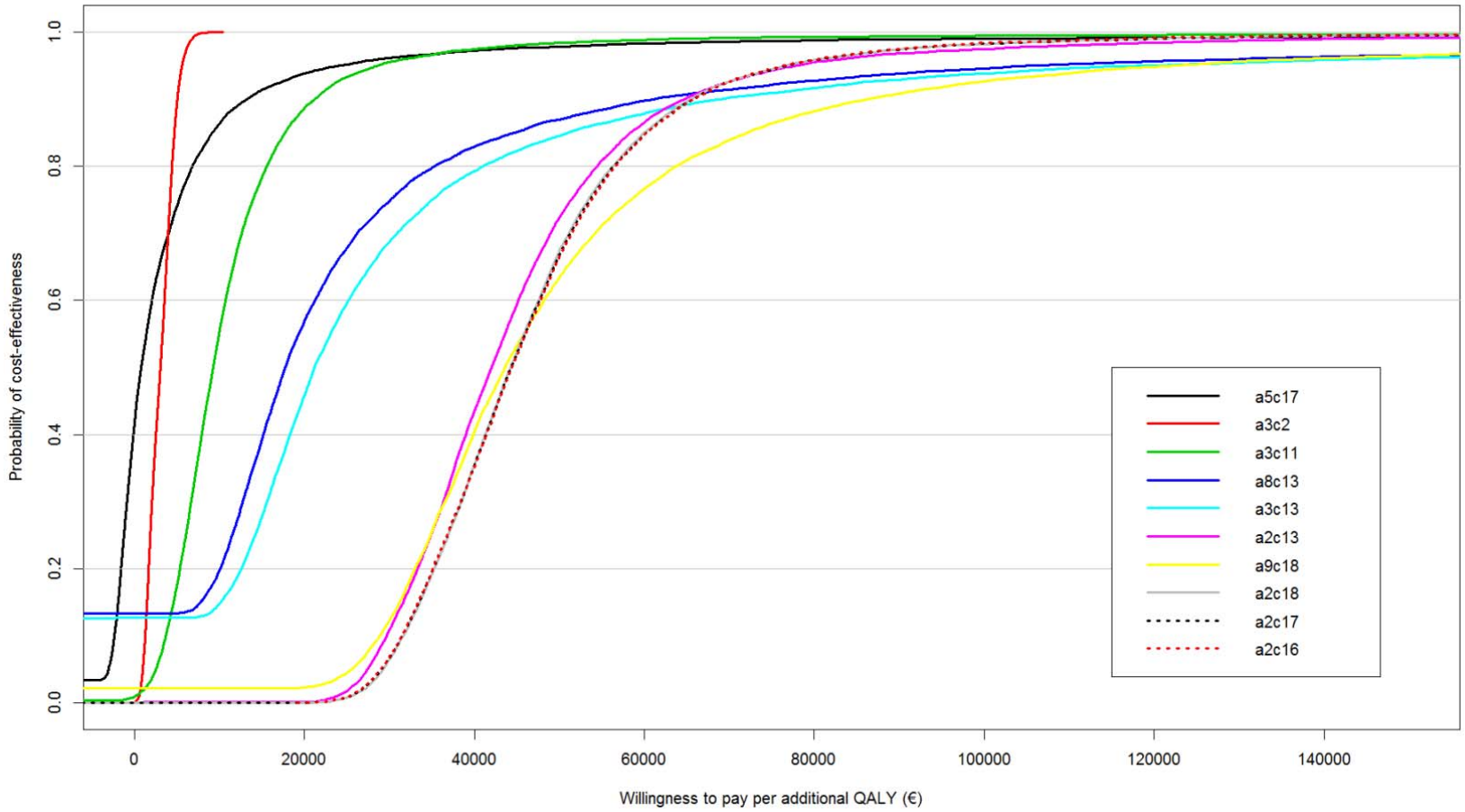


Figure 39 – CEACs for selected options versus the current situation at coverage rate of 80%



6.1.4.3 *Incremental cost-effectiveness analysis*

Table 57 illustrates that relatively small gains in QALYs are possible and savings would occur if vaccination in the oldest age groups (85+ and 95+) and in relatively young adults (18-49 years) was stopped. The gains in QALYs would be realized by vaccinating children (aged ≥5 years or all children). However, the negative sign of the median life years gained in some of these options (as opposed to the positive sign for median QALYs gained) points at deplorable consequences from such a policy change. We also find that the strategies involving ICERs below the theoretical threshold of €35 000 per QALY gained involve LAIV vaccination of older children (above 5 or 12 years of age, c18 and c13, respectively), combined with stopping adult vaccination in the 18-50 years or in the very old (>85 or >95 years of age, a9 and a8, respectively).

Table 57 – Incremental costs, life-years gained, QALYs gained and ICERs (€) for non-dominated options among 1539 child-adult vaccination scenarios over a 10 year time span, assuming a average duration of waning at 1.68 years (results based on 10 000 simulations for each vaccination scenario)

Vaccination option* (Compared to the previous listed option)	Median incremental cost	Median QALYs gained	Median life-years gained	Incremental direct costs per QALY gained			Incremental direct costs per life-year gained		
				Median	2.50%	97.50%	Median	2.50%	97.50%
a8c13cov0.6[a]	-18 404 434	83	-145	-32 571	-558 463	543 853	48 136	-1 296 843	1 396 470
a3c13cov0.6	-14 143 493	122	-115	-26 807	-406 853	337 129	31 083	-1 065 132	1 086 855
a8c16cov0.2	-4 188 702	233	-82	-10 103	-90 944	64 815	4 059	-392 814	389 585
a9c18cov0.4	-959 527	339	-636	-5 956	-71 483	63 153	494	-29 451	71 230
a8c13cov0.7	648 911	484	28	-820	-47 186	42 651	-7 349	-62 057	48 011
a3c13cov0.7	4 938 587	522	58	4 804	-110 331	106 464	5 958	-252 398	308 617
a3c18cov0.3	9 927 052	535	16	11 488	-163 954	174 349	14 304	-578 536	696 832
a8c13cov0.8	19 758 068	867	195	17 727	-175 034	221 095	44 011	-675 917	822 849
a3c13cov0.8	24 082 317	903	223	21 170	-209 193	224 179	53 740	-791 898	815 251
a8c13cov0.9	39 049 694	1 230	342	27 699	-191 636	256 376	72 177	-792 419	908 249
a9c18cov0.5	45 000 475	1 317	-209	27 899	-238 169	312 635	-69 104	-1 442 559	1 314 612
a9c17cov0.4	46 477 522	1 349	-155	28 626	-255 873	300 245	-65 787	-1 553 339	1 411 501

Vaccination option* (Compared to the previous listed option)	Median incremental cost	Median QALYs gained	Median life-years gained	Incremental direct costs per QALY gained			Incremental direct costs per life-year gained		
				Median	2.50%	97.50%	Median	2.50%	97.50%
a8c18cov0.4	51 538 252	1 513	401	31 703	-148 269	214 658	93 134	-978 376	1 134 500
a3c18cov0.4	55 871 419	1 551	430	33 765	-131 417	232 583	98 457	-915 563	1 086 895
a9c16cov0.4	70 699 881	1 855	101	34 726	-197 399	264 655	77 194	-2 288 195	2 159 396
a9c18cov0.6	90 840 571	2 278	197	37 134	-166 731	278 873	107 228	-2 617 794	2 461 391
a8c18cov0.5	97 734 624	2 471	802	38 428	-70 239	183 328	108 630	-583 286	839 327
a9c17cov0.5	104 168 471	2 568	379	38 505	-136 820	242 443	121 818	-2 131 041	2 174 541
a2c13cov0.6	112 827 320	2 768	1 181	40 740	24 785	100 429	94 969	45 366	299 753
a8c16cov0.4	123 848 359	2 983	1 084	40 765	20 921	158 348	107 562	-273 731	635 090
a9c16cov0.5	134 370 868	3 199	695	40 785	-93 217	206 286	135 030	-1 666 678	1 547 242
a9c18cov0.7	136 927 830	3 201	593	41 301	-108 318	216 466	143 340	-1 823 660	2 130 295
a8c18cov0.6	144 064 858	3 410	1 192	41 572	21 486	178 361	113 182	-444 073	708 571
a9c17cov0.6	161 586 849	3 757	900	41 907	-70 088	207 855	139 481	-1 129 784	1 585 075
a2c18cov0.4	182 264 356	4 327	1 819	42 083	26 003	88 861	99 924	48 716	277 325
a2c18cov0.5	228 155 980	5 361	2 267	42 504	26 467	92 833	100 342	49 533	290 421
a2c17cov0.4	229 766 284	5 389	2 326	42 649	26 105	90 369	98 682	48 323	267 476
a2c16cov0.4	254 067 739	5 913	2 599	42 944	26 137	88 831	97 759	47 997	252 307
a2c17cov0.5	287 372 713	6 681	2 899	42 965	26 534	93 099	98 777	48 877	268 206
a2c16cov0.5	317 619 998	7 343	3 246	43 198	26 566	91 659	97 960	48 330	256 633
a2c17cov0.6	344 825 475	7 928	3 452	43 479	26 550	92 903	99 900	48 124	262 754
a2c16cov0.6	380 786 903	8 720	3 873	43 631	26 469	91 326	98 413	47 724	251 241

Vaccination option* (Compared to the previous listed option)	Median incremental cost	Median QALYs gained	Median life-years gained	Incremental direct costs per QALY gained			Incremental direct costs per life-year gained		
				Median	2.50%	97.50%	Median	2.50%	97.50%
a2c17cov0.7	402 070 299	9 118	3 987	44 068	26 715	90 227	100 772	48 961	255 624
a2c16cov0.7	443 807 688	10 036	4 467	44 238	26 692	89 204	99 331	48 237	242 704
a2c17cov0.8	458 330 418	10 336	4 557	44 280	27 273	90 670	100 831	49 695	253 854
a2c16cov0.8	505 420 856	11 381	5 098	44 415	27 105	90 006	99 215	49 000	242 438
a2c17cov0.9	513 113 575	11 426	5 083	44 909	27 544	96 477	100 906	50 172	263 236
a2c16cov0.9	565 526 028	12 571	5 693	44 990	27 481	95 228	99 280	49 339	250 945

** The options should be read as follows: at# stands for a particular adult vaccination option (see also Table 53); c# stands for a particular child option (see Table 51), covp stands for modeled vaccination coverage p for the child option c#.*

Adults vaccination options by age group (At=adult target, I= increase vaccination coverage; II: larger increase vaccination coverage (50-64 years only); D= decrease vaccination coverage):

At1: I 75+ *At5: I 50-64 + I 75+* *At9: II 50-64 + I 75+* *At13: D 18-49 + I 75+* *At17: D18-49 + I 50-64 + I 75+* *At21: D18-49 + II 50-64 + I 75+*
At2: I 65-74 *At6: I 50-74* *At10: II 50-64 + I 65-74* *At14: D18-49 + I 65-74* *At18: D18-49 + I 50-74* *At22: D18-49 + II 50-64 + I 65-74*
At3: I 65-75+ *At7: I 50-75+* *At11: II 50-64 + I 65-75+* *At15: D18-49 + I 65-75+* *At19: D18-49 + I 50-75+* *At23: D18-49 + II 50-64 + I 65-75+*
At4: I 50-64 *At8: II 50-64* *At12: D 18-49* *At16: D18-49 + I 50-64* *At20: D18-49 + II 50-64*

Child vaccination options by age group (c=child option):

c1: TIV 0.5-2 *c5: IV 0.5-5* *c8: TIV 2-18* *c11: LAIV 2-5* *c14: TIV 0.5-2 + LAIV 2-5* *c17: LAIV 2-18*
c2: TIV 2-4 *c6: TIV 0.5-12* *c9:TIV 5-18* *c12: LAIV 5-12* *c15: TIV 0.5-2+ LAIV 2-12* *c18: LAIV 5-18*
c3: TIV 5-12 *c7: TIV 0.5-18* *c10: TIV 2-12* *c13: LAIV 12-18* *c16: TIV 0.5-2 + LAIV 2-18* *c19: LAIV 2-12*
c4: TIV 12-18

a: Compared to the current situation.

6.1.5 Sensitivity analyses

6.1.5.1 Structural and univariate sensitivity

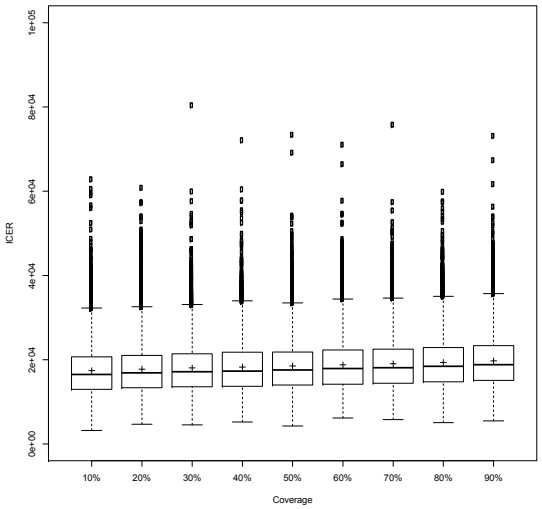
Overall impact of a slower waning rate (6 years)

Modified children options + current adult vaccination

Up till now we used the basic set of fitted parameters for the transmission model in which the rate of waning immunity was estimated 1/1.68 years. However, an alternative estimation of the fitted parameters is presented in Table 39 above, in which the rate of immunity waning was assumed at 1/6 years.

Figure 40 shows the relationship between the ICERs and the vaccination coverage levels for the child option with the lowest median ICER versus the current situation (child option c1: TIV 0.5-2), and the child option with the largest effectiveness (child option 16: TIV 0.5-2 + LAIV 2-18). Again, there is a slight increasing trend in ICER with increasing coverage. These figures also show that there is relatively little impact in variations in coverage levels.

Figure 40 – Boxplots of the distribution of the ICERs by 10% increases in vaccination coverage when only vaccinating children aged 6 months to 2 years (option c1: TIV 0.5-2, top) and when vaccinating all children <18 years (option c16: TIV 0.5-2 + LAIV 2-18, bottom) versus the current situation



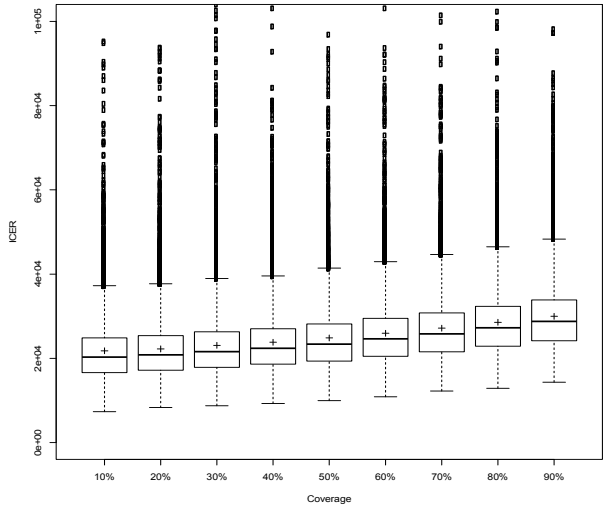


Table 58 shows that expanding the vaccination coverage up to 90% in all children younger than 18 years would be relatively cost-effective. The median incremental direct costs per QALY gained versus the next best option along the expansion path does not exceed €30 000 (and the upper limit of the 95% uncertainty interval reaches about €50 000 at the maximum). The direct costs per life year gained remained equally stable along the sequence of child options.

Compared to the previous analyses based on a waning immunity of 1/1.68 years, this alternative model specification yields a different efficiency frontier (using the ICER compared to the next best option) along the expansion path of increased vaccination coverage for the child vaccination options, whilst assuming adult vaccination remains constant and any coverage level in children may apply. The median and 95% ICERs are considerably lower as compared to Table 52. This implies a preference for younger child age groups over older ones.

In Table 58, all 9 levels of vaccination coverage for each child option were mixed together. It shows that when only low or intermediate levels of vaccination coverage can be achieved, it is more efficient to not expand the programme to age groups over 2 years (i.e. limit to child option c1: TIV 0.5-2), or over 5 years (i.e. limit to child option c14: TIV 0.5-2 + LAIV 2-5). Here again LAIV dominates TIV in the age groups for which either vaccine can be considered.

We also performed incremental analyses for each level of coverage separately, and obtained identical expansion paths for each level of coverage. Namely c1 → c14 → c15 → c16, signifying that it is preferable to vaccinate the younger children first, before starting to vaccinate older children at the same coverage rate. In each case the ICER and 95% uncertainty interval were of similar magnitude as the ICERs depicted in Table 58. Figure 41 below shows the CEACs of the incremental analyses along the paths for separate coverage levels of 30% and 80%.

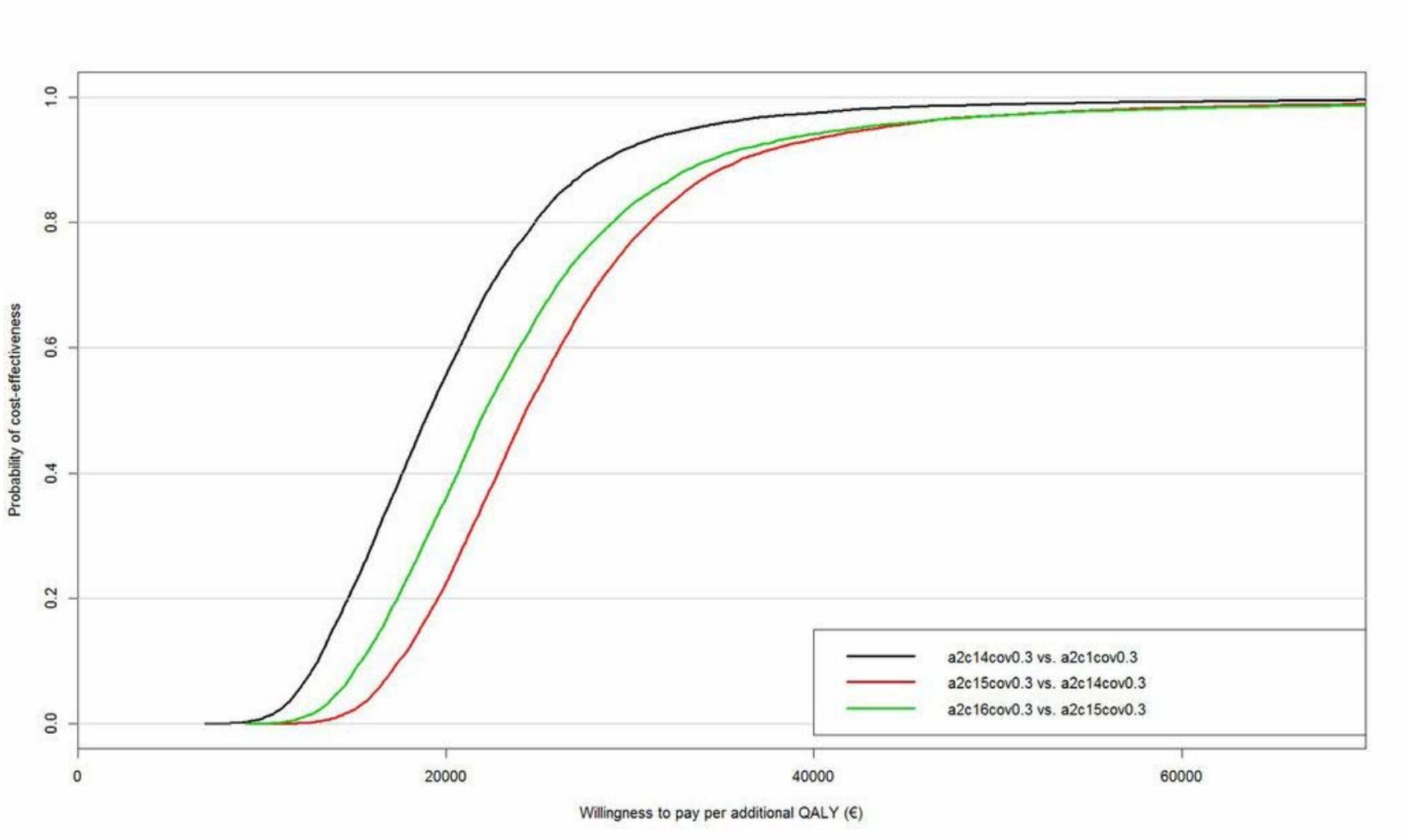
Table 58 – Incremental costs, life-years gained, QALYs gained and ICERs (€) along the expansion path of increased vaccination coverage for 19 child vaccination options with 9 different coverage levels each, whilst assuming adult vaccination remains constant over a 10 year time span, and with immunity lasting an average of 6 years (i.e. exponential waning rate of 1/6 per year)

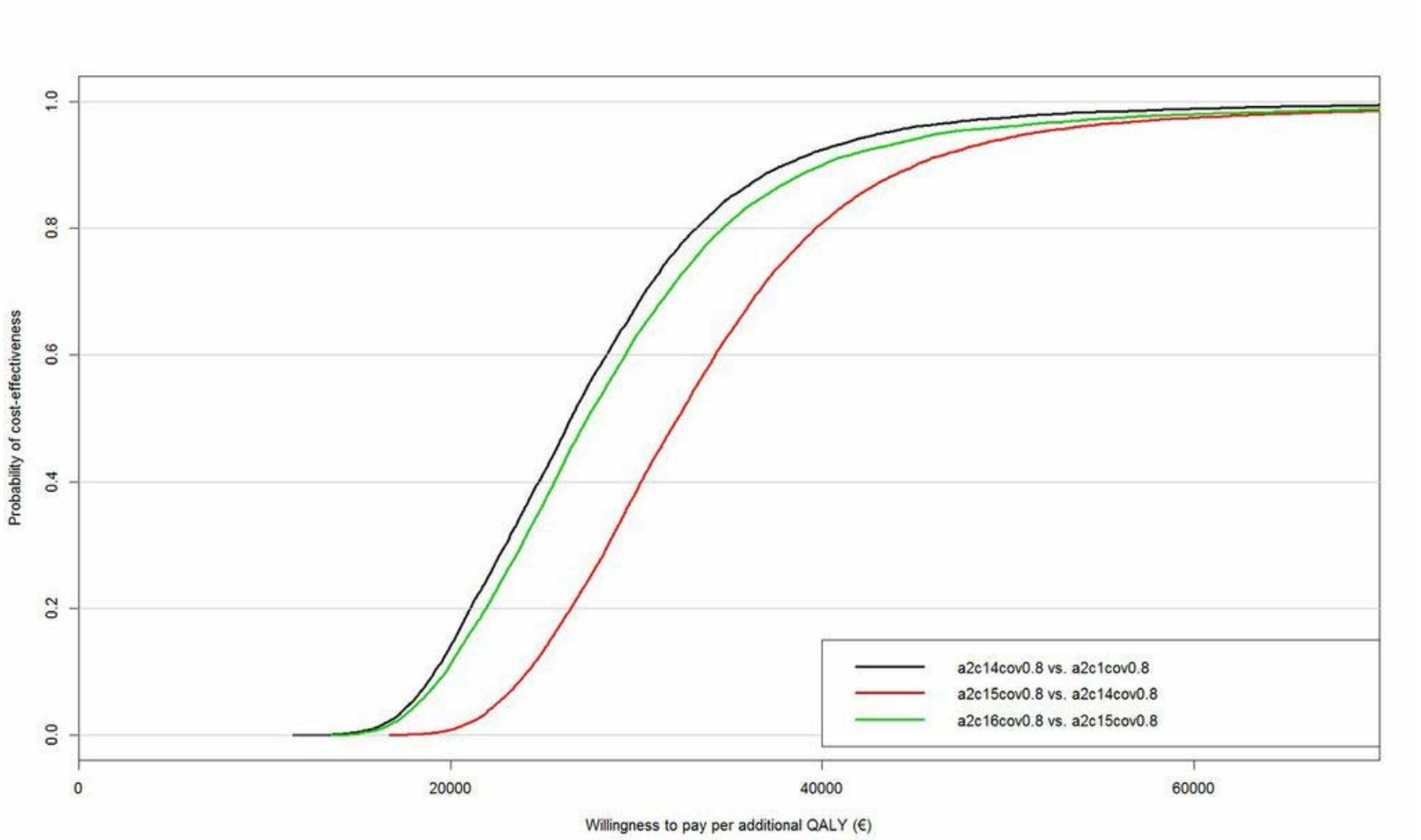
Vaccination option* (Compared to the previous listed option)	Median incremental cost	Median QALYs gained	Median life-years gained	Incremental direct costs per QALY gained			Incremental direct costs per life-year gained		
				Median	2.50%	97.50%	Median	2.50%	97.50%
a2c1cov0.1[a]	7 054 420	427	201	16 514	8 659	31 895	35 239	15 530	78 396
a2c14cov0.1	16 736 611	998	443	16 788	9 297	29 933	38 005	17 555	80 339
a2c1cov0.3	21 551 787	1 253	585	17 137	9 123	32 376	37 081	16 476	79 716
a2c1cov0.4	28 806 901	1 662	770	17 311	9 269	32 638	37 684	16 768	80 120
a2c14cov0.2	34 138 006	1 947	845	17 546	9 838	31 082	40 546	18 596	82 624
a2c1cov0.5	36 208 960	2 055	954	17 583	9 618	32 810	38 150	17 357	81 537
a2c1cov0.6	43 718 473	2 435	1 131	17 919	9 743	33 111	38 956	17 654	81 888
a2c1cov0.7	51 101 288	2 819	1 318	18 109	9 993	33 726	38 881	18 126	83 343
a2c14cov0.3	51 909 081	2 827	1 227	18 327	10 551	31 937	42 455	19 848	85 463
a2c1cov0.8	58 758 414	3 193	1 477	18 435	10 261	33 686	39 973	18 460	82 070
a2c1cov0.9	66 575 543	3 524	1 627	18 839	10 365	34 046	41 038	18 827	83 485
a2c14cov0.4	69 811 389	3 671	1 604	19 070	11 127	32 884	43 669	20 879	87 733
a2c14cov0.5	88 228 669	4 439	1 941	19 868	11 755	34 084	45 665	22 248	91 075
a2c16cov0.2	112 570 514	5 394	2 150	20 824	12 192	41 280	52 407	24 586	123 127
a2c15cov0.3	118 428 526	5 534	2 217	21 394	12 874	39 091	53 394	25 633	114 594
a2c16cov0.3	170 389 623	7 877	3 148	21 612	13 043	41 891	53 983	25 841	123 005
a2c16cov0.4	228 514 868	10 209	4 127	22 404	13 636	43 236	55 340	27 028	126 592
a2c16cov0.5	288 074 285	12 315	5 013	23 383	14 459	44 651	57 654	28 556	131 743

Vaccination option* (Compared to the previous listed option)	Median incremental cost	Median QALYs gained	Median life-years gained	Incremental direct costs per QALY gained			Incremental direct costs per life-year gained		
				Median	2.50%	97.50%	Median	2.50%	97.50%
a2c16cov0.6	348 232 237	14 157	5 809	24 622	15 309	44 893	60 253	30 175	128 841
a2c16cov0.7	408 999 740	15 818	6 544	25 800	16 446	46 144	62 654	32 157	131 794
a2c16cov0.8	469 574 008	17 226	7 121	27 261	17 480	48 043	66 014	34 142	138 152
a2c16cov0.9	529 489 648	18 435	7 613	28 781	18 443	50 070	69 634	36 215	141 493

** The options should be read as follows: a2 stands for current adult vaccination (see also Table 53); c# stands for a particular child option (see Table 51), covp stands for modelled vaccination coverage p for the child option c#. E.g.: a2c16cov0.4 : current adult vaccination supplemented with vaccination at 40% coverage in children aged 0.5-2 years using TIV, and in children aged 2-18 years using LAIV.*
c1: TIV 0.5-2; c14: TIV 0.5-2 + LAIV 2-5; c15: TIV 0.5-2 + LAIV 2-12; c16: TIV 0.5-2 + LAIV 2-18.
a: Compared to the current situation.

Figure 41 – Incremental CEACs for remaining childhood vaccination options at 30% (top) and 80% (bottom) vaccination coverage after exclusion of dominated options, whilst assuming adult vaccination remains constant over a 10 year time span, and with immunity lasting an average of 6 years (i.e. exponential waning rate of 1/6 per year)





The options should be read as follows: a2 stands for current adult vaccination (see also Table 53); c# stands for a particular child option (see Table 51), covp stands for modelled vaccination coverage p for the child option c#. E.g.: a2c16cov0.4 : current adult vaccination supplemented with vaccination at 40% coverage in children aged 0.5-2 years using TIV, and in children aged 2-18 years using LAIV. c1: TIV 0.5-2; c14: TIV 0.5-2 + LAIV 2-5; c15: TIV 0.5-2 + LAIV 2-12; c16: TIV 0.5-2 + LAIV 2-18.

Current children vaccination + modified adult vaccination targets

In the same figure and table, the impact is shown of using the transmission model parameter set when immunity was estimated to last an average of 6 years. The full sequence of options is as follows: At20→At21→At18→At5→At9→At7→At11. The latter strategy (At11) implies vaccinating all the adult age groups at the maximally considered coverage. In terms of incremental direct costs per QALY gained, this would still seem acceptable.

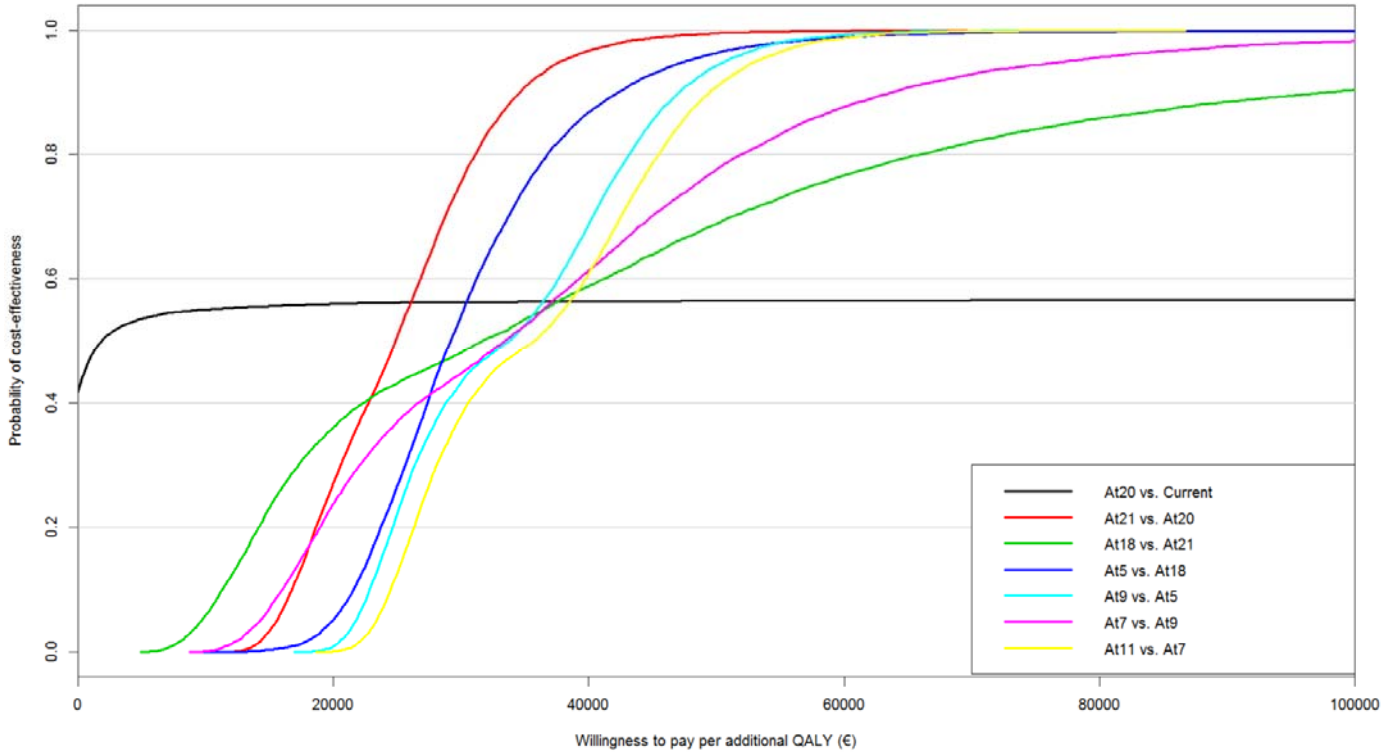
Table 59 – Incremental costs, life-years gained, QALYs gained and ICERs for adult vaccination options, whilst assuming child vaccination remains constant over a 10 year time span, and with immunity waning completely at a over an average period of 6 years

Vaccination option *	Median incremental cost	Median QALYs gained	Median life-years gained	Incremental direct costs per QALY gained			Incremental direct costs per life-year gained		
				Median	2.50%	97.50%	Median	2.50%	97.50%
Immunity lasts on average 6 years									
At20 vs. current	-162 121	-115	424	-2 735	-14 388	7 066	-342	-2 861	10 236
At21 vs. At20	11 604 313	459	433	24 861	14 608	41 429	26 394	15 368	44 345
At18 vs. At21	13 082 349	414	624	30 906	7 957	209 503	20 987	7 245	46 844
At5 vs. At18	47 145 143	1 615	27	29 171	18 553	52 964	167 388	-2 813 675	3 187 734
At9 vs. At5	60 890 791	1 811	1 033	33 744	20 912	53 907	59 087	29 898	100 370
At7 vs. At9	25 034 839	753	959	33 422	12 940	90 659	26 243	11 581	50 546
At11 vs. At7	61 239 766	1 723	956	35 717	22 507	56 477	64 150	32 692	106 503

** Vaccination options by age group (At=adult target, I: increase vaccination coverage; II: larger increase vaccination coverage (50-64 years only); D: decrease vaccination coverage):*

At1: I 75+ *At5: I 50-64 + I 75+* *At9: II 50-64 + I 75+* *At13: D 18-49 + I 75+* *At17: D18-49 + I 50-64 + I 75+* *At21: D18-49 + II 50-64 + I 75+*
At2: I 65-74 *At6: I 50-74* *At10: II 50-64 + I 65-74* *At14: D18-49 + I 65-74* *At18: D18-49 + I 50-74* *At22: D18-49 + II 50-64 + I 65-74*
At3: I 65-75+ *At7: I 50-75+* *At11: II 50-64 + I 65-75+* *At15: D18-49 + I 65-75+* *At19: D18-49 + I 50-75+* *At23: D18-49 + II 50-64 + I 65-75+*
At4: I 50-64 *At8: II 50-64* *At12: D 18-49* *At16: D18-49 + I 50-64* *At20: D18-49 + II 50-64*

Figure 42 – Incremental CEACs for remaining adult vaccination options after exclusion of dominated options, whilst assuming child vaccination remains constant over a 10 year time span, and with immunity waning completely over an average period of 6 years



Vaccination options by age group (at=adult target):

At1: I 75+	*At7: I 50-75+*	*At13: D 18-49 + I 75+*	*At19: D18-49 + I 50-75+*
At2: I 65-74	*At8: II 50-64*	*At14: D18-49 + I 65-74*	*At20: D18-49 + II 50-64*
At3: I 65-75+	*At9: II 50-64 + I 75+*	*At15: D18-49 + I 65-75+*	*At21: D18-49 + II 50-64 + I 75+*
At4: I 50-64	*At10: II 50-64 + I 65-74*	*At16: D18-49 + I 50-64*	*At22: D18-49 + II 50-64 + I 65-74*
At5: I 50-64 + I 75+	*At11: II 50-64 + I 65-75+*	*At17: D18-49 + I 50-64 + I 75+*	*At23: D18-49 + II 50-64 + I 65-75+*
At6: I 50-74	*At12: D 18-59*	*At18: D18-49 + I 50-74*	

I: increase vaccination coverage; II: larger increase vaccination coverage (50-64 years only); D: decrease vaccination coverage.

Modified children + modified adults targets

The sequence of options in Table 60 shows the efficiency frontier at a given level of coverage in children with a waning immunity at a rate of 1/6 years. The first option in the list, i.e. the most cost-effective option versus the current situation, is with the exception of option At16c1 (which tops the list for 60% and 70% coverage) always a different option. The last option at each coverage level is by definition the most clinically effective option that was not dominated by another option. This is across all the coverage levels invariably option At11c16. In Supplement 1 (Section 4), we list the incremental costs, QALYs and ICERs of all these options.

Table 60 – Combined child-adult vaccination options selected after a process of elimination by dominance and extended dominance among 3933 vaccination scenarios, with waning immunity over 6 years

Childhood vaccination option-dependent vaccination coverage in children (<18y) * :								
10%	20%	30%	40%	50%	60%	70%	80%	90%
At17c19cov0.1	At13c15cov0.2	At17c11cov0.3	At17c1cov0.4	At12c14cov0.5	At16c1cov0.6	At16c1cov0.7	At13c11cov0.8	At12c11cov0.9
At17c6cov0.1	At17c5cov0.2	At16c5cov0.3	At16c11cov0.4	At13c14cov0.5	At12c14cov0.6	At17c1cov0.7	At16c1cov0.8	At16c1cov0.9
At17c15cov0.1	At17c14cov0.2	At16c14cov0.3	At14c1cov0.4	At14c1cov0.5	At13c14cov0.6	At12c14cov0.7	At17c1cov0.8	At17c1cov0.9
At16c16cov0.1	At12c16cov0.2	At12c15cov0.3	At17c11cov0.4	At15c1cov0.5	At15c1cov0.6	At13c14cov0.7	At12c14cov0.8	At14c1cov0.9
At17c17cov0.1	At13c16cov0.2	At13c15cov0.3	At15c1cov0.4	At16c14cov0.5	At16c14cov0.6	At0c1cov0.7	At13c14cov0.8	At15c1cov0.9
At17c16cov0.1	At16c15cov0.2	At12c16cov0.3	At16c14cov0.4	At17c14cov0.5	At17c14cov0.6	At16c14cov0.7	At0c1cov0.8	At13c14cov0.9
At14c16cov0.1	At17c15cov0.2	At13c16cov0.3	At17c14cov0.4	At14c14cov0.5	At0c14cov0.6	At17c14cov0.7	At1c1cov0.8	At0c1cov0.9
At15c16cov0.1	At16c16cov0.2	At16c16cov0.3	At12c15cov0.4	At0c14cov0.5	At1c14cov0.6	At0c14cov0.7	At16c14cov0.8	At1c1cov0.9
At0c15cov0.1	At17c16cov0.2	At17c16cov0.3	At13c15cov0.4	At1c14cov0.5	At4c14cov0.6	At1c14cov0.7	At17c14cov0.8	At4c1cov0.9
At0c16cov0.1	At0c15cov0.2	At0c16cov0.3	At0c14cov0.4	At4c14cov0.5	At5c14cov0.6	At4c14cov0.7	At0c14cov0.8	At5c1cov0.9
At1c16cov0.1	At0c16cov0.2	At1c16cov0.3	At1c14cov0.4	At5c14cov0.5	At4c16cov0.6	At5c14cov0.7	At1c14cov0.8	At0c14cov0.9
At4c16cov0.1	At1c16cov0.2	At4c16cov0.3	At12c16cov0.4	At0c15cov0.5	At5c16cov0.6	At8c14cov0.7	At4c14cov0.8	At1c14cov0.9
At5c16cov0.1	At4c16cov0.2	At5c16cov0.3	At13c16cov0.4	At0c16cov0.5	At8c16cov0.6	At9c14cov0.7	At5c14cov0.8	At4c14cov0.9
At2c16cov0.1	At5c16cov0.2	At8c16cov0.3	At0c15cov0.4	At1c16cov0.5	At9c16cov0.6	At4c16cov0.7	At8c14cov0.8	At5c14cov0.9
At8c16cov0.1	At8c16cov0.2	At9c16cov0.3	At0c16cov0.4	At4c16cov0.5	At7c16cov0.6	At5c16cov0.7	At9c14cov0.8	At8c14cov0.9

At9c16cov0.1	At9c16cov0.2	At6c16cov0.3	At1c16cov0.4	At5c16cov0.5	At10c16cov0.6	At8c16cov0.7	At6c14cov0.8	At9c14cov0.9
At6c16cov0.1	At6c16cov0.2	At7c16cov0.3	At4c16cov0.4	At8c16cov0.5	At11c16cov0.6	At9c16cov0.7	At7c14cov0.8	At6c14cov0.9
At7c16cov0.1	At7c16cov0.2	At10c16cov0.3	At5c16cov0.4	At9c16cov0.5		At7c16cov0.7	At4c16cov0.8	At7c14cov0.9
At10c16cov0.1	At10c16cov0.2	At11c16cov0.3	At8c16cov0.4	At7c16cov0.5		At10c16cov0.7	At8c16cov0.8	At10c14cov0.9
At11c16cov0.1	At11c16cov0.2		At9c16cov0.4	At10c16cov0.5		At11c16cov0.7	At9c16cov0.8	At11c14cov0.9
			At6c16cov0.4	At11c16cov0.5			At10c16cov0.8	At8c16cov0.9
			At7c16cov0.4				At11c16cov0.8	At9c16cov0.9
			At10c16cov0.4					At10c16cov0.9
			At11c16cov0.4					At11c16cov0.9

** The options should be read as follows: at# stands for a particular adult vaccination option (see also Table 53); c# stands for a particular child option (see Table 51), covp stands for modelled vaccination coverage p for the child option c#.*

Adults vaccination options by age group (at=adult target, I= increase vaccination coverage; II: larger increase vaccination coverage (50-64 years only); D= decrease vaccination coverage):

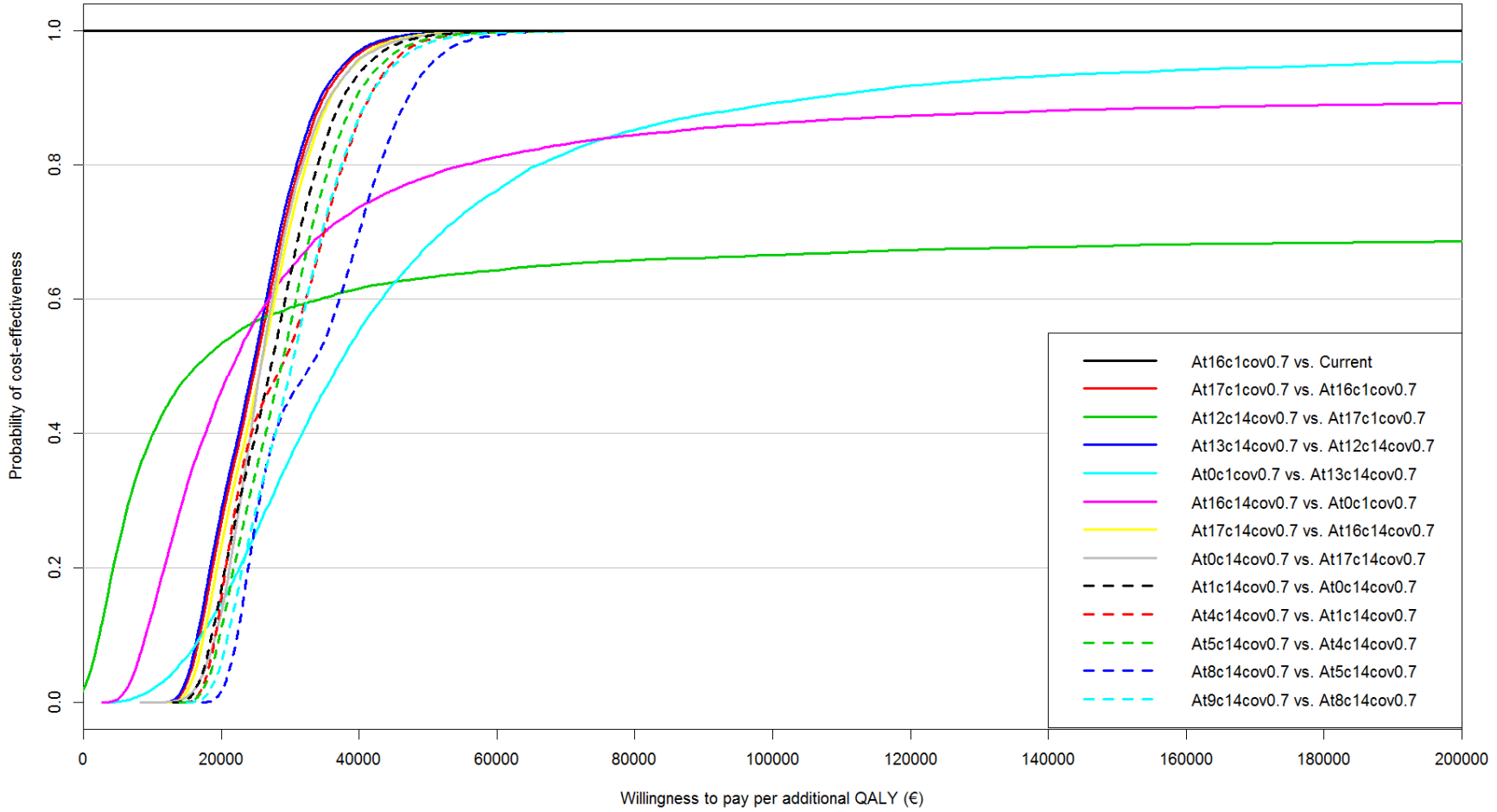
At1: I 75+	*At5: I 50-64 + I 75+*	*At9: II 50-64 + I 75+*	*At13: D 18-49 + I 75+*	*At17: D18-49 + I 50-64 + I 75+*	*At21: D18-49 + II 50-64 + I 75+*
At2: I 65-74	*At6: I 50-74*	*At10: II 50-64 + I 65-74*	*At14: D18-49 + I 65-74*	*At18: D18-49 + I 50-74*	*At22: D18-49 + II 50-64 + I 65-74*
At3: I 65-75+	*At7: I 50-75+*	*At11: II 50-64 + I 65-75+*	*At15: D18-49 + I 65-75+*	*At19: D18-49 + I 50-75+*	*At23: D18-49 + II 50-64 + I 65-75+*
At4: I 50-64	*At8: II 50-64*	*At12: D 18-49*	*At16: D18-49 + I 50-64*	*At20: D18-49 + II 50-64*	

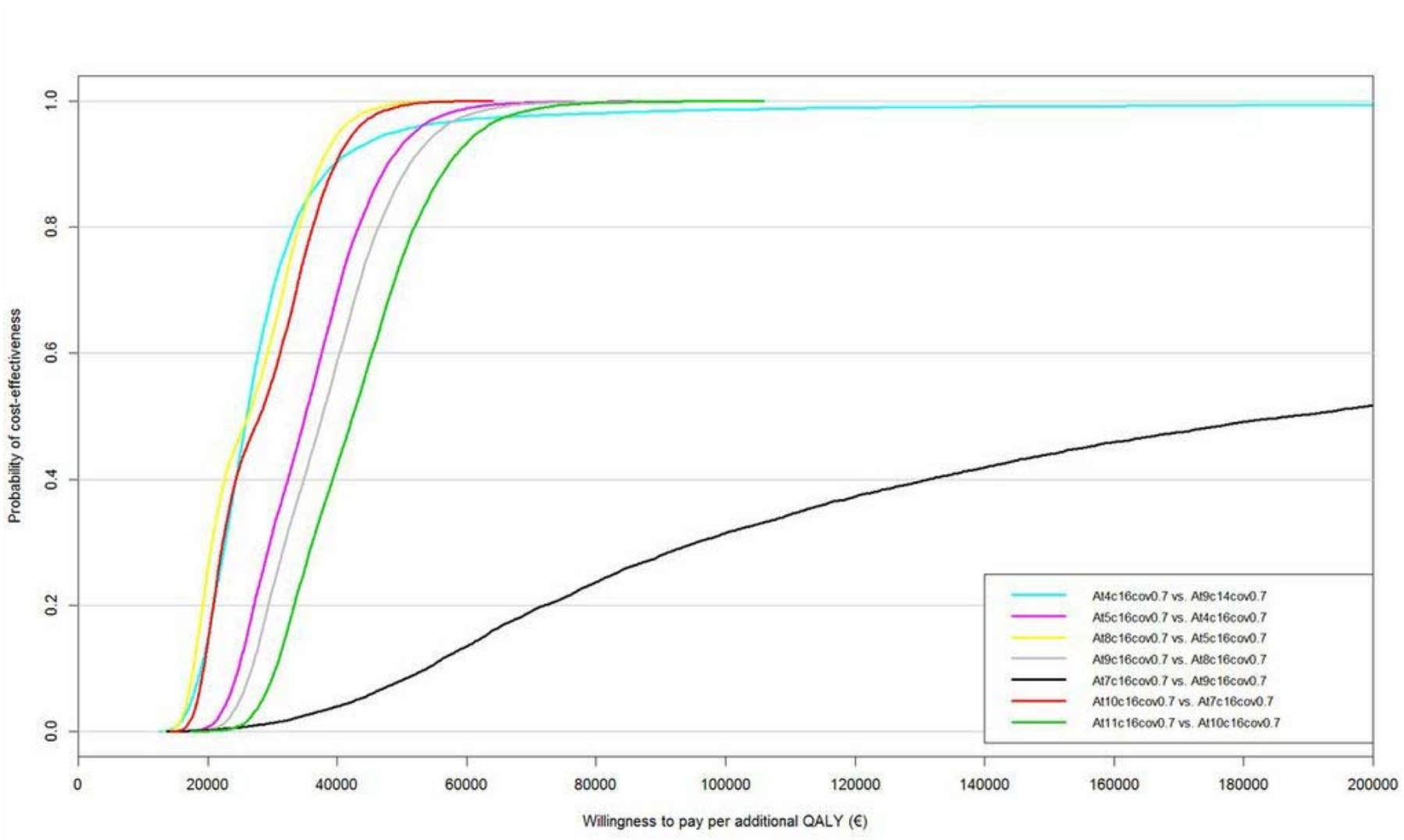
Child vaccination options by age group (c=child option):

c1: TIV 0.5-2	*c5: IV 0.5-5*	*c8: TIV 2-18*	*c11: LAIV 2-5*	*c14: TIV 0.5-2 + LAIV 2-5*	*c17: LAIV 2-18*
c2: TIV 2-4	*c6: TIV 0.5-12*	*c9:TIV 5-18*	*c12: LAIV 5-12*	*c15: TIV 0.5-2+ LAIV 2-12*	*c18: LAIV 5-18*
c3: TIV 5-12	*c7: TIV 0.5-18*	*c10: TIV 2-12*	*c13: LAIV 12-18*	*c16: TIV 0.5-2 + LAIV 2-18*	*c19: LAIV 2-12*
c4: TIV 12-18					

Figure 43, Figure 44 and Figure 45 present the CEACs of these strategies for the coverage levels of 70%, 80% and 90%. Other scenarios are shown in Supplement 1 (Section 4). They show that the option At16c1 is very attractive versus the current situation, across the range of willingness to pay levels (see Figure 43, first panel), with high net savings in health care costs, if the child component can be carried out at high vaccination coverage. Other vaccination options with attractive incremental CEACs include At13c14, At14c16, At8c16, At17c1 since they exhibit a steep profile at a median ICER that can be considered cost-effective. The most effective option, At11c16, shows a relatively acceptable CEAC versus its next best option, which expresses little uncertainty (i.e. which is steep).

Figure 43 – CEACs of the incremental analyses on child-adult combined vaccination options after elimination of dominated options at a 70% coverage level of the child components of the options with waning immunity over 6 years




Probability of cost-effectiveness
0.0
0.2
0.4
0.6
0.8
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20000
40000
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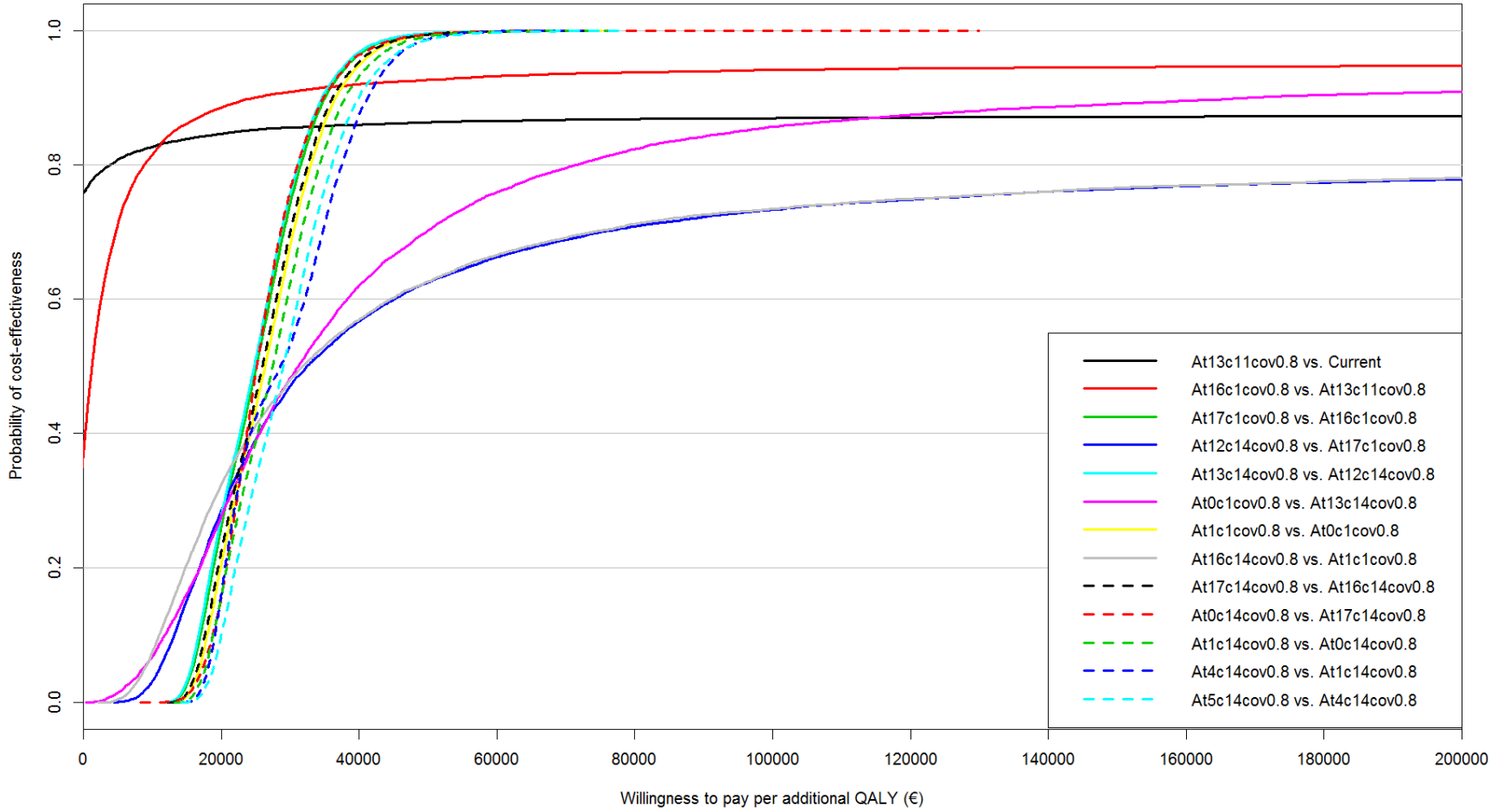
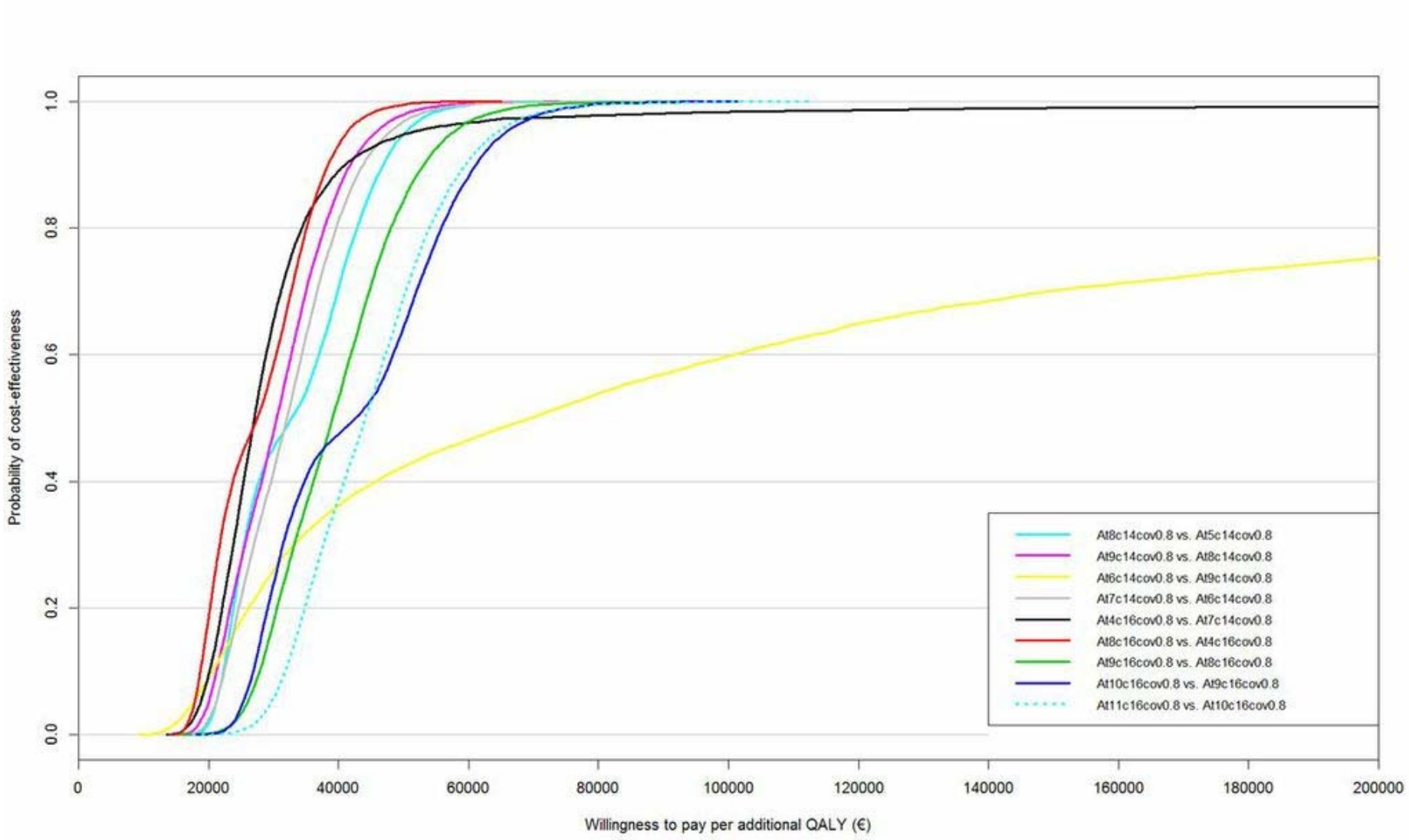
120000
140000
160000
180000
200000
Willingness to pay per additional QALY (€)
At4c16cov0.7 vs. At9c14cov0.7
At5c16cov0.7 vs. At4c16cov0.7
At8c16cov0.7 vs. At5c16cov0.7
At9c16cov0.7 vs. At8c16cov0.7
At7c16cov0.7 vs. At9c16cov0.7
At10c16cov0.7 vs. At7c16cov0.7
At11c16cov0.7 vs. At10c16cov0.7

Figure 44 – CEACs of the incremental analyses on child-adult combined vaccination options after elimination of dominated options at a 80% coverage level of the child components of the options with waning immunity over 6 years




Probability of cost-effectiveness
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0.4
0.6
0.8
1.0
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20000
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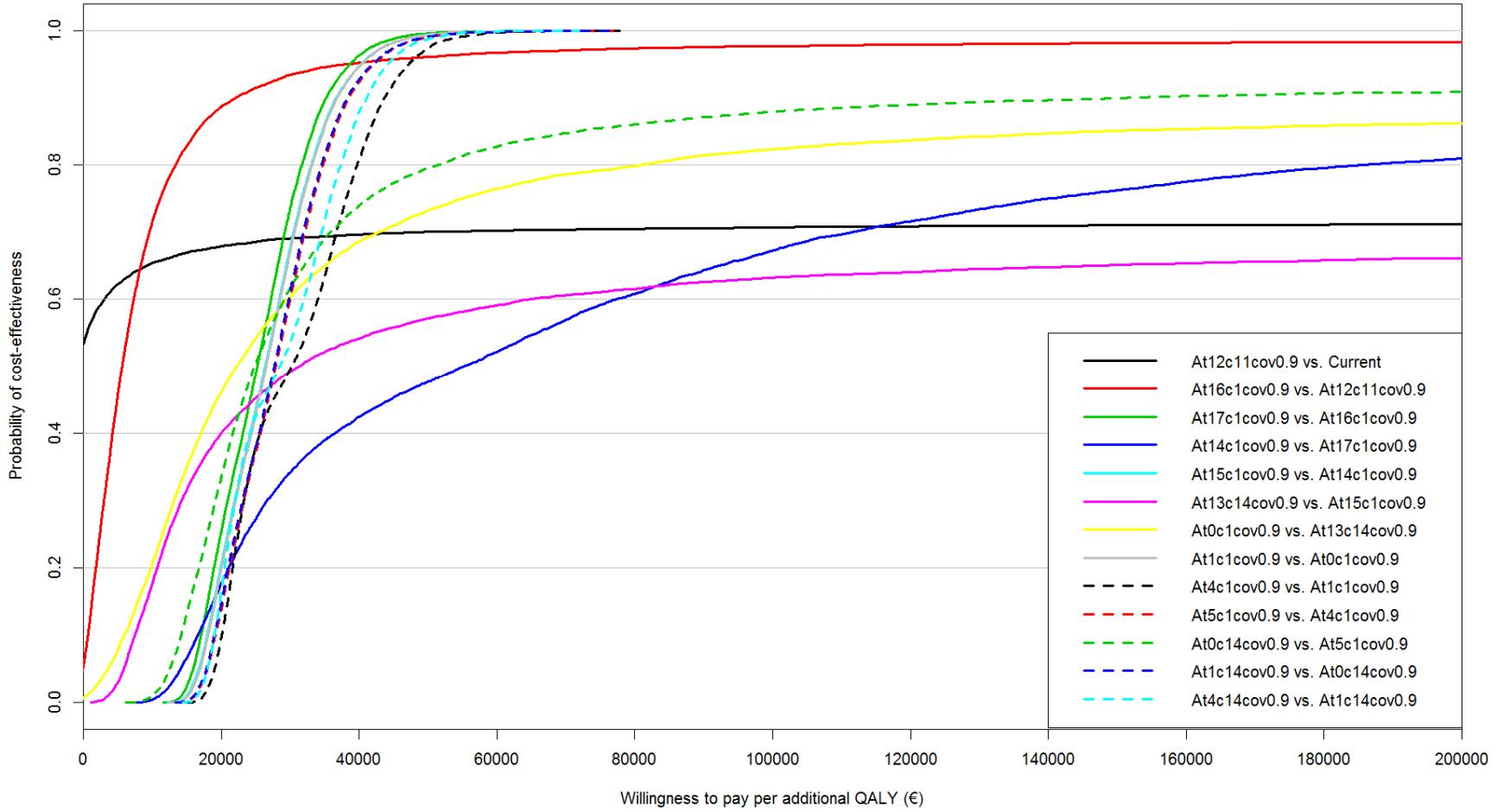
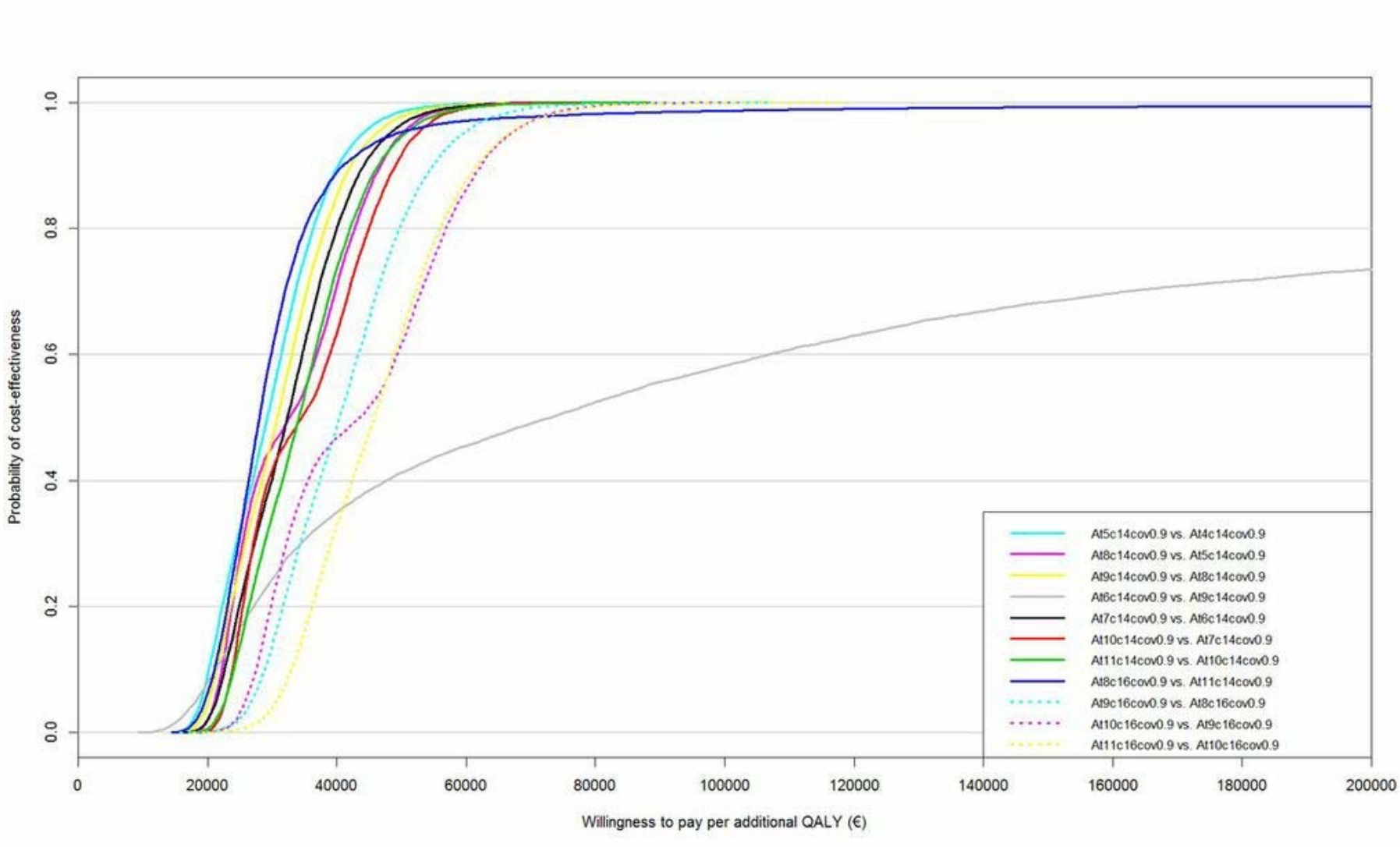
100000
120000
140000
160000
180000
200000
Willingness to pay per additional QALY (€)
At8c14cov0.8 vs. At5c14cov0.8
At9c14cov0.8 vs. At8c14cov0.8
At6c14cov0.8 vs. At9c14cov0.8
At7c14cov0.8 vs. At6c14cov0.8
At4c16cov0.8 vs. At7c14cov0.8
At8c16cov0.8 vs. At4c16cov0.8
At9c16cov0.8 vs. At8c16cov0.8
At10c16cov0.8 vs. At9c16cov0.8
At11c16cov0.8 vs. At10c16cov0.8

Figure 45 – CEACs of the incremental analyses on child-adult combined vaccination options after elimination of dominated options at a 90% coverage level of the child components of the options with waning immunity over 6 years




Probability of cost-effectiveness
0.0
0.2
0.4
0.6
0.8
1.0
0
20000
40000
60000
80000
100000
120000
140000
160000
180000
200000
Willingness to pay per additional QALY (€)
At5c14cov0.9 vs. At4c14cov0.9
At8c14cov0.9 vs. At5c14cov0.9
At9c14cov0.9 vs. At8c14cov0.9
At6c14cov0.9 vs. At9c14cov0.9
At7c14cov0.9 vs. At6c14cov0.9
At10c14cov0.9 vs. At7c14cov0.9
At11c14cov0.9 vs. At10c14cov0.9
At8c16cov0.9 vs. At11c14cov0.9
At9c16cov0.9 vs. At8c16cov0.9
At10c16cov0.9 vs. At9c16cov0.9
At11c16cov0.9 vs. At10c16cov0.9

The same selection process as described above was performed on all 3933 vaccination scenarios combined (i.e. joint consideration of all these different coverage levels), leading to 50 selected vaccination scenarios (i.e. 49 incremental analyses, as shown in Table 61), assuming immunity lasts on average 6 years. Figure 46 shows the CEACs associated with the analyses listed in Table 61. These analyses show that option At12c14 (adult: D 18-49; child: TIV 0.5-2 + LAIV 2-5) with 50% vaccination coverage leads to the greatest cost-savings versus the current situation.

Furthermore the ICER for these incremental analyses is always lower than €50 000 and often than €20 000 per QALY. That is, even if coverage is already high and all children <18y are part of the vaccination programme (c16), the incremental cost-effectiveness of expanding the adult programme from At10 (II 50-64 + I 65-74) to At11 (II 50-64 + I 65-75+) is still worth considering.

Table 61 – Incremental costs, life-years gained, QALYs gained and ICERs for non-dominated options among 3933 child-adult vaccination scenarios over a 10 year time span, and with immunity lasting an average of 6 years (results based on 10 000 simulations for each vaccination scenario)

Vaccination option *	Median incremental cost	Median QALYs gained	Median life-years gained	Incremental direct costs per QALY gained			Incremental direct costs per life-year gained		
				Median	2.50%	97.50%	Median	2.50%	97.50%
At12c14cov0.5 vs. current	-30 971 085	188	-23	-80 030	-1 192 811	1 056 289	85 828	-3 967 092	4 085 268
At16c1cov0.6 vs. At12c14cov0.5	14 621 008	199	515	21 559	-560 630	647 648	28 135	6 295	112 354
At13c14cov0.5 vs. At16c1cov0.6	-3 363 551	277	-77	-7 765	-80 602	56 436	1 438	-211 544	194 236
At12c14cov0.6 vs. At13c14cov0.5	7 618 548	179	-154	41 938	17 464	209 427	-49 302	-175 545	-29 620
At12c16cov0.2 vs. At12c14cov0.6	5 944 572	216	-84	9 348	-207 190	214 899	-29 720	-541 052	529 756
At12c15cov0.3 vs. At12c16cov0.2	5 754 106	135	60	38 732	-219 766	419 103	86 248	-706 704	1 090 756
At13c14cov0.6 vs. At12c15cov0.3	-457 263	124	470	-5 750	-46 359	42 445	-1 001	-6 243	11 949
At13c16cov0.2 vs. At13c14cov0.6	5 948 853	213	-86	9 387	-217 841	212 450	-30 354	-571 095	537 916
At13c15cov0.3 vs. At13c16cov0.2	5 754 149	136	60	38 752	-212 973	415 709	86 364	-692 301	1 037 785
At13c14cov0.7 vs. At13c15cov0.3	7 160 090	256	298	16 684	-345 616	391 250	24 153	3 146	121 578
At17c14cov0.4 vs. At13c14cov0.7	3 292 246	79	368	4 757	-237 256	191 983	8 361	1 246	30 421
At12c14cov0.8 vs. At17c14cov0.4	4 045 127	-3	-578	-6 771	-205 531	202 106	-6 629	-14 976	-2 650
At16c14cov0.5 vs. At12c14cov0.8	3 261 657	247	437	7 933	-186 918	229 314	7 008	1 242	21 886
At12c15cov0.4 vs. At16c14cov0.5	12 179 594	385	-432	15 882	-289 836	274 562	-27 252	-205 463	-13 010

At17c14cov0.5 vs. At12c15cov0.4	-914 530	74	855	-5 031	-27 346	17 730	-1 057	-5 251	8 002
At12c16cov0.3 vs. At17c14cov0.5	12 154 415	632	-558	10 396	-180 140	186 528	-21 148	-101 641	-11 322
At13c16cov0.3 vs. At12c16cov0.3	11 624 913	453	425	25 213	15 058	41 548	26 871	15 899	44 941
At11c1cov0.9 vs. At13c16cov0.3	14 819 690	119	499	328	-307 291	241 177	23 585	-308 266	458 202
At11c14cov0.4 vs. At11c1cov0.9	2 909 812	198	3	4 681	-147 801	138 827	-3 402	-357 183	397 756
At10c14cov0.5 vs. At11c14cov0.4	7 008 520	327	-67	21 386	11 554	54 509	-74 947	-1 263 686	1 200 756
At11c14cov0.5 vs. At10c14cov0.5	11 716 338	432	406	26 622	16 093	43 557	28 404	16 993	46 960
At12c16cov0.4 vs. At11c14cov0.5	11 824 390	570	-387	8 347	-158 121	173 945	-25 603	-245 040	194 008
At16c16cov0.3 vs. At12c16cov0.4	-178 454	72	460	-3 536	-22 938	15 153	-360	-4 688	9 497
At13c16cov0.4 vs. At16c16cov0.3	11 561 088	374	-51	24 818	-227 269	267 833	-30 609	-564 555	690 481
At17c16cov0.3 vs. At13c16cov0.4	-141 747	64	454	-3 493	-21 485	14 929	-295	-4 673	9 768
At10c16cov0.3 vs. At17c16cov0.3	46 777 350	2 054	465	22 767	14 374	38 699	100 502	43 248	270 089
At1c16cov0.3 vs. At10c16cov0.3	11 787 751	412	386	28 182	17 255	45 797	30 093	18 237	49 552
At10c16cov0.4 vs. At11c16cov0.3	47 001 634	1 891	559	24 821	15 383	51 293	82 747	34 346	276 134
At11c16cov0.4 vs. At10c16cov0.4	11 833 499	398	372	29 291	18 047	47 380	31 366	19 101	51 443
At4c16cov0.4 vs. At11c16cov0.4	47 000 129	1 879	892	25 088	15 066	41 638	52 813	23 599	94 310
At5c16cov0.4 vs. At4c16cov0.4	11 913 596	377	352	31 192	19 408	49 979	33 407	20 543	54 374
At4c16cov0.5 vs. At5c16cov0.4	47 540 221	1 765	540	26 937	17 172	51 624	87 067	38 118	254 886
At5c16cov0.5 vs. At4c16cov0.5	11 958 700	363	339	32 488	20 246	51 981	34 882	21 471	56 488
At8c16cov0.5 vs. At5c16cov0.5	47 657 105	1 727	810	27 716	17 062	45 350	58 932	26 933	101 850
At9c16cov0.5 vs. At8c16cov0.5	12 034 572	343	320	34 643	21 743	55 011	37 222	23 059	59 841
At8c16cov0.6 vs. At9c16cov0.5	48 097 272	1 600	498	30 050	19 728	54 092	95 836	43 967	255 577
At9c16cov0.6 vs. At8c16cov0.6	12 074 252	330	307	36 172	22 639	57 274	38 947	23 988	62 360
At8c16cov0.7 vs. At9c16cov0.6	48 609 656	1 372	416	35 454	23 739	60 805	115 589	53 352	299 496
At9c16cov0.7 vs. At8c16cov0.7	12 109 171	318	296	37 675	23 581	59 391	40 643	25 020	64 905

At10c16cov0.6 vs. At9c16cov0.7	14 568 434	222	687	21 706	-846 094	803 610	21 040	7 373	51 093
At11c16cov0.6 vs. At10c16cov0.6	12 180 647	297	276	40 616	25 720	63 423	43 712	27 284	69 142
At8c16cov0.8 vs. At11c16cov0.6	22 010 299	633	-586	30 497	-220 200	260 700	-37 011	-97 942	-17 704
At9c16cov0.8 vs. At8c16cov0.8	12 141 266	308	286	39 054	24 430	61 452	42 193	25 977	67 388
At10c16cov0.7 vs. At9c16cov0.8	14 802 359	398	737	27 689	-410 457	538 601	20 054	7 347	45 163
At11c16cov0.7 vs. At10c16cov0.7	12 215 655	286	265	42 398	26 846	65 991	45 726	28 451	72 152
At8c16cov0.9 vs. At11c16cov0.7	20 701 862	266	-713	38 992	-596 310	748 363	-28 717	-60 120	-15 605
At10c16cov0.8 vs. At8c16cov0.9	28 028 747	848	1 062	32 973	12 904	95 896	26 473	11 767	51 234
At11c16cov0.8 vs. At10c16cov0.8	12 243 243	275	255	44 105	27 880	68 634	47 613	29 595	75 131
At10c16cov0.9 vs. At11c16cov0.8	47 575 093	953	262	49 911	34 506	80 710	178 233	83 038	432 950
At11c16cov0.9 vs. At10c16cov0.9	12 271 390	266	247	45 740	28 914	71 042	49 408	30 754	77 923

** The options should be read as follows: at# stands for a particular adult vaccination option (see also Table 53); c# stands for a particular child option (see Table 51), covp stands for modelled vaccination coverage p for the child option c#.*

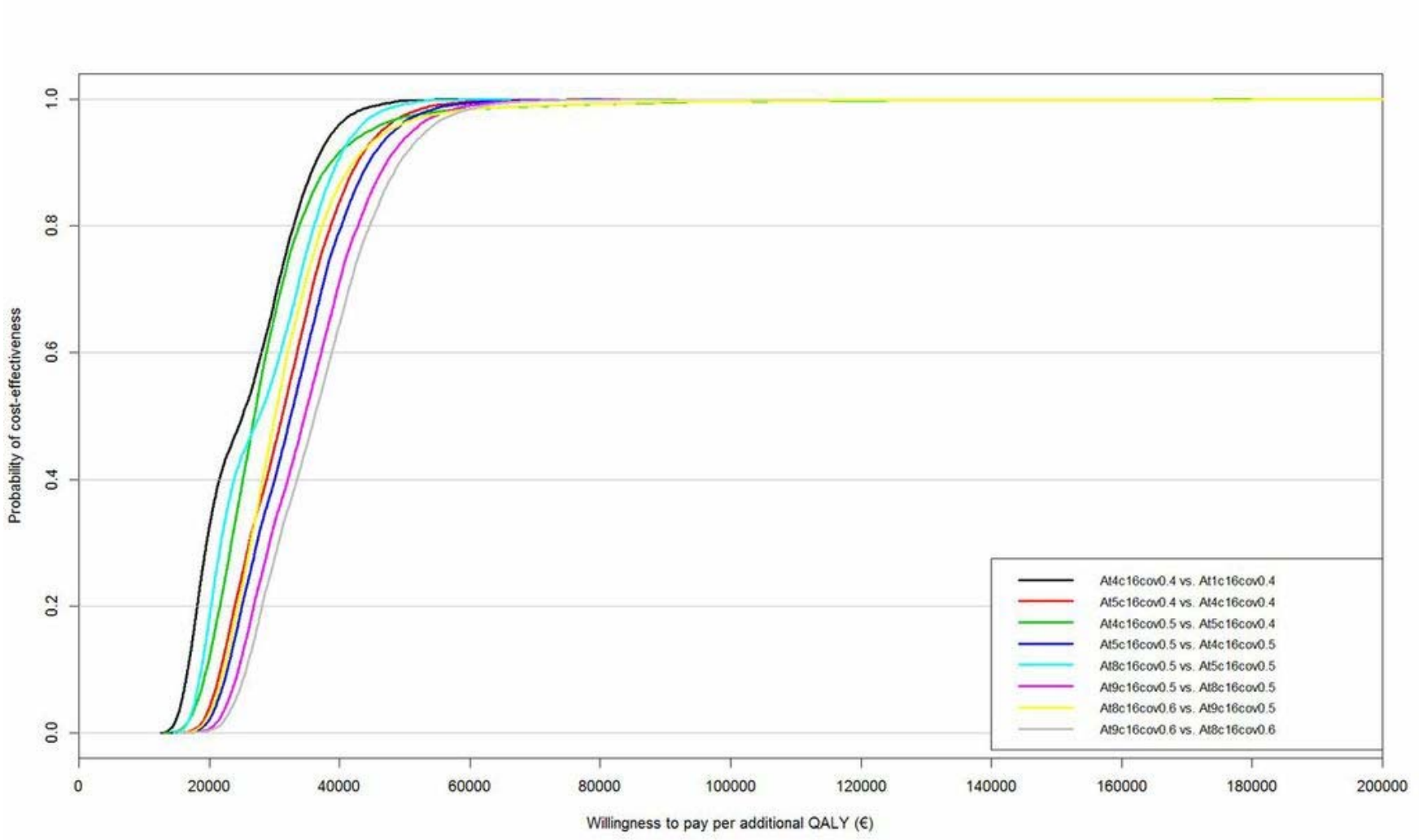
Adults vaccination options by age group (at=adult target, I= increase vaccination coverage; II: larger increase vaccination coverage (50-64 years only); D= decrease vaccination coverage):

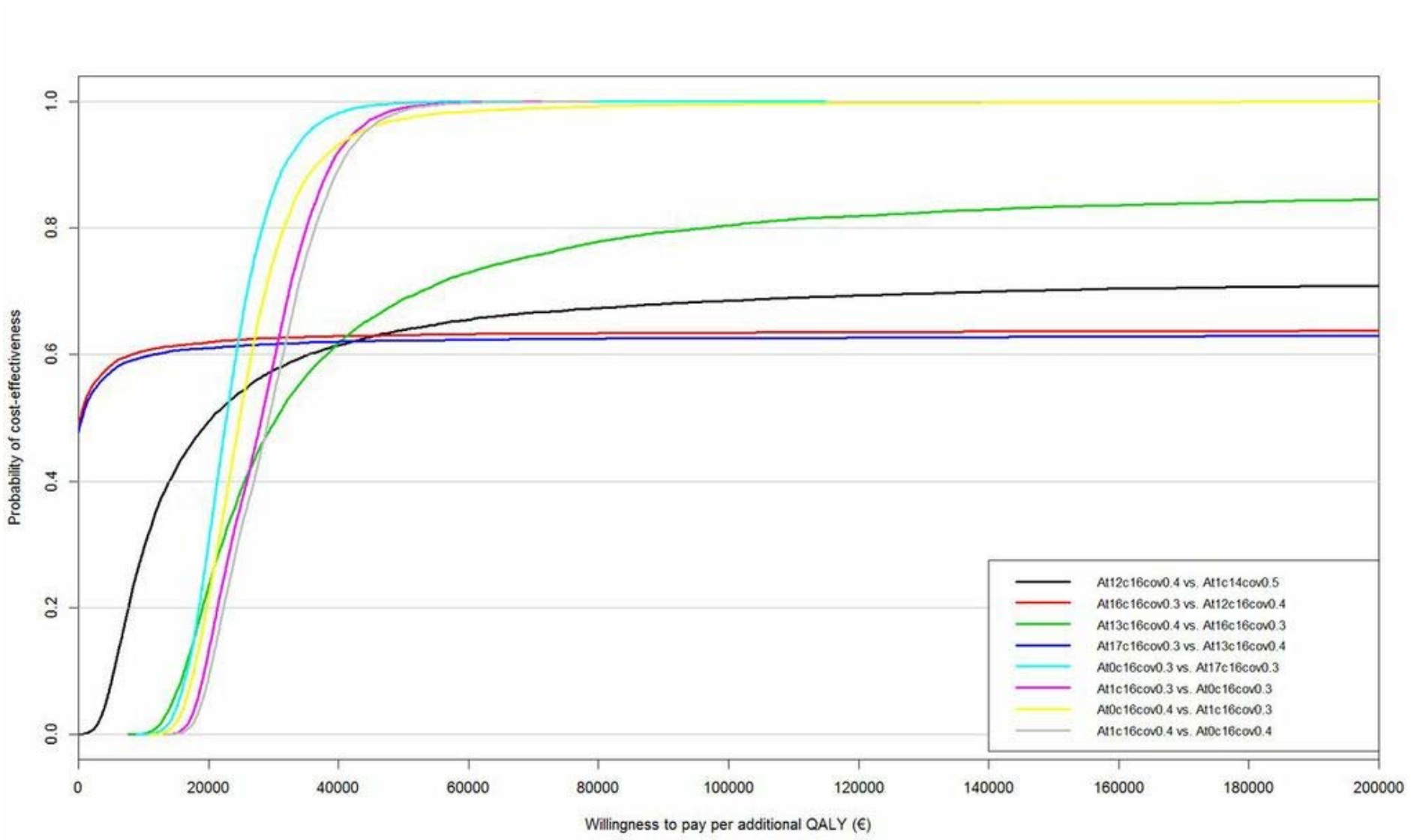
At1: I 75+	*At5: I 50-64 + I 75+*	*At9: II 50-64 + I 75+*	*At13: D 18-49 + I 75+*	*At17: D18-49 + I 50-64 + I 75+*	*At21: D18-49 + II 50-64 + I 75+*
At2: I 65-74	*At6: I 50-74*	*At10: II 50-64 + I 65-74*	*At14: D18-49 + I 65-74*	*At18: D18-49 + I 50-74*	*At22: D18-49 + II 50-64 + I 65-74*
At3: I 65-75+	*At7: I 50-75+*	*At11: II 50-64 + I 65-75+*	*At15: D18-49 + I 65-75+*	*At19: D18-49 + I 50-75+*	*At23: D18-49 + II 50-64 + I 65-75+*
At4: I 50-64	*At8: II 50-64*	*At12: D 18-49*	*At16: D18-49 + I 50-64*	*At20: D18-49 + II 50-64*	

Child vaccination options by age group (c=child option):

c1: TIV 0.5-2	*c5: IV 0.5-5*	*c8: TIV 2-18*	*c11: LAIV 2-5*	*c14: TIV 0.5-2 + LAIV 2-5*	*c17: LAIV 2-18*
c2: TIV 2-4	*c6: TIV 0.5-12*	*c9:TIV 5-18*	*c12: LAIV 5-12*	*c15: TIV 0.5-2+ LAIV 2-12*	*c18: LAIV 5-18*
c3: TIV 5-12	*c7: TIV 0.5-18*	*c10: TIV 2-12*	*c13: LAIV 12-18*	*c16: TIV 0.5-2 + LAIV 2-18*	*c19: LAIV 2-12*
c4: TIV 12-18					

Figure 46 – CEACs of the incremental analyses on child-adult combined vaccination options after elimination of dominated options for all coverage levels of the child components of the options combined (immunity lasts on average 6 years) (6 panels)




Probability of cost-effectiveness
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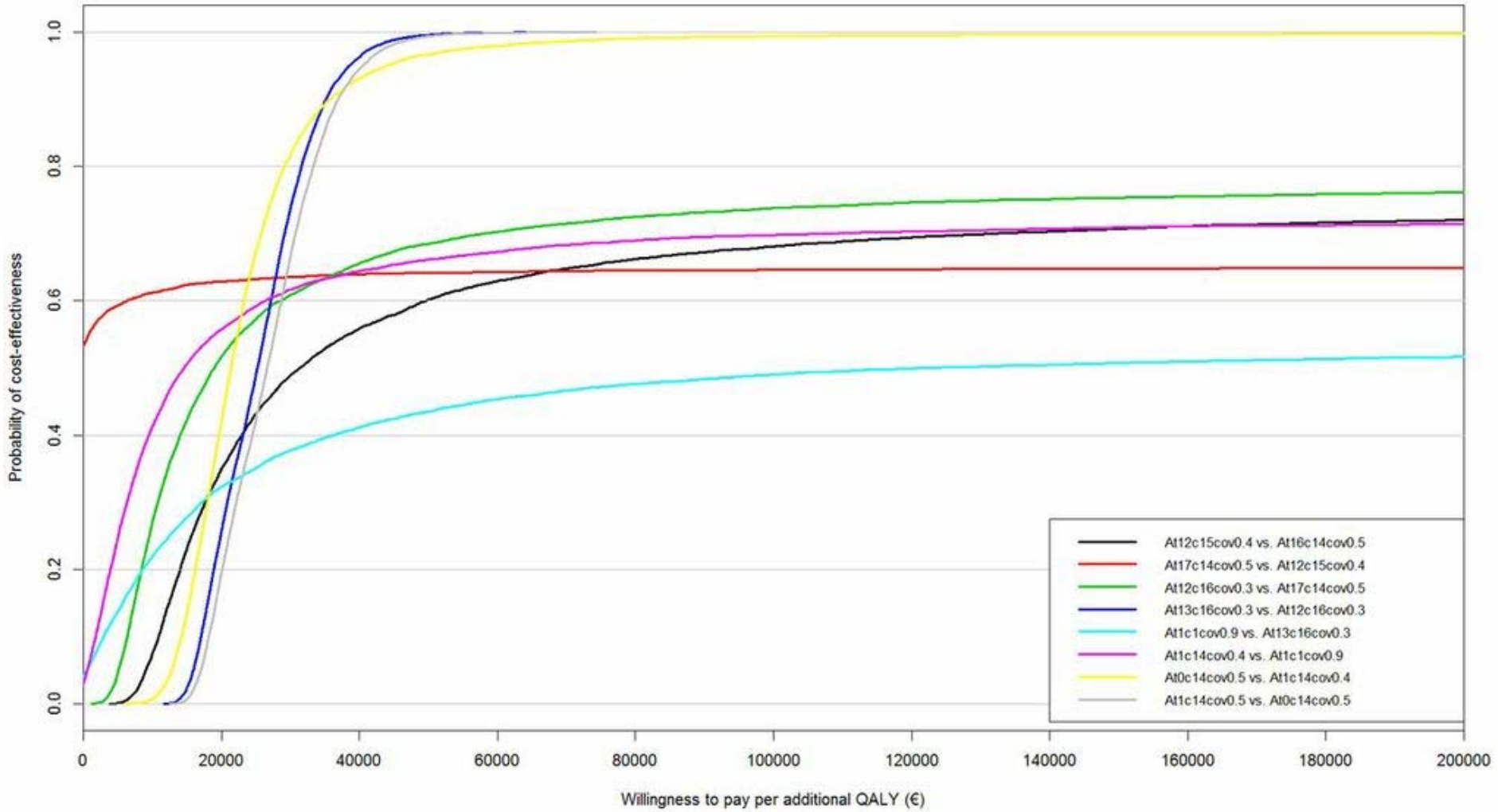
0.4
0.6
0.8
1.0
0
20000
40000
60000
80000
100000
120000
140000
160000
180000
200000
Willingness to pay per additional QALY (€)
At12c16cov0.4 vs. At1c14cov0.5
At16c16cov0.3 vs. At12c16cov0.4
At13c16cov0.4 vs. At16c16cov0.3
At17c16cov0.3 vs. At13c16cov0.4
At0c16cov0.3 vs. At17c16cov0.3
At1c16cov0.3 vs. At0c16cov0.3
At0c16cov0.4 vs. At1c16cov0.3
At1c16cov0.4 vs. At0c16cov0.4


Probability of cost-effectiveness
0.0
0.2
0.4
0.6
0.8
1.0
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20000
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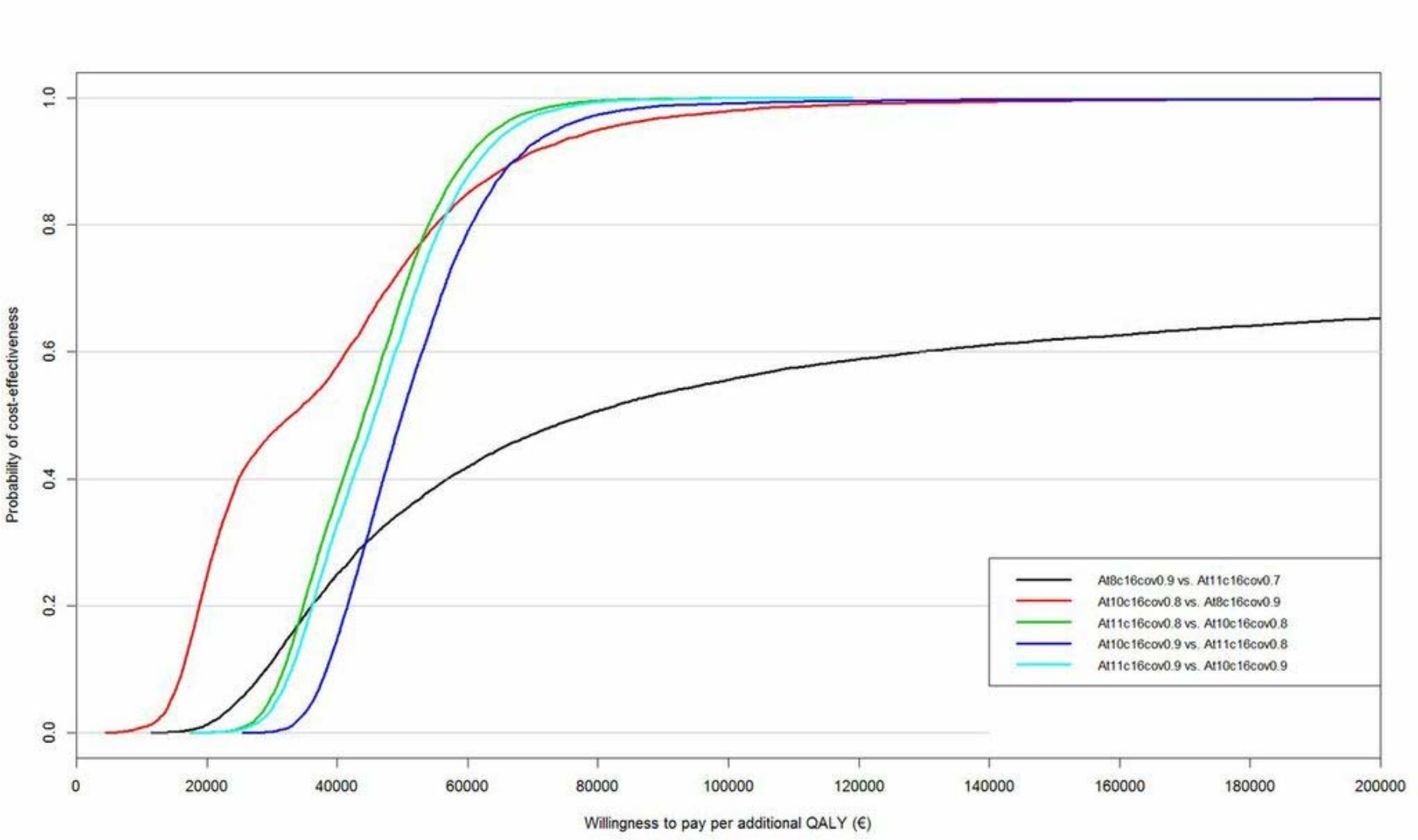
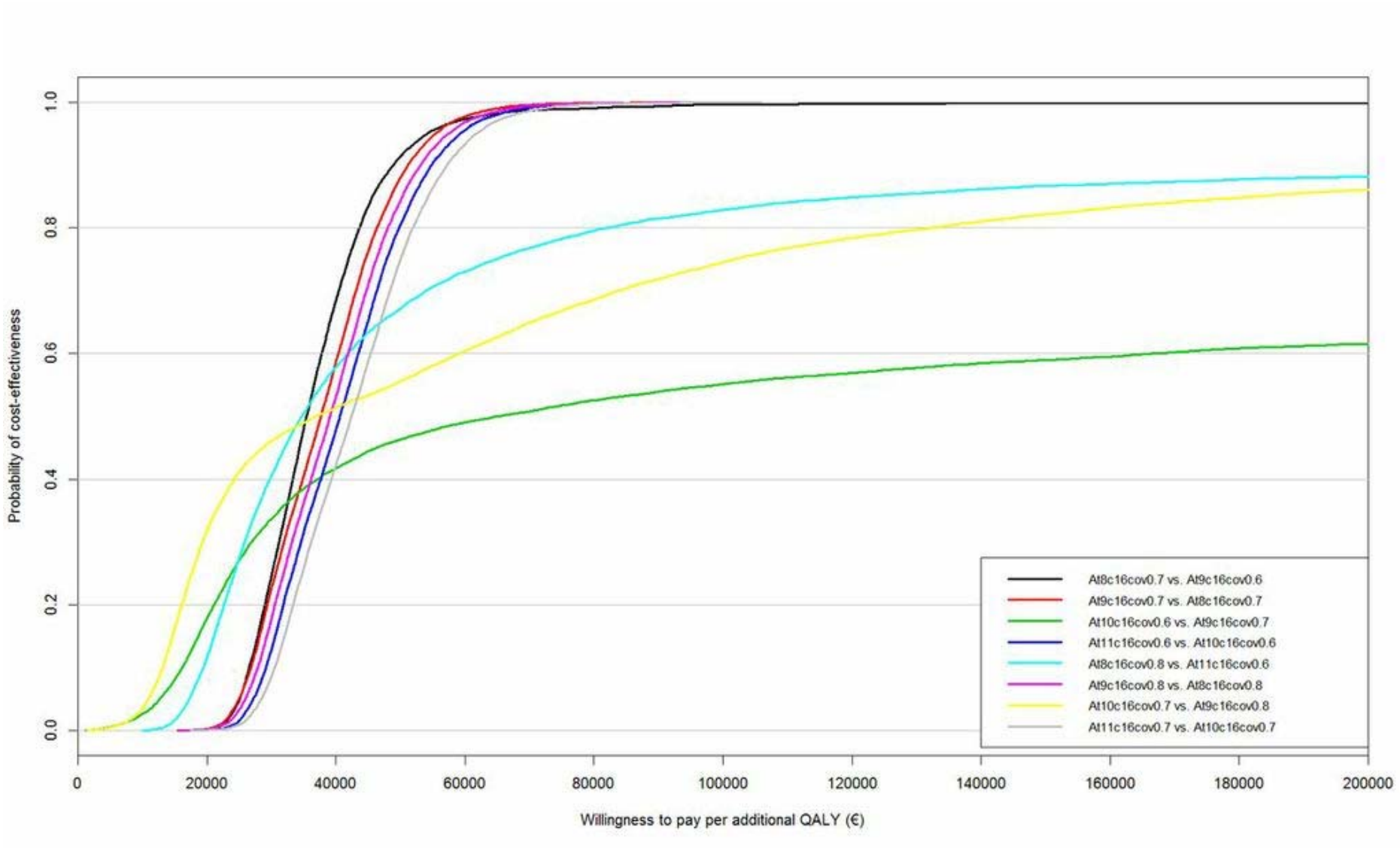
60000
80000
100000
120000
140000
160000
180000
200000
Willingness to pay per additional QALY (€)
At12c15cov0.4 vs. At16c14cov0.5
At17c14cov0.5 vs. At12c15cov0.4
At12c16cov0.3 vs. At17c14cov0.5
At13c16cov0.3 vs. At12c16cov0.3
At1c1cov0.9 vs. At13c16cov0.3
At1c14cov0.4 vs. At1c1cov0.9
At0c14cov0.5 vs. At1c14cov0.4
At1c14cov0.5 vs. At0c14cov0.5


Probability of cost-effectiveness
0.0
0.2
0.4
0.6
0.8
1.0
0
20000
40000
60000
80000
100000
120000
140000
160000
180000
200000
Willingness to pay per additional QALY (€)
At8c16cov0.9 vs. At11c16cov0.7
At10c16cov0.8 vs. At8c16cov0.9
At11c16cov0.8 vs. At10c16cov0.8
At10c16cov0.9 vs. At11c16cov0.8
At11c16cov0.9 vs. At10c16cov0.9


Probability of cost-effectiveness
0.0
0.2
0.4
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0.8
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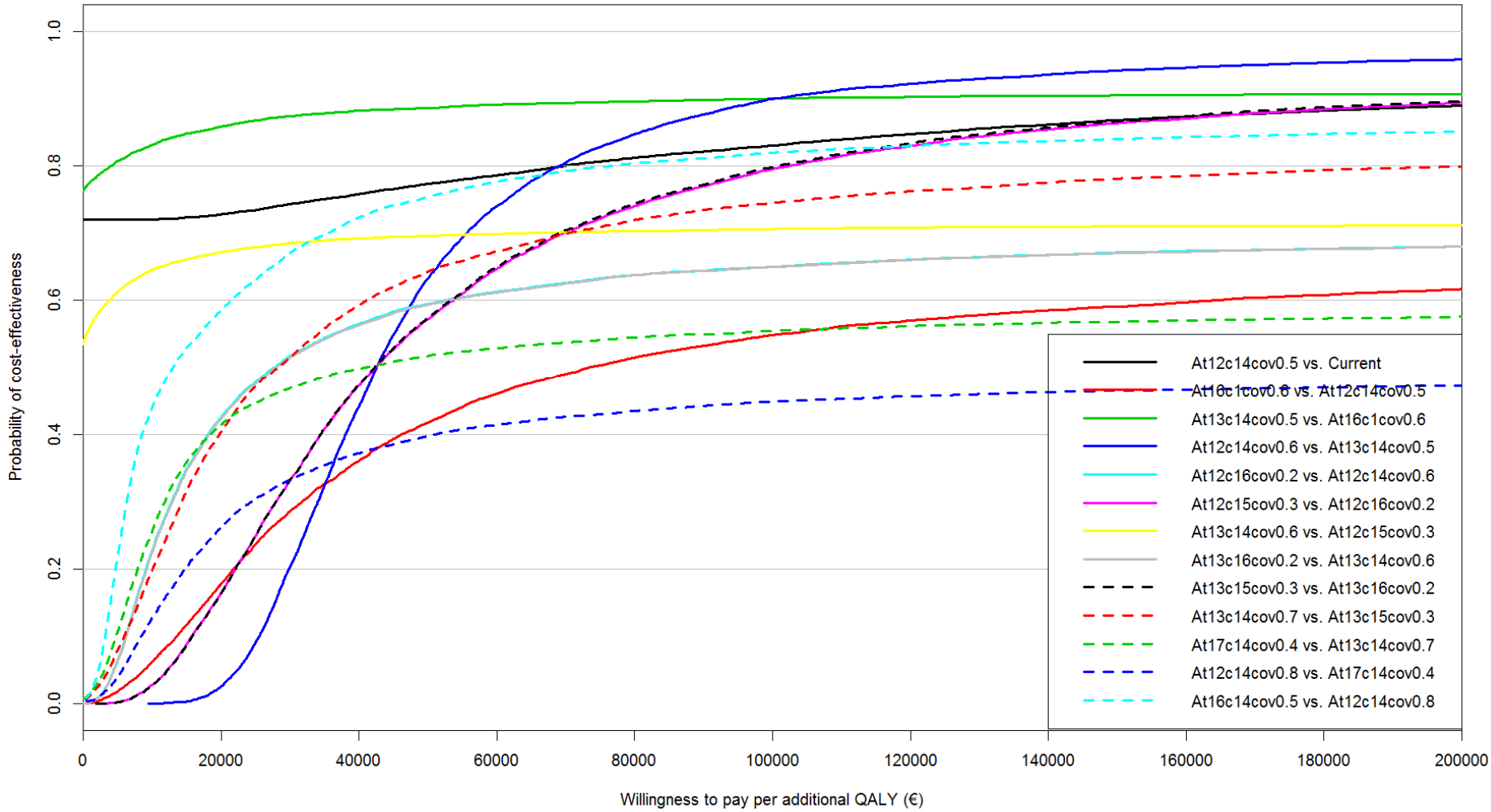
140000
160000
180000
200000
Willingness to pay per additional QALY (€)
At8c16cov0.7 vs. At9c16cov0.6
At9c16cov0.7 vs. At8c16cov0.7
At10c16cov0.6 vs. At9c16cov0.7
At11c16cov0.6 vs. At10c16cov0.6
At8c16cov0.8 vs. At11c16cov0.6
At9c16cov0.8 vs. At8c16cov0.8
At10c16cov0.7 vs. At9c16cov0.8
At11c16cov0.7 vs. At10c16cov0.7


Probability of cost-effectiveness
0.0
0.2
0.4
0.6
0.8
1.0
0
20000
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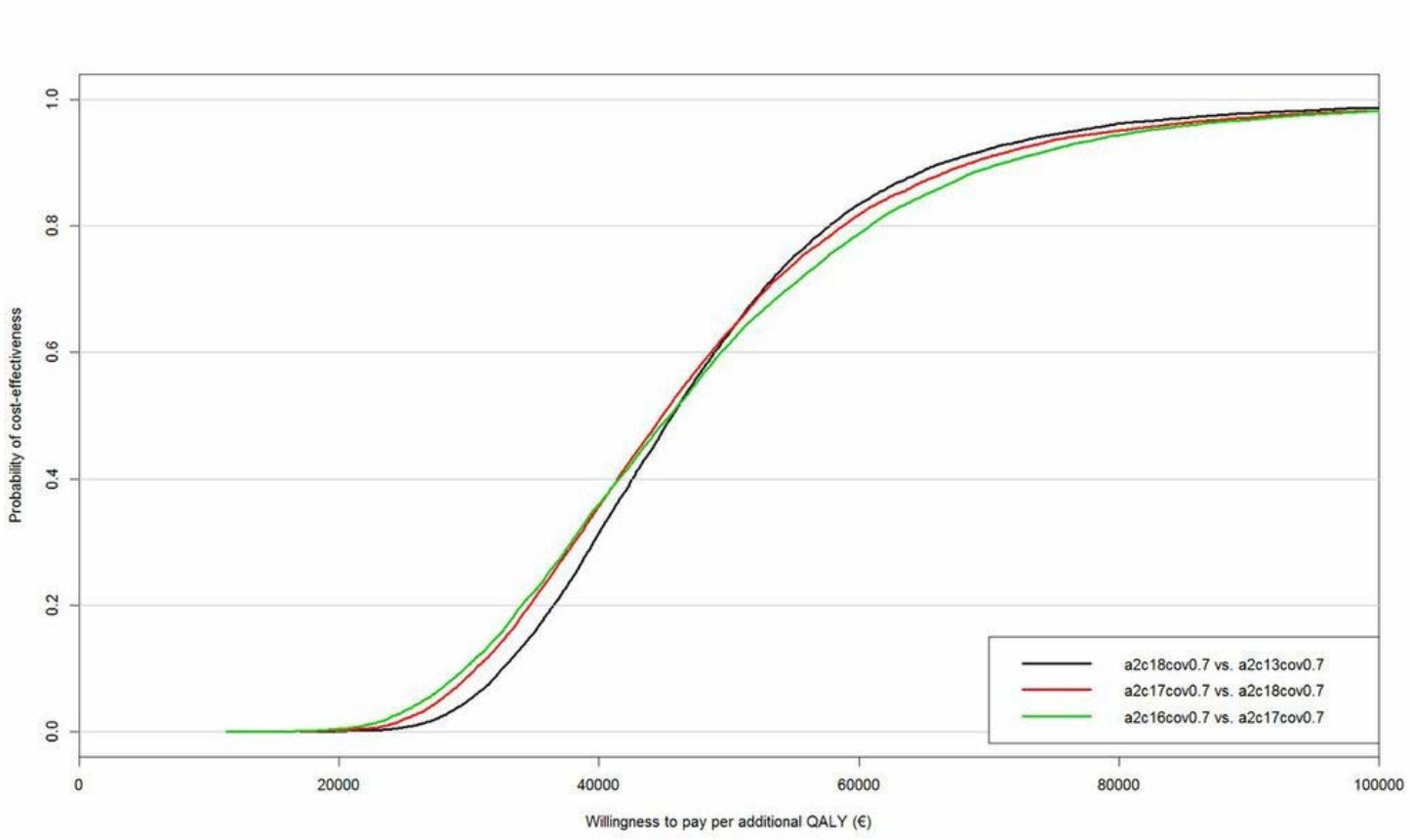
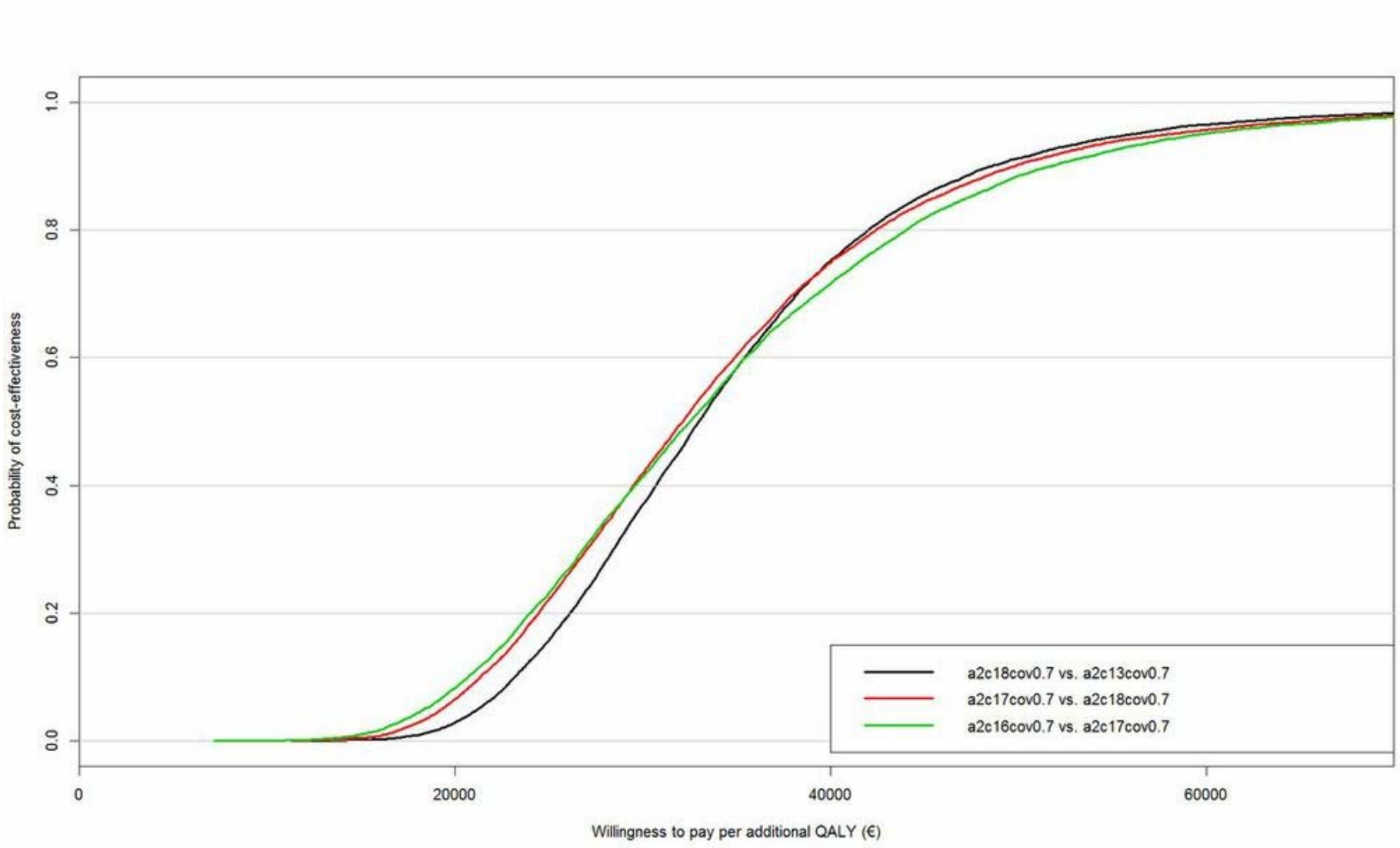
60000
80000
100000
120000
140000
160000
180000
200000
Willingness to pay per additional QALY (€)
At12c14cov0.5 vs. Current
At16c1cov0.6 vs. At12c14cov0.5
At13c14cov0.5 vs. At16c1cov0.6
At12c14cov0.6 vs. At13c14cov0.5
At12c16cov0.2 vs. At12c14cov0.6
At12c15cov0.3 vs. At12c16cov0.2
At13c14cov0.6 vs. At12c15cov0.3
At13c16cov0.2 vs. At13c14cov0.6
At13c15cov0.3 vs. At13c16cov0.2
At13c14cov0.7 vs. At13c15cov0.3
At17c14cov0.4 vs. At13c14cov0.7
At12c14cov0.8 vs. At17c14cov0.4
At16c14cov0.5 vs. At12c14cov0.8

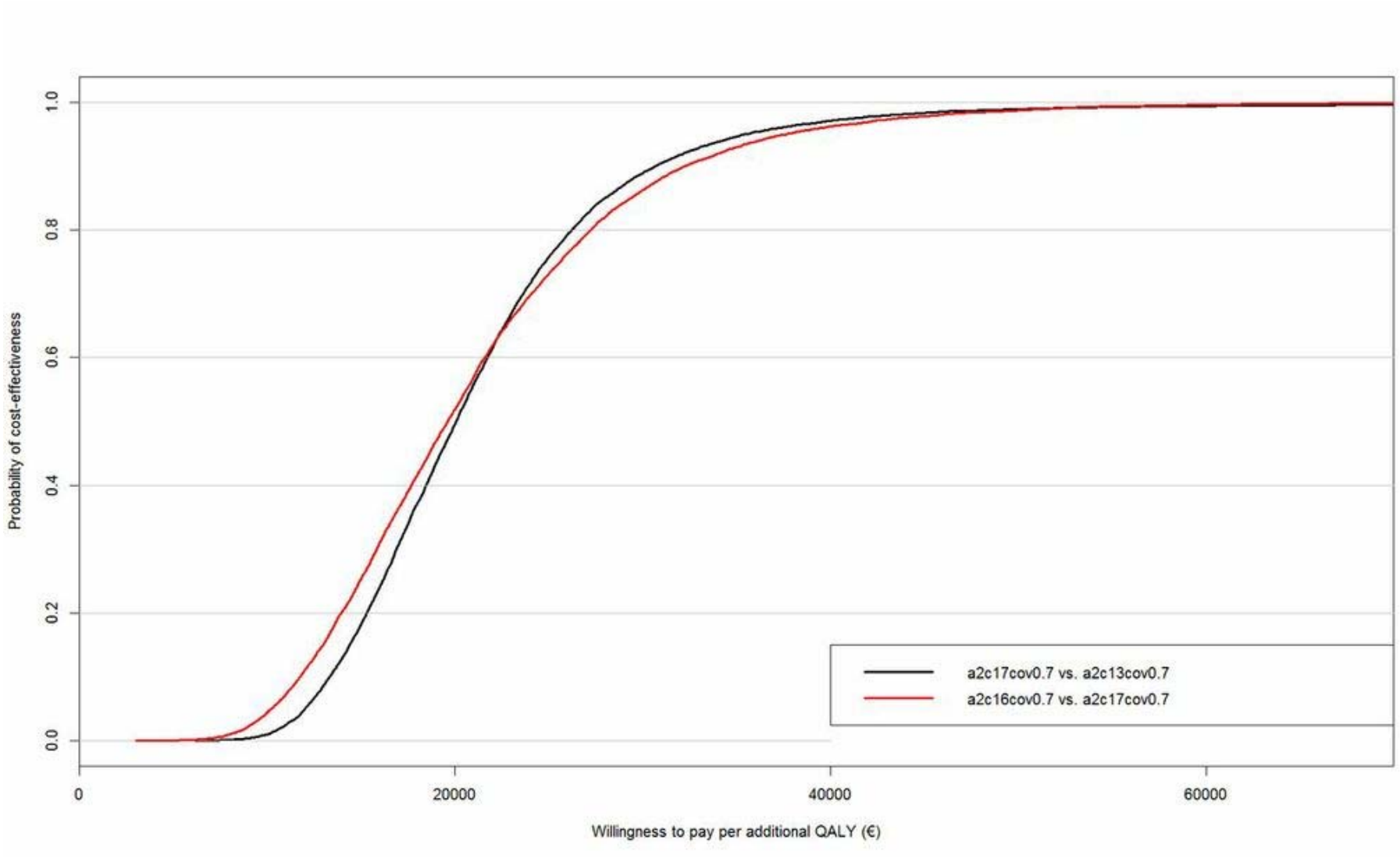
Overall impact of vaccination costs

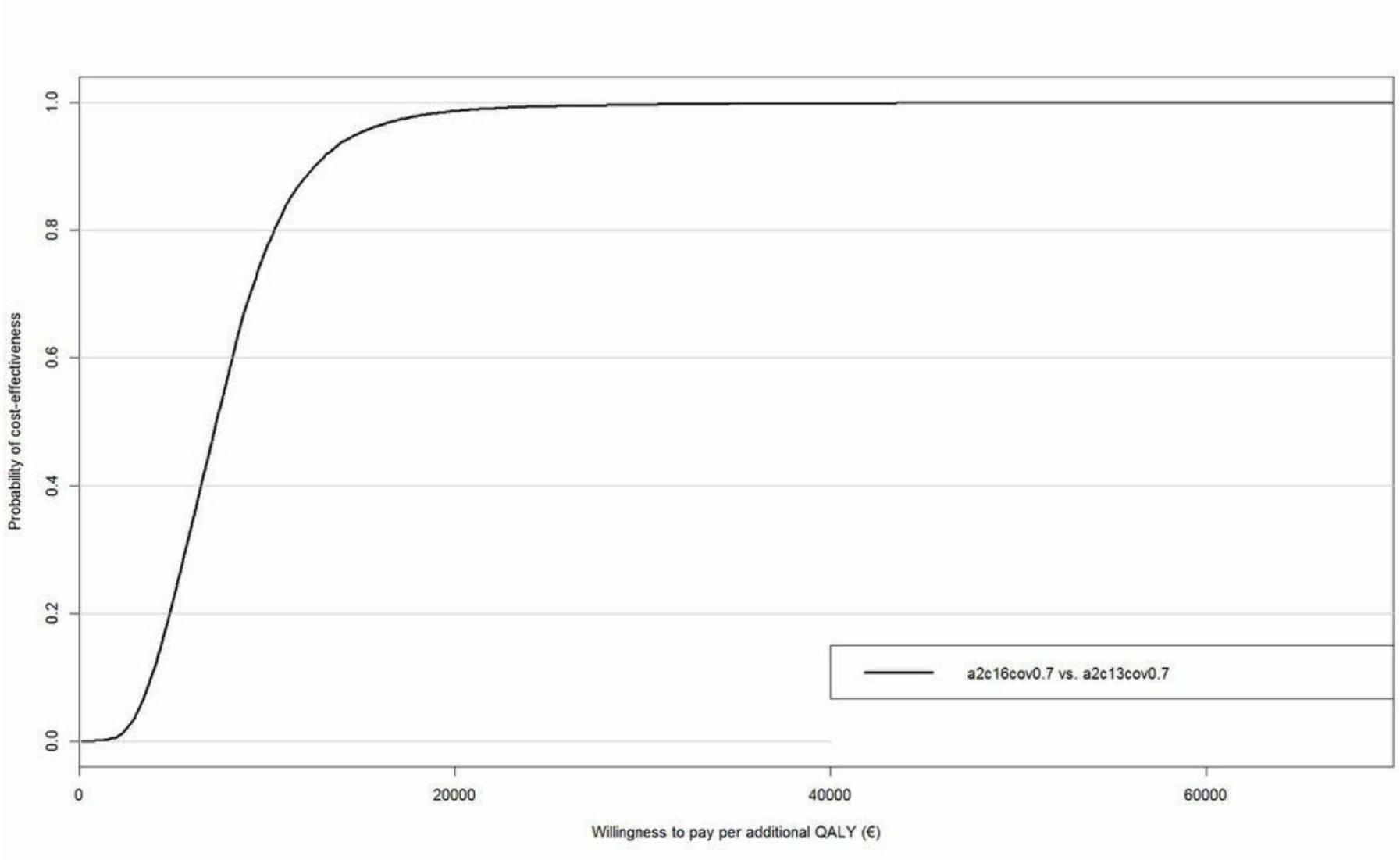
Here, we explore the impact of lowering the vaccination costs per dose by 25%, 50% or 75% for the case of adding childhood vaccination to current adult vaccination. Figure 47 shows that the impact is very high, basically shifting the CEACs from the incremental analysis to the left and upward, indicating that the ICERs becomes considerably more attractive and less uncertain when vaccination costs can be reduced. The hierarchy of the most cost-effective options is similar than the one shown with the base case cost, if adult vaccination remains constant (see figures below).

Figure 47 – Influence of decreased vaccination costs per dose on dominant vaccination options for adding childhood vaccination at 70% coverage to the current adult vaccination options, when immunity lasts on average 1.68 years. From top to bottom: no decrease, 25%, 50% and 75% decrease in vaccination costs per dose




Probability of cost-effectiveness
0.0
0.2
0.4
0.6
0.8
1.0
0
20000
40000
60000
Willingness to pay per additional QALY (€)
a2c18cov0.7 vs. a2c13cov0.7
a2c17cov0.7 vs. a2c18cov0.7
a2c16cov0.7 vs. a2c17cov0.7


Probability of cost-effectiveness
0.0
0.2
0.4
0.6
0.8
1.0
0
20000
40000
60000
Willingness to pay per additional QALY (€)
a2c17cov0.7 vs. a2c13cov0.7
a2c16cov0.7 vs. a2c17cov0.7


Probability of cost-effectiveness
0.0
0.2
0.4
0.6
0.8
1.0
0
20000
40000
60000
Willingness to pay per additional QALY (€)
a2c16cov0.7 vs. a2c13cov0.7

Identifying the optimal expansion path under decreasing vaccination costs in children

First we examine the case of continued adult vaccination at current vaccination coverage (a2), with the potential addition of 19 childhood vaccination targets (see Table 51) at 9 different levels of coverage (i.e. 171 options), assuming an immunity waning on an average of 1.68 years (Table 62).

Table 62 – Incremental costs, life-years gained, QALYs gained and ICERs (€) along the expansion path of increased vaccination coverage for 19 child vaccination options with 9 different coverage levels each, whilst assuming vaccination costs per dose are 25% lower for children (<18y) than for adults, adult vaccination remains constant over a 10 year time span, and with immunity lasting on average 1.68 years

Vaccination option *	Median incremental cost	Median QALYs gained	Median life-years gained	Incremental direct costs per QALY gained			Incremental direct costs per life-year gained		
				Median	2.50%	97.50%	Median	2.50%	97.50%
a2c13cov0.2	26 844 539	978	417	27 349	16 070	68 257	63 969	29 359	207 362
a2c13cov0.3	40 428 720	1 441	611	28 000	16 453	68 142	65 764	30 336	197 997
a2c13cov0.4	54 015 699	1 903	815	28 337	16 671	69 174	65 924	30 783	206 098
a2c13cov0.5	67 698 501	2 347	1 005	28 851	17 150	71 668	67 063	31 489	211 447
a2c13cov0.6	81 491 242	2 768	1 181	29 421	17 455	74 082	68 603	31 809	220 792
a2c13cov0.7	95 328 214	3 175	1 355	29 972	17 747	71 972	69 901	32 549	206 817
a2c18cov0.3	98 542 887	3 256	1 353	30 237	18 129	66 200	72 578	34 099	200 999
a2c18cov0.4	131 563 413	4 327	1 819	30 381	18 260	65 346	72 071	34 275	204 338
a2c17cov0.4	165 514 851	5 389	2 326	30 714	18 295	66 445	71 055	33 821	195 906
a2c16cov0.4	182 898 676	5 913	2 599	30 867	18 302	65 310	70 425	33 569	185 283
a2c17cov0.5	207 116 152	6 681	2 899	30 958	18 643	68 522	71 168	34 237	196 854
a2c16cov0.5	228 763 699	7 343	3 246	31 132	18 611	67 284	70 626	33 782	188 458
a2c17cov0.6	248 642 847	7 928	3 452	31 350	18 652	68 205	72 051	33 685	192 926
a2c16cov0.6	274 361 394	8 720	3 873	31 409	18 546	67 034	70 936	33 319	184 935
a2c17cov0.7	290 097 076	9 118	3 987	31 807	18 756	66 309	72 630	34 368	187 973

a2c16cov0.7	320 003 888	10 036	4 467	31 914	18 702	65 468	71 629	33 800	178 170
a2c17cov0.8	330 819 568	10 336	4 557	32 009	19 235	66 617	72 836	35 011	185 933
a2c16cov0.8	364 562 469	11 381	5 098	32 058	19 058	66 099	71 587	34 427	177 984
a2c17cov0.9	370 536 596	11 426	5 083	32 443	19 400	70 909	72 882	35 239	193 480
a2c16cov0.9	408 128 448	12 571	5 693	32 460	19 317	70 032	71 705	34 656	184 562

** The options should be read as follows: a2 stands for current adolescent vaccination; c# stands for a particular child option (see Table 51), covp stands for modelled vaccination coverage p for the child option c#. Eg: a2c16cov0.4 : current adult vaccination supplemented with vaccination at 40% coverage in children aged 0.5-2 years using TIV, and in children aged 2-18 years using LAIV. Each incremental analysis uses as reference strategy the previous listed option.*

The optimal path selection is compared for different assumptions regarding childhood vaccination costs per dose, in Table 63 for a waning of 1.68 years and in Table 64 for a waning of immunity of 6 years. Both tables demonstrate that under a given duration of waning immunity, reductions in the vaccination costs per dose for children do not alter the optimal path selection dramatically. However, the optimal path becomes considerably shorter for a shorter duration of immunity, and with progressively lower vaccination costs. As shown above, the ICERs are considerably lower (i.e. more attractive) when immunity wanes less rapidly. For sufficiently low vaccination costs (75% reduction from base) and a decline in waning immunity over 6 years, many of the additional options along the expansion path show cost savings. These results also indicate that at accelerated waning over 1.68 years, and for a rather small (25%) reduction in vaccination costs per dose, the ICERs of the most effective options along the path remain below €35 000 per QALY.

Table 63 – Selection of optimal expansion paths along the efficiency frontier, identified by criteria of dominance and extended dominance for 19 child options for vaccination at 9 different coverage levels combined with continued current adult vaccination strategies (i.e. 171 options), assuming various levels of vaccination costs per dose for child (<18y) vaccination and an average duration until waned immunity of 1.68 years

Vaccination costs per dose	Base		25% reduction from base		50% reduction from base		75% reduction from base	
	Option	ICER	Option	ICER	Option	ICER	Option	ICER
Rank 1	a2c13cov0.2	38 008	a2c13cov0.2	27 349	a2c13cov0.2	16 708	a2c13cov0.1	6093
Rank 2	a2c13cov0.3	38 856	a2c13cov0.3	28 000	a2c13cov0.3	17 171	a2c13cov0.2	6101
Rank 3	a2c13cov0.4	39 345	a2c13cov0.4	28 337	a2c13cov0.4	17 378	a2c13cov0.3	6316
Rank 4	a2c13cov0.5	39 959	a2c13cov0.5	28 851	a2c13cov0.5	17 737	a2c13cov0.4	6421
Rank 5	a2c13cov0.6	40 740	a2c13cov0.6	29 421	a2c13cov0.6	18 109	a2c13cov0.5	6603

Vaccination costs per dose	Base		25% reduction from base		50% reduction from base		75% reduction from base	
	Option	ICER	Option	ICER	Option	ICER	Option	ICER
Rank 6	a2c13cov0.7	41 515	a2c13cov0.7	29 972	a2c13cov0.7	18 471	a2c17cov0.2	6709
Rank 7	a2c18cov0.3	41 895	a2c18cov0.3	30 237	a2c18cov0.3	18 563	a2c16cov0.2	6730
Rank 8	a2c13cov0.8	42 046	a2c18cov0.4	30 381	a2c18cov0.4	18 666	a2c16cov0.4	6844
Rank 9	a2c18cov0.4	42 083	a2c17cov0.4	30 714	a2c17cov0.4	18 781	a2c16cov0.5	6945
Rank 10	a2c18cov0.5	42 504	a2c16cov0.4	30 867	a2c16cov0.4	18 863	a2c16cov0.6	7050
Rank 11	a2c17cov0.4	42 649	a2c17cov0.5	30 958	a2c17cov0.5	18 973	a2c16cov0.7	7216
Rank 12	a2c16cov0.4	42 944	a2c16cov0.5	31 132	a2c16cov0.5	19 042	a2c16cov0.8	7293
Rank 13	a2c17cov0.5	42 965	a2c17cov0.6	31 350	a2c17cov0.6	19 203	a2c16cov0.9	7430
Rank 14	a2c16cov0.5	43 198	a2c16cov0.6	31 409	a2c16cov0.6	19 232		
Rank 15	a2c17cov0.6	43 479	a2c17cov0.7	31 807	a2c17cov0.7	19 513		
Rank 16	a2c16cov0.6	43 631	a2c16cov0.7	31 914	a2c16cov0.7	19 557		
Rank 17	a2c17cov0.7	44 068	a2c17cov0.8	32 009	a2c16cov0.8	19 685		
Rank 18	a2c16cov0.7	44 238	a2c16cov0.8	32 058	a2c16cov0.9	19 943		
Rank 19	a2c17cov0.8	44 280	a2c17cov0.9	32 443				
Rank 20	a2c16cov0.8	44 415	a2c16cov0.9	32 460				
Rank 21	a2c17cov0.9	44 909						
Rank 22	a2c16cov0.9	44 990						

The amounts listed are the incremental direct costs per QALY gained versus the next best alternative (i.e. the previously ranked option).

Table 64 – Selection of optimal expansion path along the efficiency frontier, identified by criteria of dominance and extended dominance for 19 child options for vaccination at 9 different coverage levels combined with continued current adult vaccination strategies (i.e. 171 options), assuming various levels of vaccination costs per dose for child (<18y) vaccination and an average duration until waned immunity of 6 years

Vaccination costs per dose	Base		25% reduction from base		50% reduction from base		75% reduction from base	
	Option	ICER	Option	ICER	Option	ICER	Option	ICER
Rank 1	a2c1cov0.1	16 514	a2c1cov0.1	10 646	a2c1cov0.1	4784	a2c1cov0.1	cost saving
Rank 2	a2c14cov0.1	16 788	a2c14cov0.1	10 890	a2c1cov0.2	4945	a2c1cov0.2	cost saving
Rank 3	a2c1cov0.3	17 137	a2c1cov0.3	11 141	a2c14cov0.1	4996	a2c1cov0.3	cost saving
Rank 4	a2c1cov0.4	17 311	a2c1cov0.4	11 244	a2c1cov0.3	5110	a2c1cov0.4	cost saving
Rank 5	a2c14cov0.2	17 546	a2c1cov0.5	11 467	a2c1cov0.4	5164	a2c1cov0.5	cost saving
Rank 6	a2c1cov0.5	17 583	a2c1cov0.6	11 708	a2c1cov0.5	5337	a2c1cov0.6	cost saving
Rank 7	a2c1cov0.6	17 919	a2c1cov0.7	11 835	a2c1cov0.6	5506	a2c1cov0.7	cost saving
Rank 8	a2c1cov0.7	18 109	a2c14cov0.3	12 091	a2c1cov0.7	5566	a2c1cov0.8	cost saving
Rank 9	a2c14cov0.3	18 327	a2c1cov0.8	12 120	a2c1cov0.8	5779	a2c1cov0.9	cost saving
Rank 10	a2c1cov0.8	18 435	a2c1cov0.9	12 413	a2c1cov0.9	5975	a2c14cov0.4	cost saving
Rank 11	a2c1cov0.9	18 839	a2c14cov0.4	12 617	a2c14cov0.4	6174	a2c14cov0.5	cost saving
Rank 12	a2c14cov0.4	19 070	a2c14cov0.5	13 253	a2c14cov0.5	6607	a2c14cov0.6	206
Rank 13	a2c14cov0.5	19 868	a2c14cov0.6	13 964	a2c14cov0.6	7091	a2c14cov0.7	421
Rank 14	a2c16cov0.2	20 824	a2c16cov0.2	14 256	a2c14cov0.7	7497	a2c14cov0.8	678
Rank 15	a2c15cov0.3	21 394	a2c15cov0.3	14 559	a2c14cov0.8	7996	a2c14cov0.9	902
Rank 16	a2c16cov0.3	21 612	a2c14cov0.7	14 560	a2c16cov0.3	8066	a2c15cov0.4	1146
Rank 17	a2c16cov0.4	22 404	a2c16cov0.3	14 835	a2c16cov0.4	8452	a2c16cov0.3	1295
Rank 18	a2c16cov0.5	23 383	a2c16cov0.4	15 418	a2c16cov0.5	8960	a2c15cov0.5	1439
Rank 19	a2c16cov0.6	24 622	a2c16cov0.5	16 169	a2c16cov0.6	9567	a2c16cov0.4	1484

Rank 20	a2c16cov0.7	25 800	a2c16cov0.6	17 102	a2c16cov0.7	10 176	a2c16cov0.5	1753
Rank 21	a2c16cov0.8	27 261	a2c16cov0.7	18 008	a2c16cov0.8	10 920	a2c16cov0.6	2056
Rank 22	a2c16cov0.9	28 781	a2c16cov0.8	19 083	a2c16cov0.9	11 679	a2c16cov0.7	2374
Rank 23			a2c16cov0.9	20 215			a2c16cov0.8	2747
Rank 24							a2c16cov0.9	3118

The amounts listed are the incremental direct costs per QALY gained versus the next best alternative (i.e. the previously ranked option).

Table 65 show that the selection of options does not differ substantially under different levels of vaccination costs per dose, but that the associated incremental cost-effectiveness ratios become substantially lower for children options that use lower cost doses in children, whereas the expansion of adult options when childhood vaccination is already widespread at high levels of coverage is less attractive, and – as one would expect – independent of changes to vaccination costs for children.

Table 65 – Selection of optimal expansion path along the efficiency frontier, identified by criteria of dominance and extended dominance for 19 child options for vaccination at 9 different coverage levels combined with 23 adult vaccination strategies (i.e. 3933 options), assuming various levels of vaccination costs per dose for child (<18y) vaccination and an average duration until waned immunity of 1.68 years; the amounts listed are the incremental direct costs (€) per QALY gained versus the next best alternative

Vaccination costs per dose	Base		25% reduction from base		50% reduction from base		75% reduction from base	
	Option	ICER	Option	ICER	Option	ICER	Option	ICER
Rank 1	At17c4cov0.2 vs. At17c12cov0.1	65 639	At13c7cov0.2 vs. At13c4cov0.6	99494	At13c7cov0.2 vs. At13c6cov0.3	-113 895	At13c7cov0.2 vs. At13c6cov0.3	-46 612
Rank 2	At17c19cov0.1	-703	At17c4cov0.2	-17 411	At12c4cov0.8	-1618	At12c4cov0.8	-46 551
Rank 3	At17c13cov0.2	-10 324	At13c13cov0.5	-31 474	At13c9cov0.3	43 449	At13c5cov0.8	46 656
Rank 4	At15c1cov0.1	-10 033	At17c19cov0.1	30 067	At13c4cov0.7	-37 760	At13c9cov0.3	-30 684
Rank 5	At15c11cov0.1	48 153	At16c17cov0.1	-8591	At13c3cov0.6	172 892	At12c3cov0.7	-4581
Rank 6	At15c1cov0.2	45 049	At13c19cov0.3	-26 003	At13c17cov0.2	-48 040	At12c6cov0.4	-53 314
Rank 7	At15c4cov0.1	7811	At17c13cov0.2	6221	At12c13cov0.7	-14 326	At12c8cov0.3	-11 020
Rank 8	At15c13cov0.1	-4628	At13c17cov0.2	-16 604	At12c18cov0.3	20 391	At13c4cov0.7	12 681

Rank 9	At15c12cov0.1	85 043	At13c13cov0.6	-11 054	At13c13cov0.6	-1592	At12c10cov0.5	7571
Rank 10	At15c13cov0.2	30 092	At13c16cov0.2	67 043	At13c15cov0.3	55 135	At12c4cov0.9	-41 209
Rank 11	At15c18cov0.1	73 574	At15c13cov0.1	1856	At13c16cov0.2	-38 954	At12c9cov0.4	31 994
Rank 12	At15c13cov0.3	32 820	At13c13cov0.7	-6911	At12c13cov0.8	-1332	At13c14cov0.8	24
Rank 13	At15c16cov0.1	125 904	At13c18cov0.3	37 385	At13c13cov0.7	17 075	At13c4cov0.8	-4747
Rank 14	At15c13cov0.4	28 663	At13c13cov0.8	29 271	At13c18cov0.3	20 774	At12c7cov0.3	-38 855
Rank 15	At19c13cov0.1	8880	At12c18cov0.4	58 186	At12c15cov0.4	64 022	At13c16cov0.2	-9728
Rank 16	At15c13cov0.5	26 099	At13c13cov0.9	10 436	At13c19cov0.4	-3772	At13c6cov0.4	4750
Rank 17	At19c13cov0.2	10 090	At13c18cov0.4	33 488	At12c17cov0.3	-14 888	At13c8cov0.3	-11 041
Rank 18	At19c18cov0.1	72 256	At13c16cov0.3	44 284	At12c13cov0.9	-4039	At12c13cov0.8	-24 119
Rank 19	At19c13cov0.3	32 087	At12c18cov0.5	38 588	At13c13cov0.8	17 156	At12c10cov0.6	1937
Rank 20	At19c13cov0.4	43 395	At12c17cov0.4	334	At12c18cov0.4	12 933	At12c15cov0.4	-26 244
Rank 21	At19c13cov0.5	44 686	At13c18cov0.5	22 691	At12c16cov0.3	22 132	At13c19cov0.4	47 389
Rank 22	At23c13cov0.2	8783	At13c17cov0.4	582	At13c17cov0.3	27 175	At12c12cov0.7	-23 346
Rank 23	At19c13cov0.6	26 654	At12c16cov0.4	38 234	At13c13cov0.9	-4031	At12c17cov0.3	-29 739
Rank 24	At23c13cov0.3	10 394	At13c16cov0.4	24 302	At13c18cov0.4	19 600	At12c13cov0.9	-6497
Rank 25	At23c13cov0.4	42 574	At13c18cov0.6	34 132	At13c16cov0.3	22 251	At12c19cov0.5	10 362
Rank 26	At23c13cov0.5	43 870	At13c17cov0.5	33 502	At12c18cov0.5	15 188	At12c9cov0.5	-2460
Rank 27	At23c13cov0.6	45 310	At12c16cov0.5	55 582	At12c17cov0.4	-9158	At13c13cov0.8	-12 651
Rank 28	At23c13cov0.7	46 902	At13c16cov0.5	24 801	At12c16cov0.4	21 442	At12c18cov0.4	-31 844
Rank 29	At23c18cov0.3	53 418	At13c18cov0.7	7360	At12c18cov0.6	22 971	At12c16cov0.3	145
Rank 30	At23c13cov0.8	39 025	At12c17cov0.6	29 755	At13c16cov0.4	-5141	At13c17cov0.3	70 528
Rank 31	At23c13cov0.9	50 655	At13c17cov0.6	24 983	At12c17cov0.5	12 223	At13c13cov0.9	-6986
Rank 32	At23c18cov0.4	44 823	At13c16cov0.6	35 108	At13c18cov0.6	33 384	At12c15cov0.5	-17 128
Rank 33	At11c13cov0.4	36 439	At13c17cov0.7	38 651	At13c17cov0.5	18 198	At12c19cov0.6	15 297

Rank 34	At11c13cov0.5	41 121	At13c16cov0.7	34 845	At12c16cov0.5	9085	At12c12cov0.9	33 202
Rank 35	At11c13cov0.6	42 597	At13c17cov0.8	45 370	At12c18cov0.7	8249	At13c16cov0.3	-8257
Rank 36	At11c13cov0.7	44 274	At17c16cov0.6	6279	At13c16cov0.5	18 931	At12c17cov0.4	-10 253
Rank 37	At11c18cov0.3	49 600	At17c17cov0.7	37 003	At12c17cov0.6	3442	At12c15cov0.6	31 329
Rank 38	At11c13cov0.8	40 699	At13c16cov0.8	27 881	At13c17cov0.6	24 983	At12c16cov0.4	-11 036
Rank 39	At11c18cov0.4	42 297	At13c17cov0.9	43 259	At12c16cov0.6	14 178	At12c18cov0.6	12 059
Rank 40	At11c18cov0.5	42 799	At17c16cov0.7	20 484	At13c18cov0.8	30 630	At13c16cov0.4	10 104
Rank 41	At11c17cov0.4	15 353	At17c17cov0.8	43 227	At12c17cov0.7	8362	At12c15cov0.7	-2930
Rank 42	At11c18cov0.6	43 013	At13c16cov0.9	32 079	At13c16cov0.6	-1414	At12c17cov0.5	-16 669
Rank 43	At11c17cov0.5	42 071	At17c16cov0.8	30 773	At12c18cov0.9	-14 476	At13c18cov0.6	55 670
Rank 44	At11c16cov0.5	45 835	At17c17cov0.9	43 348	At13c17cov0.7	13 378	At12c16cov0.5	-13 760
Rank 45	At11c18cov0.7	7010	At21c16cov0.7	23 220	At12c16cov0.7	15 862	At12c18cov0.7	9077
Rank 46	At11c17cov0.6	40 150	At17c16cov0.9	32 037	At12c17cov0.8	30 059	At12c17cov0.6	4524
Rank 47	At11c16cov0.6	45 712	At21c16cov0.8	36 550	At13c16cov0.7	15 114	At12c18cov0.8	17 461
Rank 48	At11c17cov0.7	44 302	At21c17cov0.9	43 105	At13c17cov0.8	30 209	At12c16cov0.6	-1325
Rank 49	At11c16cov0.7	45 871	At21c16cov0.9	33 987	At12c16cov0.8	16 636	At12c17cov0.7	11 194
Rank 50	At11c17cov0.8	51 010	At5c16cov0.8	41 186	At12c17cov0.9	30 062	At12c18cov0.9	30 301
Rank 51	At11c16cov0.8	46 184	At5c17cov0.9	42 844	At13c16cov0.8	18 434	At12c16cov0.7	2454
Rank 52	At11c17cov0.9	55 326	At5c16cov0.9	32 597	At13c17cov0.9	30 180	At12c17cov0.8	14 966
Rank 53	At11c16cov0.9	46 810	At9c16cov0.8	37 480	At12c16cov0.9	17 170	At13c16cov0.7	29 912
Rank 54			At9c16cov0.9	34 617	At13c16cov0.9	27 100	At12c16cov0.8	-779
Rank 55			At7c16cov0.9	59 066	At16c16cov0.8	72 218	At12c17cov0.9	17 117
Rank 56			At10c16cov0.8	18 979	At16c17cov0.9	29 908	At13c16cov0.8	22 908
Rank 57			At11c16cov0.8	33 868	At17c16cov0.8	20 078	At12c16cov0.9	-1151
Rank 58			At11c17cov0.9	42 294	At16c16cov0.9	19 843	At13c16cov0.9	27 100

Rank 59	At11c16cov0.9	33 589	At17c16cov0.9	28 311	At16c16cov0.8	126 100
Rank 60			At14c16cov0.9	35 521	At16c17cov0.9	16 965
Rank 61			At15c16cov0.9	28 762	At16c16cov0.9	7174
Rank 62			At20c16cov0.9	33 161	At17c16cov0.9	28 311
Rank 63			At21c16cov0.9	29 586	At14c16cov0.9	35 521
Rank 64			At18c16cov0.9	38 693	At15c16cov0.9	28 762
Rank 65			At19c16cov0.9	30 081	At20c16cov0.9	33 161
Rank 66			At4c16cov0.9	30 366	At21c16cov0.9	29 586
Rank 67			At5c16cov0.9	31 041	At18c16cov0.9	38 693
Rank 68			At22c16cov0.9	10 080	At19c16cov0.9	30 081
Rank 69			At23c16cov0.9	31 457	At4c16cov0.9	30 366
Rank 70			At8c16cov0.9	26 975	At5c16cov0.9	31 041
Rank 71			At9c16cov0.9	32 634	At22c16cov0.9	10 080
Rank 72			At6c16cov0.9	36 948	At23c16cov0.9	31 457
Rank 73			At7c16cov0.9	33 162	At8c16cov0.9	26 975
Rank 74			At10c16cov0.9	37 597	At9c16cov0.9	32 634
Rank 75			At11c16cov0.9	34 904	At6c16cov0.9	36 948
Rank 76					At7c16cov0.9	33 162
Rank 77					At10c16cov0.9	37 597
Rank 78					At11c16cov0.9	34 904

Each incremental analysis uses as reference strategy the previous listed option.

Impact of replacing the trivalent vaccine by the upcoming quadrivalent vaccine

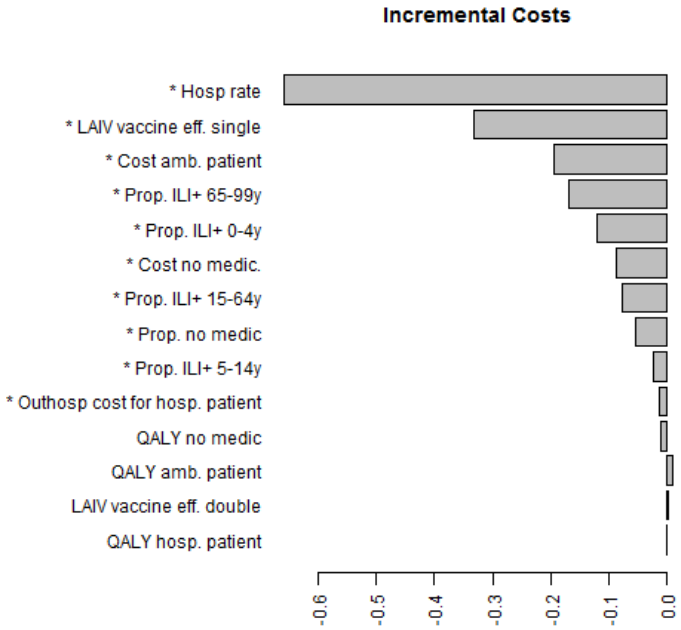
The analyses in this report, although focusing on the currently licensed trivalent influenza vaccines, are also valid for the upcoming quadrivalent vaccines. That is, the only expected difference is that the quadrivalent vaccines would, on average, be marginally more effective than the trivalent vaccines. The impact on the selection of optimal strategies and the estimates of the median ICERs would be very low. For instance, assuming that a quadrivalent vaccine would be given at the same costs, but would increase the effectiveness by 10% (compared to LAIV in the current study), the median ICER of vaccinating children 2-18 years versus the current situation would be €38 845 (95%CI €24 882–60 567) per QALY gained versus €44 280 currently. This also suggests that the quadrivalent vaccination options should have similar costs as the trivalent options we modeled.

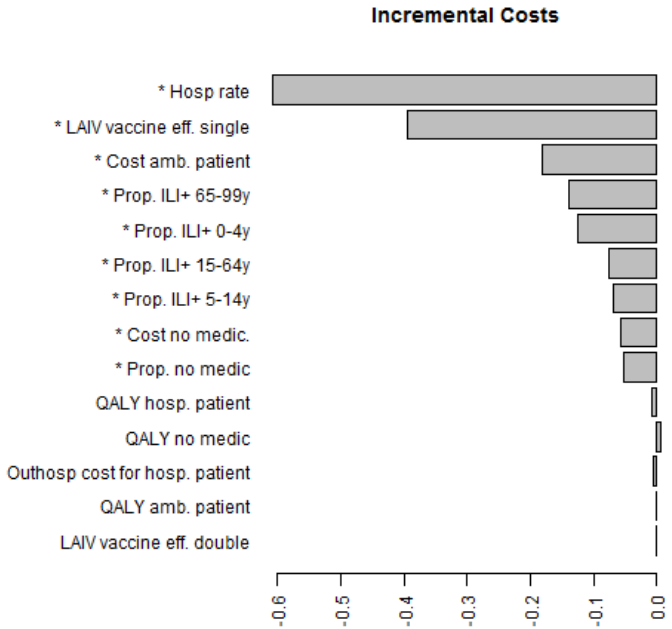
6.1.5.2 Variable importance analysis

The probabilistic sensitivity analysis (PSA) is conducted on all variables to which a (data driven) probability distribution was assigned for the projections (i.e. all parameters in Table 44), and is based on a linear regression analysis of the 10 000 simulations conducted for each of the 5667 vaccination options. This excludes parameters that were estimated by fitting the dynamic transmission model to Belgian data (including the TIV vaccine efficacy estimates). From the latter set of data, we have tested the robustness of the findings by estimating the entire transmission parameter set through two separate fittings. One fitting in which vaccine and naturally induced immunity is left to be a free parameter in the fitting process. Then the best fitting parameter set includes an estimate for this immunity to wane relatively rapidly (average duration of immunity of 1.68 years). Another entirely separate fitting was carried out in which this immunity parameter is copied from a selection of the literature, and not made part of the fitting process (i.e. immunity to the circulating strain wanes more slowly with an average duration of protection of 6 years). The latter is the parameter imputation used in two other published dynamic transmission models. In these published analyses, the assumed duration of waning is not tested, and often a single point estimate is used for all vaccine efficacies (see Section 3.4). In sum, we estimated two parameter sets from fitting the dynamic transmission model (see also Table 39 and Table 40), and applied PSA using a large set of data driven distributions. In this section we illustrate the uncertainty associated with both parameter sets, by applying PSA using the two differently defined models (as we have also done for the main results above).

For the sake of limiting the main output shown in this report, we illustrate the PSA using the example of one vaccination option: continued current adult vaccination (adult option a2, see Table 53) combined with child option c16 (childhood vaccination for all <18 years, using LAIV when possible) at 70% coverage only. We present results separately for incremental costs, life years, QALYs and net benefits (the latter approach was used to avoid inconsistencies arising from ICERs occurring in the four different quadrants of the cost-effectiveness plane, and was implemented by using a fixed value of €35 000 per QALY).

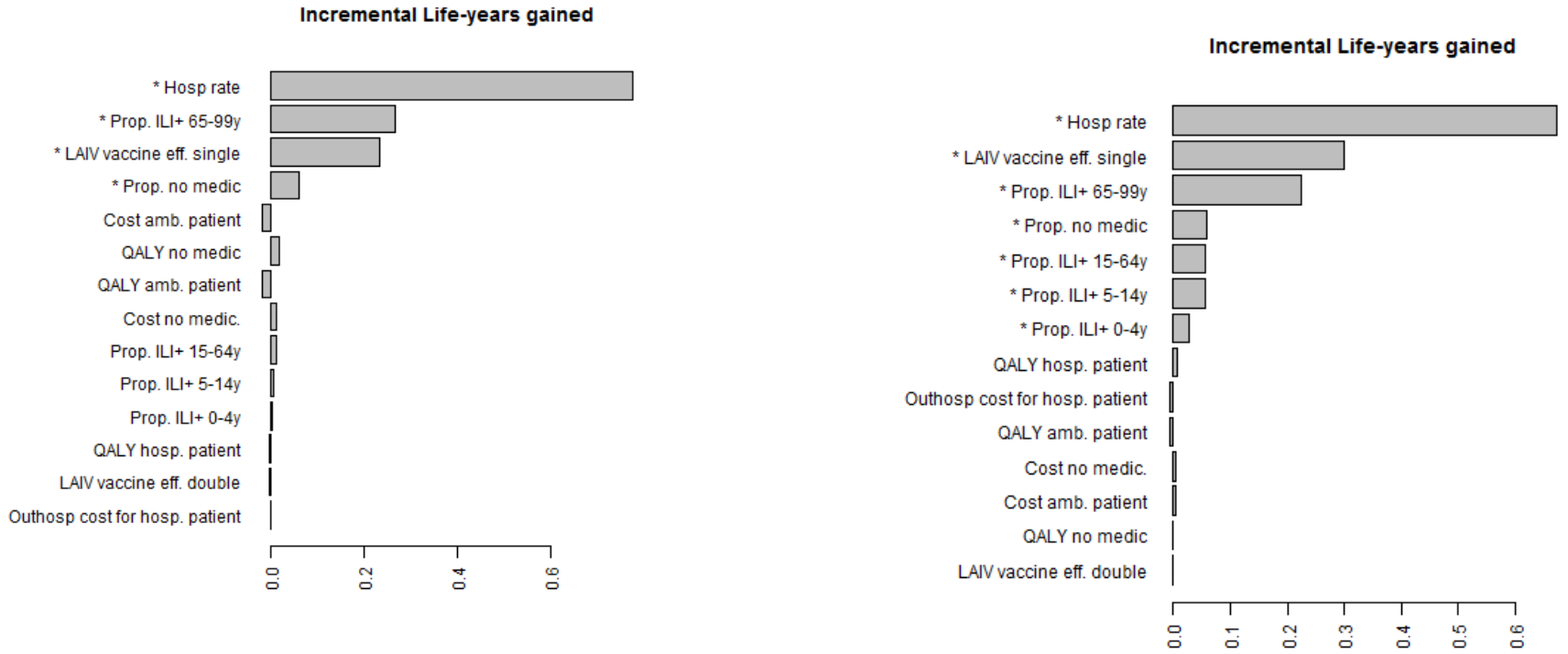
Figure 48 – Regression coefficients of influential parameters for the projected incremental costs of vaccinating with LAIV all children under the age of 18 years combined with continued vaccination of adults, versus the current situation. Top: immunity wanes over 6 years, bottom: immunity wanes over 1.68 years





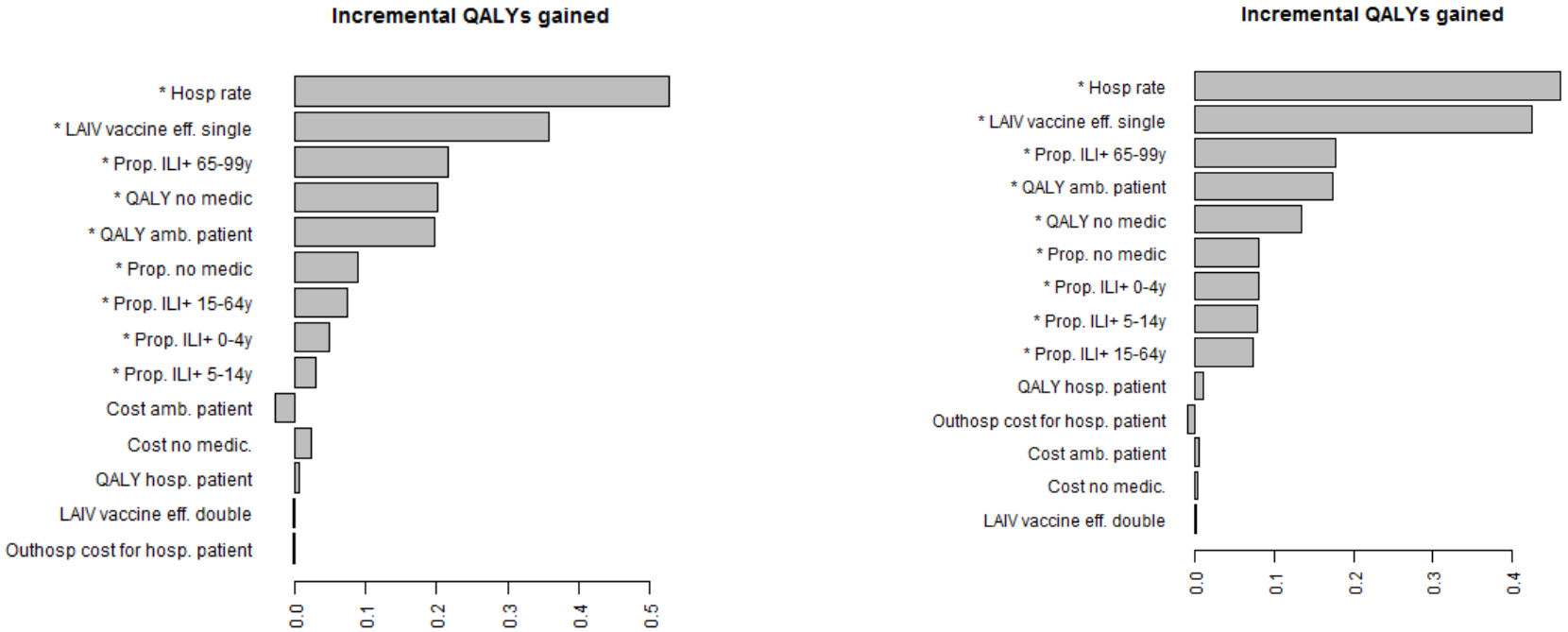
*Significant parameters denoted by * ($p \leq 0.05$).*

Figure 49 – Regression coefficients of influential parameters for the projected incremental life-years gained of vaccinating with LAIV all children under the age of 18 years combined with continued vaccination of adults, versus the current situation. Top: immunity wanes over 6 years, bottom: immunity wanes over 1.68 years



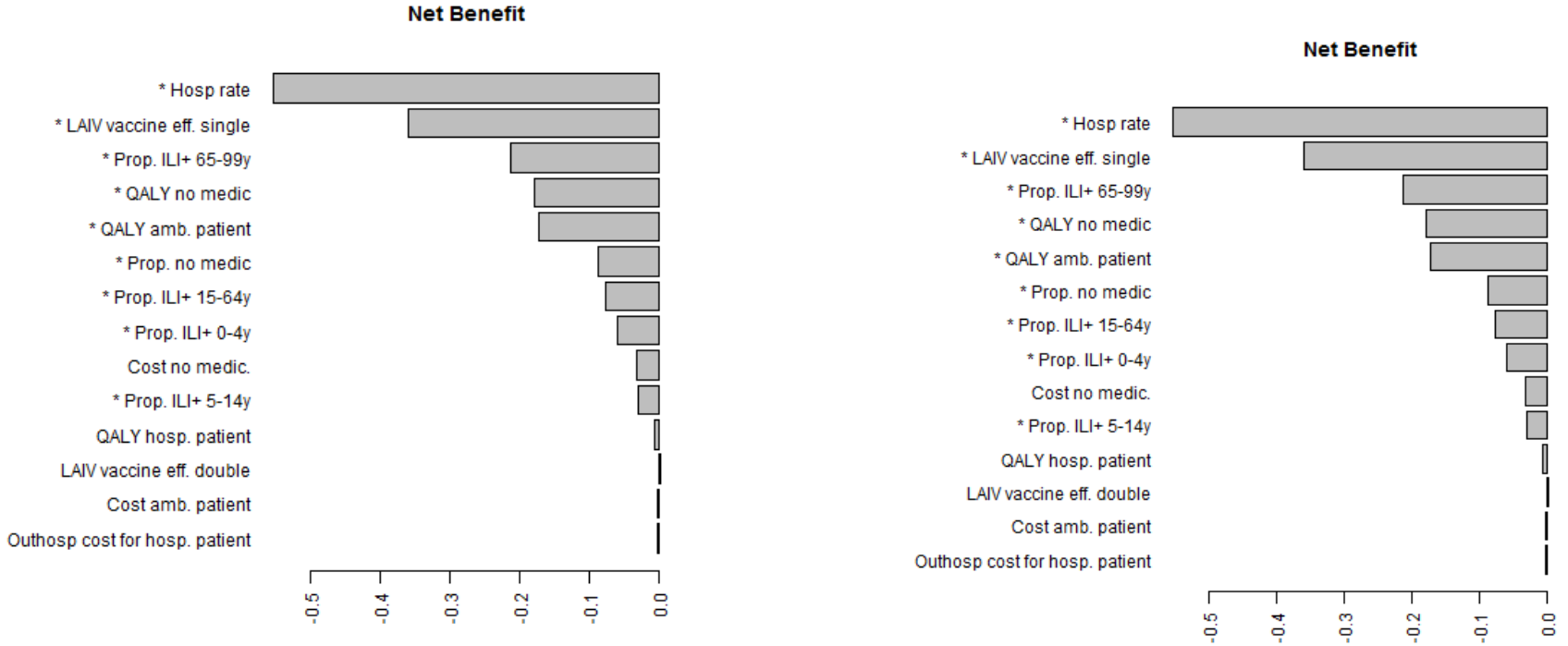
*Significant parameters denoted by * ($p \leq 0.05$).*

Figure 50 – Regression coefficients of influential parameters for the projected incremental quality adjusted life-years (QALY) gained of vaccinating with LAIV all children under the age of 18 years combined with continued vaccination of adults, versus the current situation. Top: immunity wanes over 6 years, bottom: immunity wanes over 1.68 years



*Significant parameters denoted by * ($p \leq 0.05$).*

Figure 51 – Regression coefficients of influential parameters for the projected incremental direct costs per quality adjusted life-year (QALY) gained of vaccinating all children under the age of 18 years with LAIV combined with continued vaccination of adults, versus the current situation. Top: immunity wanes over 6 years, bottom: immunity wanes over 1.68 years



*Significant parameters denoted by * ($p \leq 0.05$).*

Figure 48 to Figure 51 show that the most influential parameter is the hospitalization rate. However, it is important to realize that due to the nature of the data the simulations of 10 000 hospitalizations and case-fatality ratios are in accordance with each other, and only one of them can be selected in the regression analysis. In other words, the hospitalization rates may be replaced by case-fatality ratios in any of these figures. LAIV vaccine efficacy is also an important parameter, and particularly single dose LAIV vaccine efficacy, because most administered doses over the 10 year time span are administered in a single dose. Furthermore the age specific proportions of ILI+ cases are influential in the analysis, as are some QALY and some of the cost estimates.

We have explored variable importance for many other scenarios, and generally found the same parameters to be important. The impact of other coverage levels is very small in the variable selection. Other results are in line with expectations: if no LAIV is administered (e.g. child option 6) then LAIV vaccine efficacy is no longer a significant parameter. If relatively few children are additionally vaccinated (e.g. child option 3) then the influence of the proportion of ILI+ is smaller for children age groups.

6.2 Options considered with the static models

6.2.1 Vaccinating pregnant women

This analysis focused on vaccinating second or third term pregnant women between 1st October and 31st December. The period over which cases can be prevented in this analysis starts at the onset of vaccine protection, assumed on average 4 weeks after vaccine administration. The end of the season is defined at week 25, this choice is not influential due to the lack of cases around that period.

6.2.1.1 Main analysis

This strategy was found to be very cost-effective versus no vaccination (see Table 66), with a median incremental direct cost of €6589 per QALY gained.

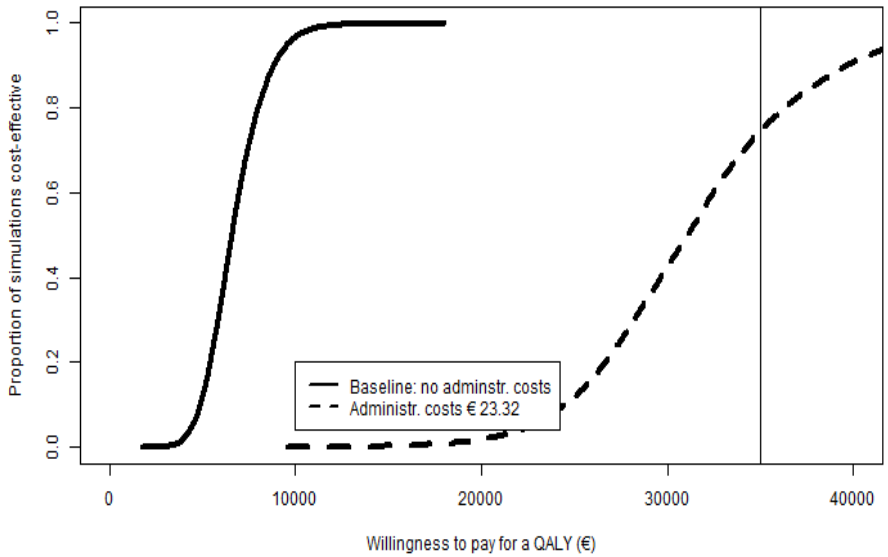
Table 66 – Incremental costs, incremental effects and ICER for annually vaccinating 2nd or 3rd term pregnant women (assuming €0 marginal administration costs), results from 10 000 simulations

Output element	Median	Mean	2.5th percentile	97.5th percentile
Hospitalisations prevented - neonate	25.98	26.04	19.76	32.92
Hospitalisations prevented - mother	2.59	2.72	0.89	5.28
Deaths prevented - neonate	0.07	0.09	0.04	0.33
Deaths prevented - mother	0.00	0.04	0.00	0.32
Incremental direct costs	€384 540	€382 997	€307 841	€450 693
Incremental QALYs	58.05	59.07	39.99	85.10
ICER	€6 589	€6 752	€4 073	€10 249

A crucial question in this analysis is whether gynecologists or GPs would be willing to administer the vaccine at €0 marginal administration costs to the health care payer (i.e. assuming it would be part of a routine check-up during pregnancy in the second or third term), or would the costs of an additional consultation be charged for vaccine administration, or something in between?

The CEACs in Figure 52 show that the impact of adding administration costs (€23.32 per consultation) is large. However, the distribution of the ICERs remains relatively attractive when including these administration costs, with the median ICER still well below €35 000 per QALY gained.

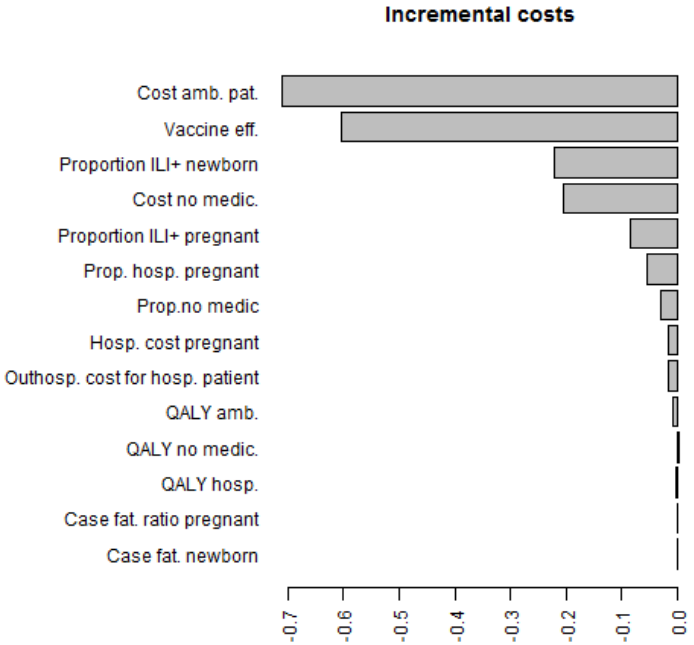
Figure 52 – CEACs for vaccinating 2nd or 3rd term pregnant women (assuming two different marginal administration costs per dose), results from 10 000 simulations

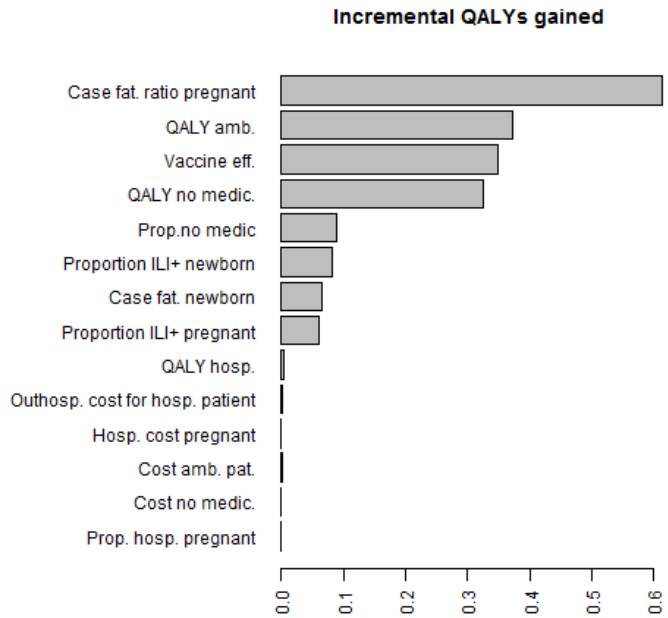


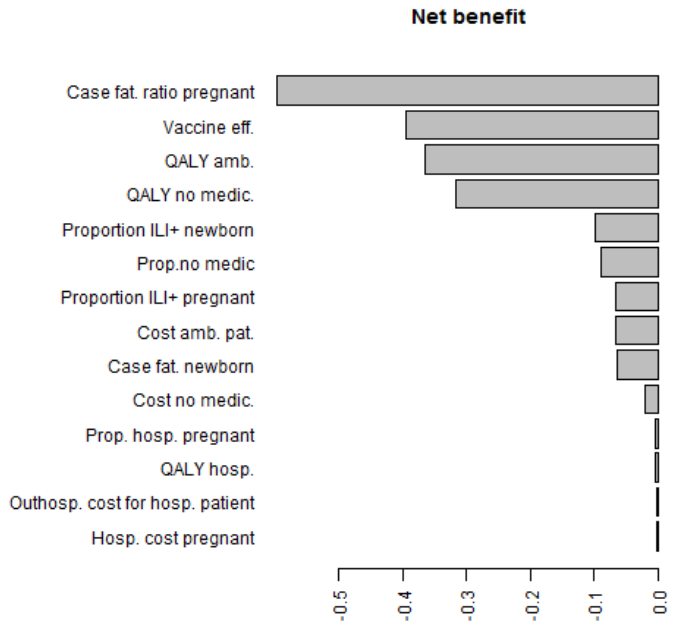
6.2.1.2 *Probabilistic sensitivity analysis (PSA)*

We investigated variable importance through PSA on QALYs, costs and net benefits (again using €35 000 per QALY gained, as above). The results are shown in Figure 53, indicating that the most important variables are the case-fatality ratio, vaccine efficacy and QALY impact.

Figure 53 – Variable importance by standardized coefficients in a linear regression model for vaccination of pregnant women versus no vaccination (€0 administration costs). Top: incremental costs, middle: incremental QALYs, bottom: net benefits



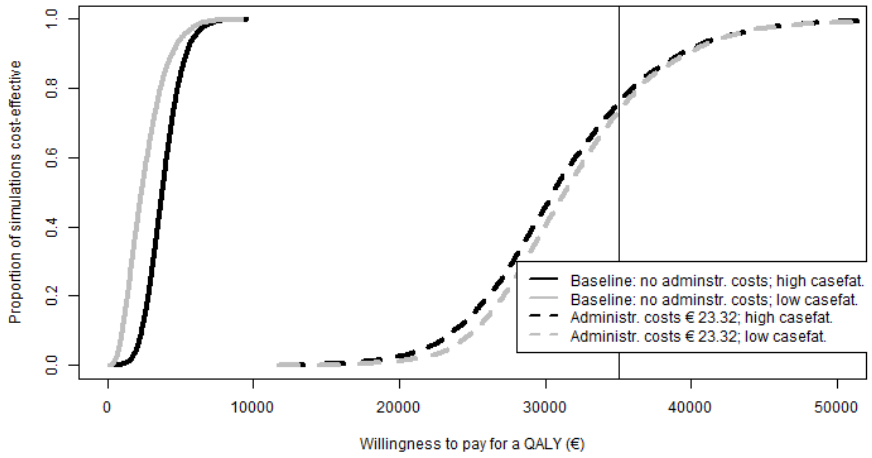

Incremental QALYs gained
Case fat. ratio pregnant
QALY amb.
Vaccine eff.
QALY no medic.
Prop.no medic
Proportion ILI+ newborn
Case fat. newborn
Proportion ILI+ pregnant
QALY hosp.
Outhosp. cost for hosp. patient
Hosp. cost pregnant
Cost amb. pat.
Cost no medic.
Prop. hosp. pregnant
0.0
0.1
0.2
0.3
0.4
0.5
0.6


Net benefit
Case fat. ratio pregnant
Vaccine eff.
QALY amb.
QALY no medic.
Proportion ILI+ newborn
Prop.no medic
Proportion ILI+ pregnant
Cost amb. pat.
Case fat. newborn
Cost no medic.
Prop. hosp. pregnant
QALY hosp.
Outhosp. cost for hosp. patient
Hosp. cost pregnant
-0.5
-0.4
-0.3
-0.2
-0.1
0.0

6.2.1.3 *Sensitivity analysis: The impact of administration costs and case-fatality*

Since the case-fatality ratio and administration costs are of clear importance to the main results, Figure 54 shows how they both impact on the CEACs. It indicates that the median of the distribution of ICERs falls below €35 000 per QALY, even for the two scenarios with the worst outcomes (i.e. furthest to the right). The impact of the case fatality ratio is not highly important in comparison to the influence of the administration costs.

Figure 54 – CEACs of vaccinating pregnant women, with various assumptions for marginal administration costs and case-fatality rate



6.2.1.4 *Sensitivity analysis: The impact of the assumed no-program vaccine coverage in the denominator, which determines the case fatality ratio and hospitalization rates*

Figure 55 – CEACs of vaccinating pregnant women, with various assumptions for marginal administration costs and no-program vaccine coverage in the denominator for estimating the case fatality ratio and hospitalization rates

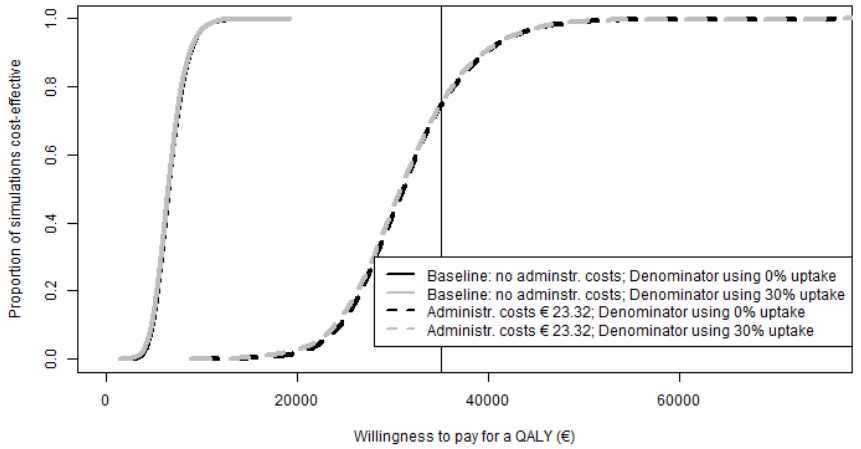
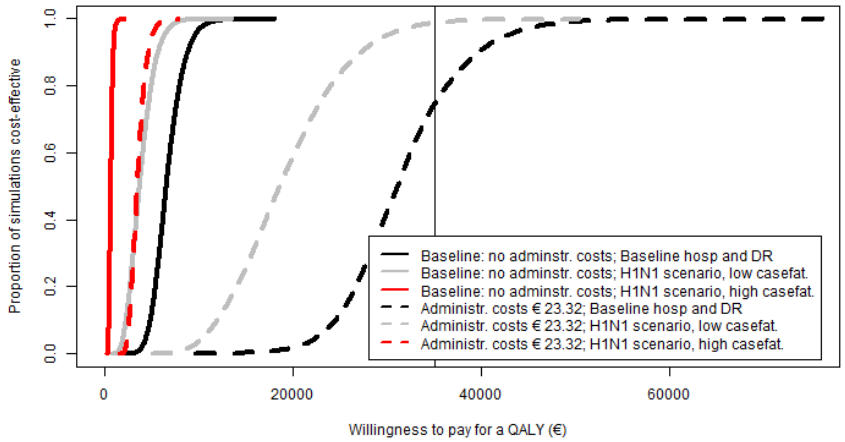


Figure 55 illustrates that the assumption on the level of vaccination uptake required to estimate the hospitalization rates and case-fatality ratios for this analysis (i.e. 0% at baseline, 30% in sensitivity analysis) has very little influence on the estimated cost-effectiveness and CEACs.

6.2.1.5 *Sensitivity analysis: The impact of H1N1 case-fatality and hospitalization rates*

Figure 56 illustrates the impact of using the substantially higher hospitalization rates and case-fatality ratios based on the experience with H1N1. The cost effectiveness improves drastically under this scenario, even when using the low case-fatality ratios based on H1N1.

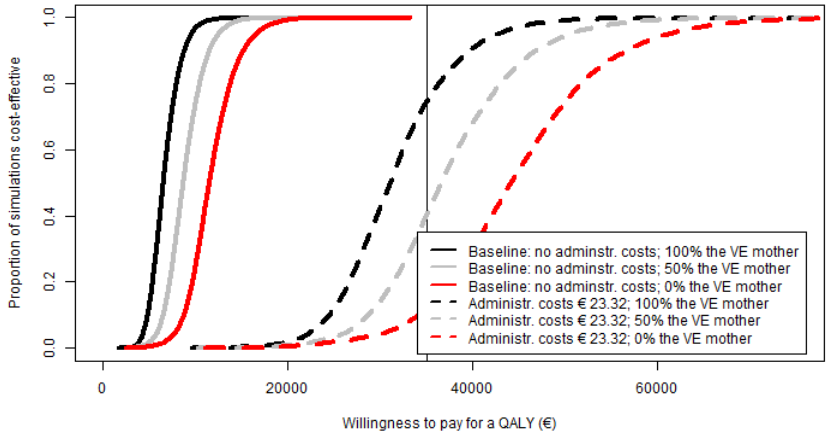
Figure 56 – CEACs of vaccinating pregnant women, with various assumptions for marginal administration costs and H1N1 assumed hospitalization and case-fatality ratios



6.2.1.6 *Sensitivity analysis: The impact of varying vaccine efficacy transferred from mother to neonate*

Until now, we assumed that vaccine efficacy would be fully transferred from mother to neonate. In Figure 57, we show the impact of reducing this transfer by a factor of 50% or 100% (i.e. no transfer at all). We see that even without transfer of vaccine efficacy to the neonate, and without marginal vaccine administration costs, the ICERs fall far below the threshold of €35 000 per QALY. When administration cost are taken into account, reducing the transfer of vaccine efficacy moves the median ICER value over the €35 000 threshold (at 50% VE of the mother).

Figure 57 – CEACs of vaccinating pregnant women, when reducing the transfer of vaccine efficacy from mother to neonate



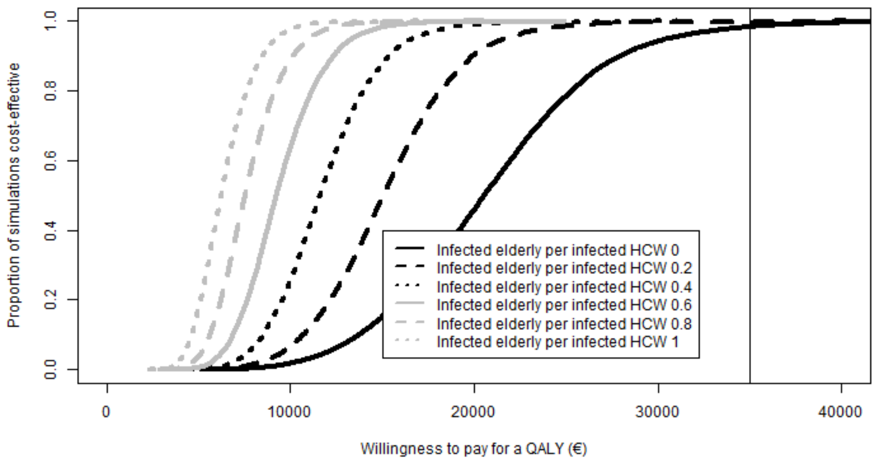
6.2.2 *Vaccinating health care workers (HCWs)*

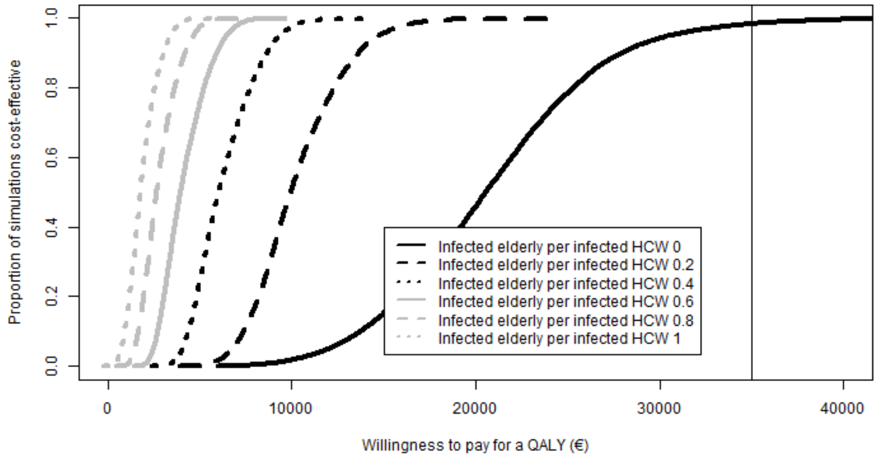
This set of analyses focuses on vaccinating HCWs of different age groups, and investigates the potential impact of preventing both primary infections in the HCWs and secondary infections in patients contacted by the HCWs. In the absence of data, the definition of these secondary infections has been limited to an overall age specification and is not linked to specific comorbidities or to a specific health care setting.

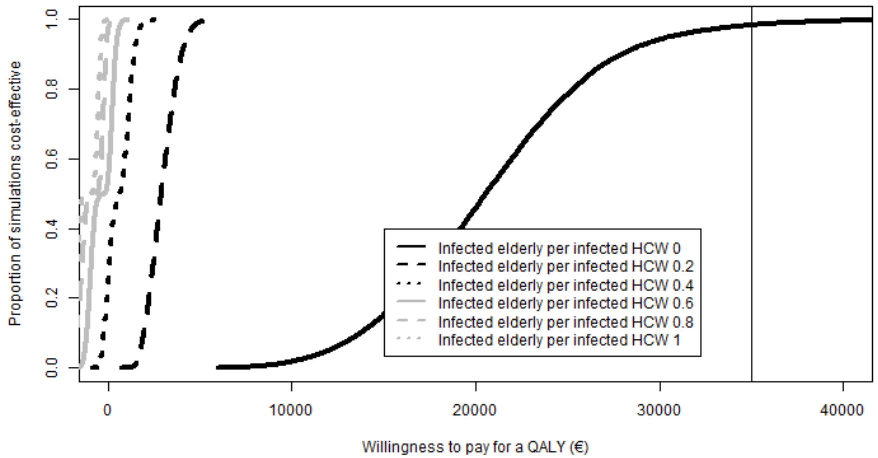
6.2.2.1 *HCW of any age without marginal administration costs*

Figure 58 shows that vaccination of HCWs of any age (i.e. 20-65 years), at €0 marginal administration costs, would result in acceptable incremental cost-effectiveness ratios, even if these HCWs would not cause any secondary infections in patients. Results per age-category of HCWs (20-29, 30-49 and 50-65 years separately) are equally favourable and are presented in Supplement 1.

Figure 58 – CEACs for vaccinating HCWs aged 20-65 years at no marginal administration costs, assuming varying numbers of secondary infections in patient groups aged 50+ due to a primary infection in a health care worker; from top to bottom: secondary infections in adults aged 50-64, 65-74 and 75+ years



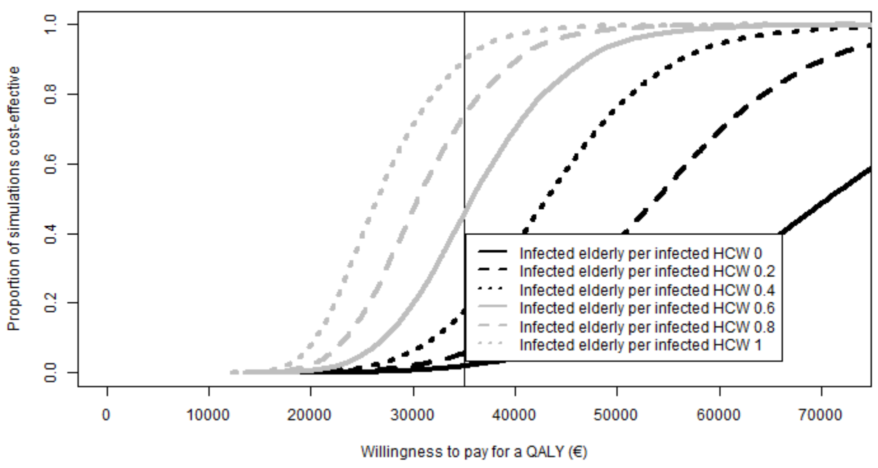


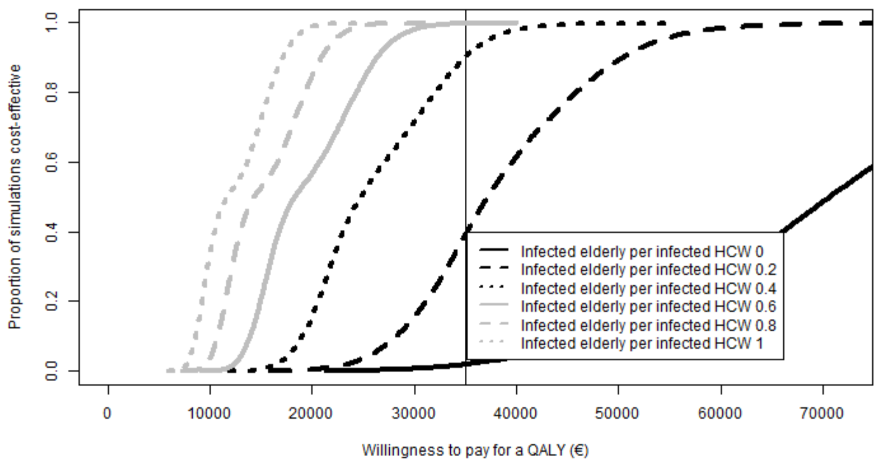


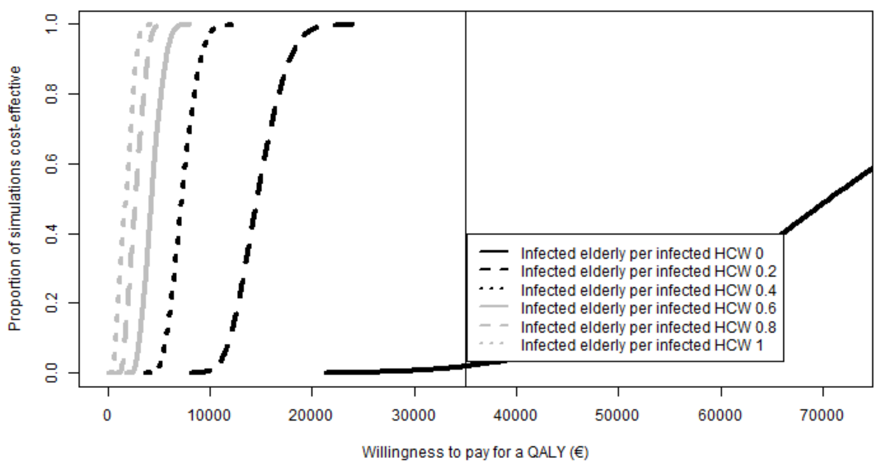
6.2.2.2 HCWs of any age with marginal administration costs

Figure 59 shows that with the addition of marginal administration costs, vaccinating HCWs is much less likely to yield cost-effective ratios less than €35 000, especially if the patients they contact are younger than 65 years. Results per age-category of HCW (20-29, 30-49 and 50-65 years) are presented in Supplement 1.

Figure 59 – CEACs for vaccinating HCWs aged 20-65 years at €23.32 marginal administration costs, assuming varying numbers of secondary infections in patient groups aged 50+ due to a primary infection in a health care worker; from top to bottom: secondary infections in adults aged 50-64, 65-74 and 75+ years



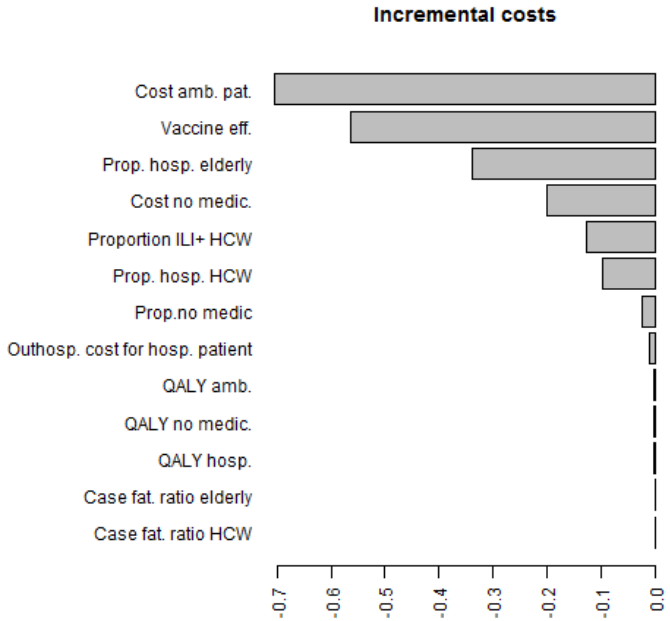


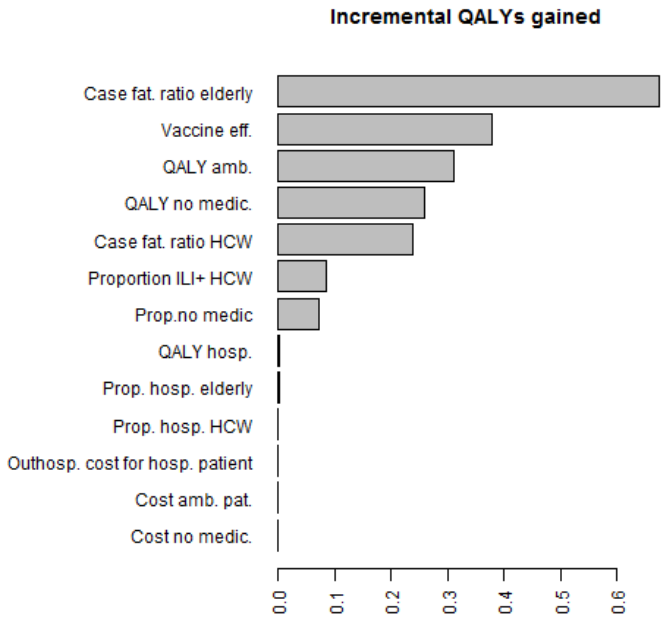


6.2.2.3 Probabilistic sensitivity analysis (PSA)

We investigated variable importance through PSA on QALYs, costs and net benefits (again using €35 000 per QALY gained, as above). The results are shown in Figure 60 to Figure 62, indicating that generally the most important variable is the case-fatality ratio of patients contacted by the health care workers (named “the elderly” in the figures below). We illustrate these findings with a small number of examples. In these examples, one secondary infection is assumed to occur from a primary infection in a health care worker.

Figure 60 – Variable importance by standardized coefficients in a linear regression model for vaccination of Health Care Workers aged 20-29 years, patients aged 50-64 years versus no vaccination (€0 administration costs), Top: incremental costs, middle: incremental QALYs, bottom: net benefits




Incremental QALYs gained
Case fat. ratio elderly
Vaccine eff.
QALY amb.
QALY no medic.
Case fat. ratio HCW
Proportion ILI+ HCW
Prop.no medic
QALY hosp.
Prop. hosp. elderly
Prop. hosp. HCW
Outhosp. cost for hosp. patient
Cost amb. pat.
Cost no medic.
0.0
0.1
0.2
0.3
0.4
0.5
0.6

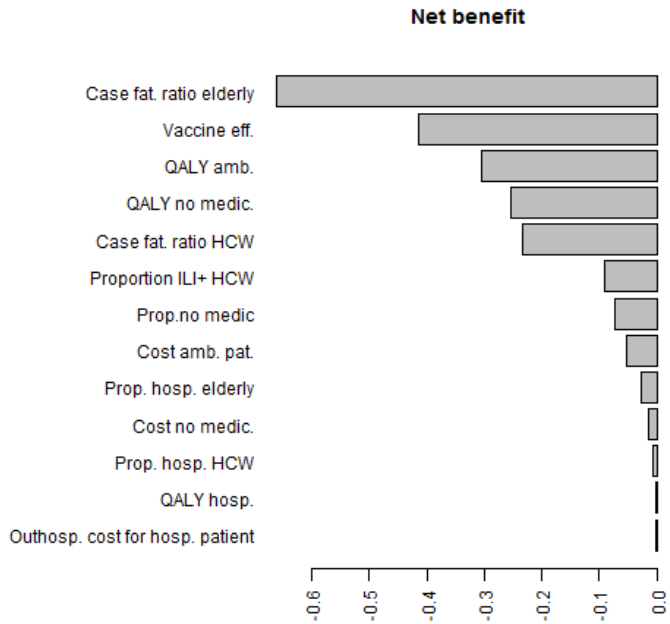
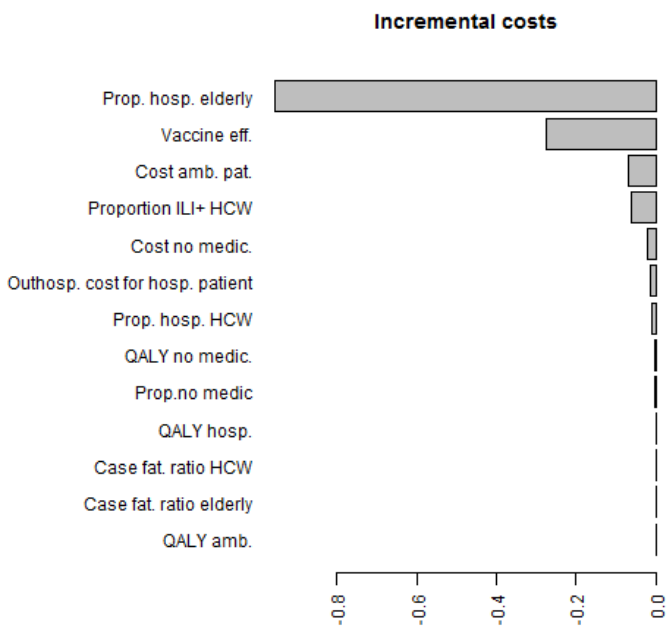

Net benefit
Case fat. ratio elderly
Vaccine eff.
QALY amb.
QALY no medic.
Case fat. ratio HCW
Proportion ILI+ HCW
Prop.no medic
Cost amb. pat.
Prop. hosp. elderly
Cost no medic.
Prop. hosp. HCW
QALY hosp.
Outhosp. cost for hosp. patient
-0.6
-0.5
-0.4
-0.3
-0.2
-0.1
0.0

Figure 61 – Variable importance by standardized coefficients in a linear regression model for vaccination of Health Care Workers aged 30-49 years, patients aged 50-64 years versus no vaccination (€0 administration costs), Top: incremental costs, middle: incremental QALYs, bottom: net benefits



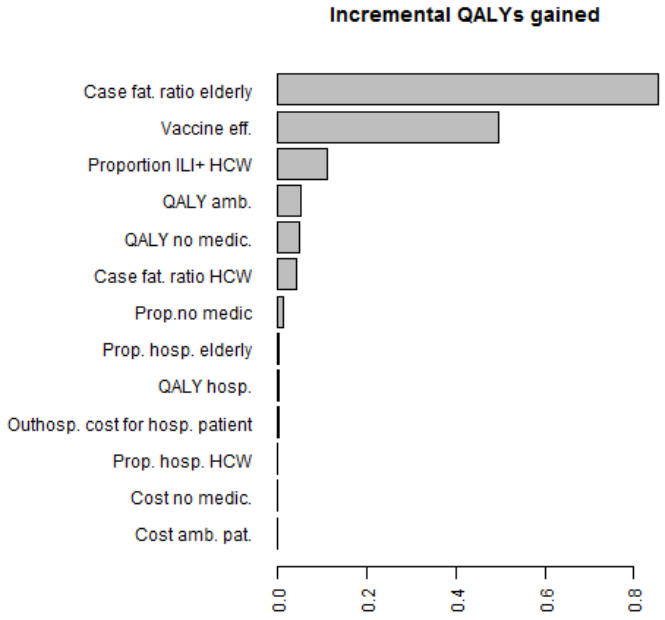
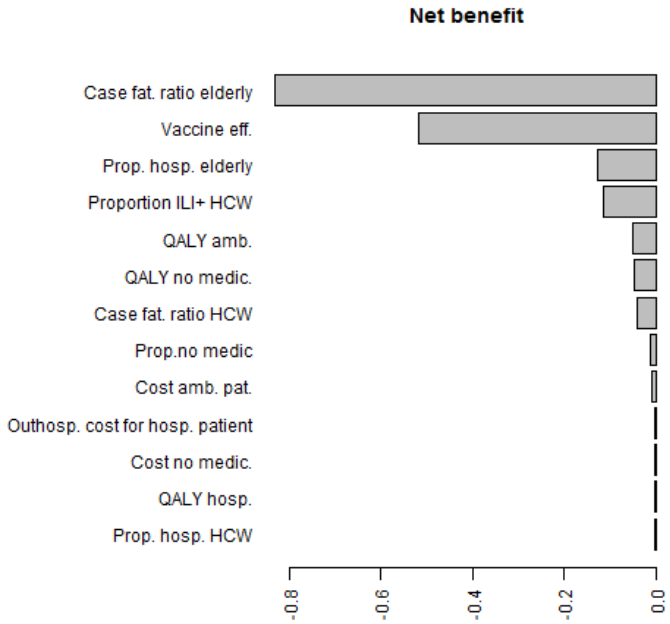
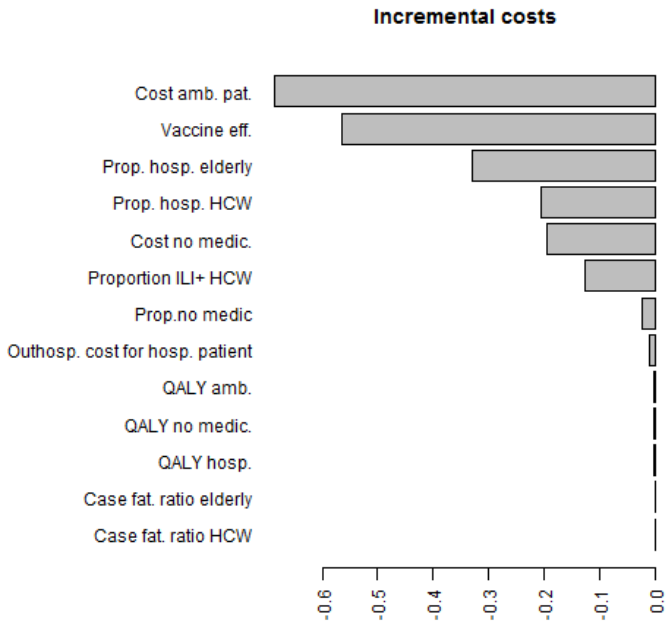
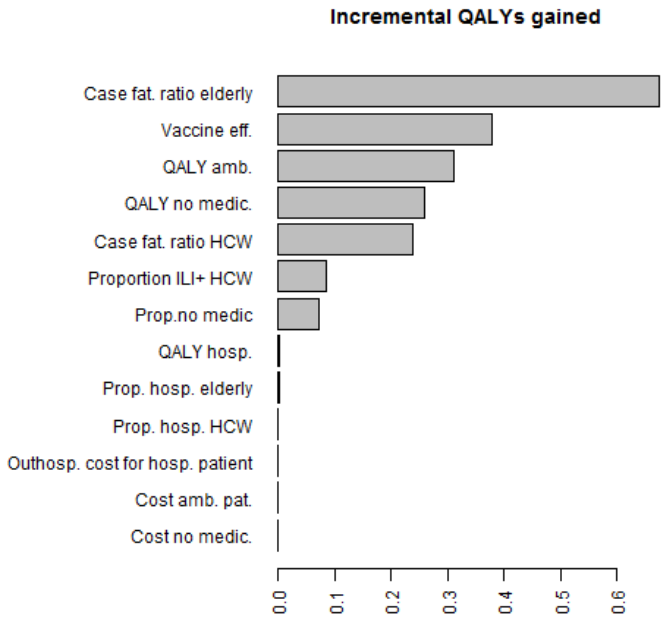
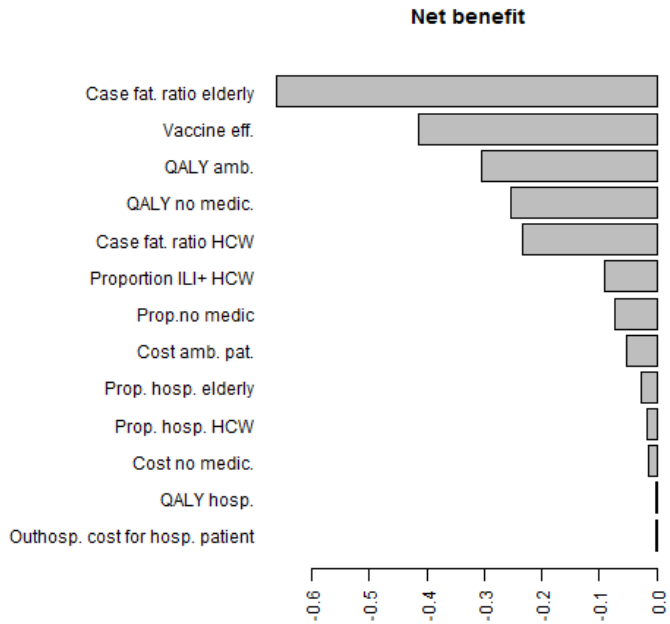


Figure 62 – Variable importance by standardized coefficients in a linear regression model for vaccination of Health Care Workers aged 50-65 years, patients aged 75+ years versus no vaccination (€0 administration costs), Top: incremental costs, middle: incremental QALYs, bottom: net benefits






Incremental QALYs gained
Case fat. ratio elderly
Vaccine eff.
QALY amb.
QALY no medic.
Case fat. ratio HCW
Proportion ILI+ HCW
Prop.no medic
QALY hosp.
Prop. hosp. elderly
Prop. hosp. HCW
Outhosp. cost for hosp. patient
Cost amb. pat.
Cost no medic.
0.0
0.1
0.2
0.3
0.4
0.5
0.6


Net benefit
Case fat. ratio elderly
Vaccine eff.
QALY amb.
QALY no medic.
Case fat. ratio HCW
Proportion ILI+ HCW
Prop.no medic
Cost amb. pat.
Prop. hosp. elderly
Prop. hosp. HCW
Cost no medic.
QALY hosp.
Outhosp. cost for hosp. patient
-0.6
-0.5
-0.4
-0.3
-0.2
-0.1
0.0

6.2.3 Vaccinating people with comorbidities

6.2.3.1 Main analysis

This set of analyses focuses on vaccinating people with underlying comorbidities. In these analyses we assume that every vaccination incurs administration costs equivalent to the costs of a GP visit. Figure 63 shows that the distribution of ICERs is acceptable for all age groups. Table 67 summarizes this information for various health outcomes.

Figure 63 – CEACs for vaccinating people with comorbidities in different age groups versus no vaccination

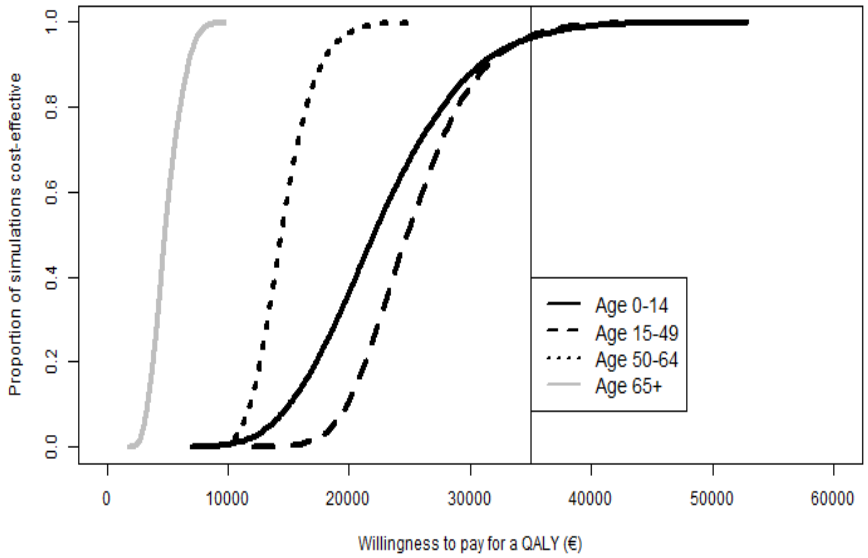


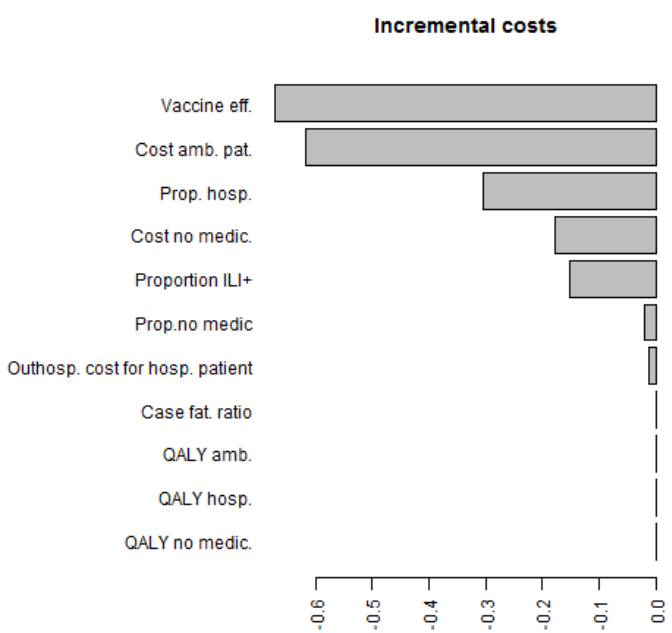
Table 67 – Incremental direct costs and effects for vaccinating people with comorbidities in various age groups

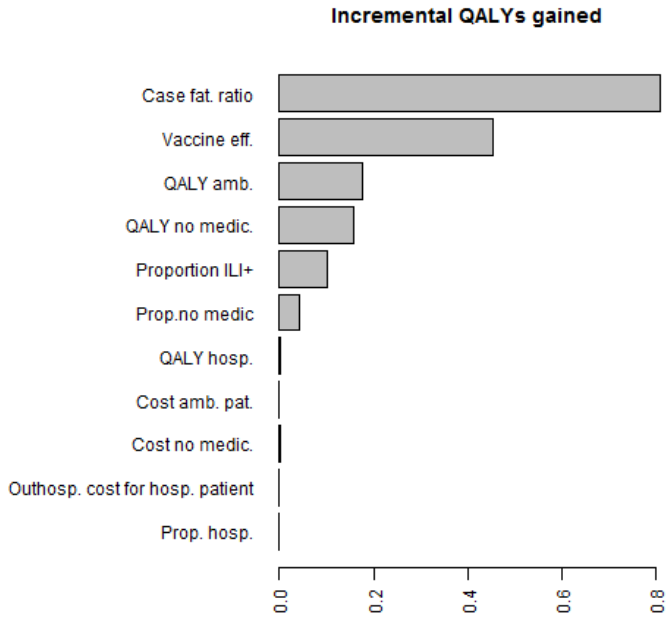
Age group	Output element	Median	Mean	2.5th percentile	97.5th percentile
0-14	Hospitalisations prevented	10.09	10.15	7.60	13.07
	Deaths prevented	0.23	0.27	0.03	0.77
	Incremental direct costs (€)	689 687.21	689 189.08	658 693.94	716 876.65
	Incremental QALYs	31.27	32.94	19.16	56.28
	ICER (€)	22 007.83	22 595.79	12 179.20	36 574.39
15-49	Hospitalizations prevented	16.90	16.96	13.38	20.93
	Deaths prevented	1.02	1.06	0.45	1.93
	Incremental direct costs (€)	2 476 026.86	2 473 748.26	2 388 545.38	2 552 104.03
	Incremental QALYs	99.83	101.01	70.14	138.87
	ICER (€)	24 767.73	25 277.89	17 622.86	35 724.06
50-64	Hospitalizations prevented	21.30	21.37	17.08	26.18
	Deaths prevented	3.96	4.02	2.63	5.77
	Incremental direct costs (€)	1 902 263.13	1 901 101.93	1 830 150.67	1 967 351.83
	Incremental QALYs	132.12	133.29	96.59	176.29
	ICER (€)	14 377.55	14 609.85	10 627.39	20 005.41
65+	Hospitalizations prevented	155.93	166.05	99.33	249.44
	Deaths prevented	42.41	43.53	31.10	58.71
	Incremental direct costs (€)	2 587 383.36	2 513 986.82	1 857 678.47	3 044 346.13
	Incremental QALYs	517.81	528.91	381.77	708.08
	ICER (€)	4784.14	4931.88	2797.36	7607.00

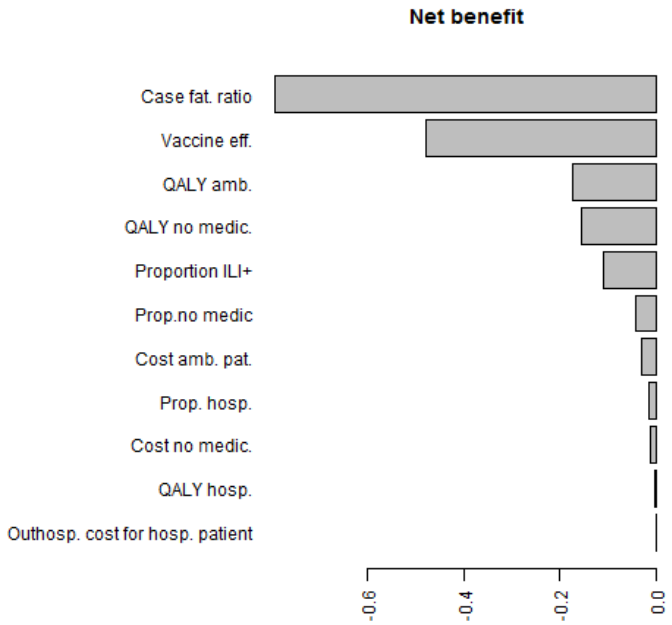
6.2.3.2 *Probabilistic sensitivity analysis*

We investigated variable importance through PSA on QALYs, costs and net benefits (again using €35 000 per QALY gained, as above). We repeated the analysis for all age groups, but only display the results for the age group 50-64, because the important variables are the same for other age groups. The results are shown in Figure 64, indicating that generally the most important variable is the case-fatality ratio.

Figure 64 – Variable importance by standardized coefficients in a linear regression model for vaccination of people with comorbidities aged 50-64 years, Top: incremental costs, middle: incremental QALYs, bottom: net benefits



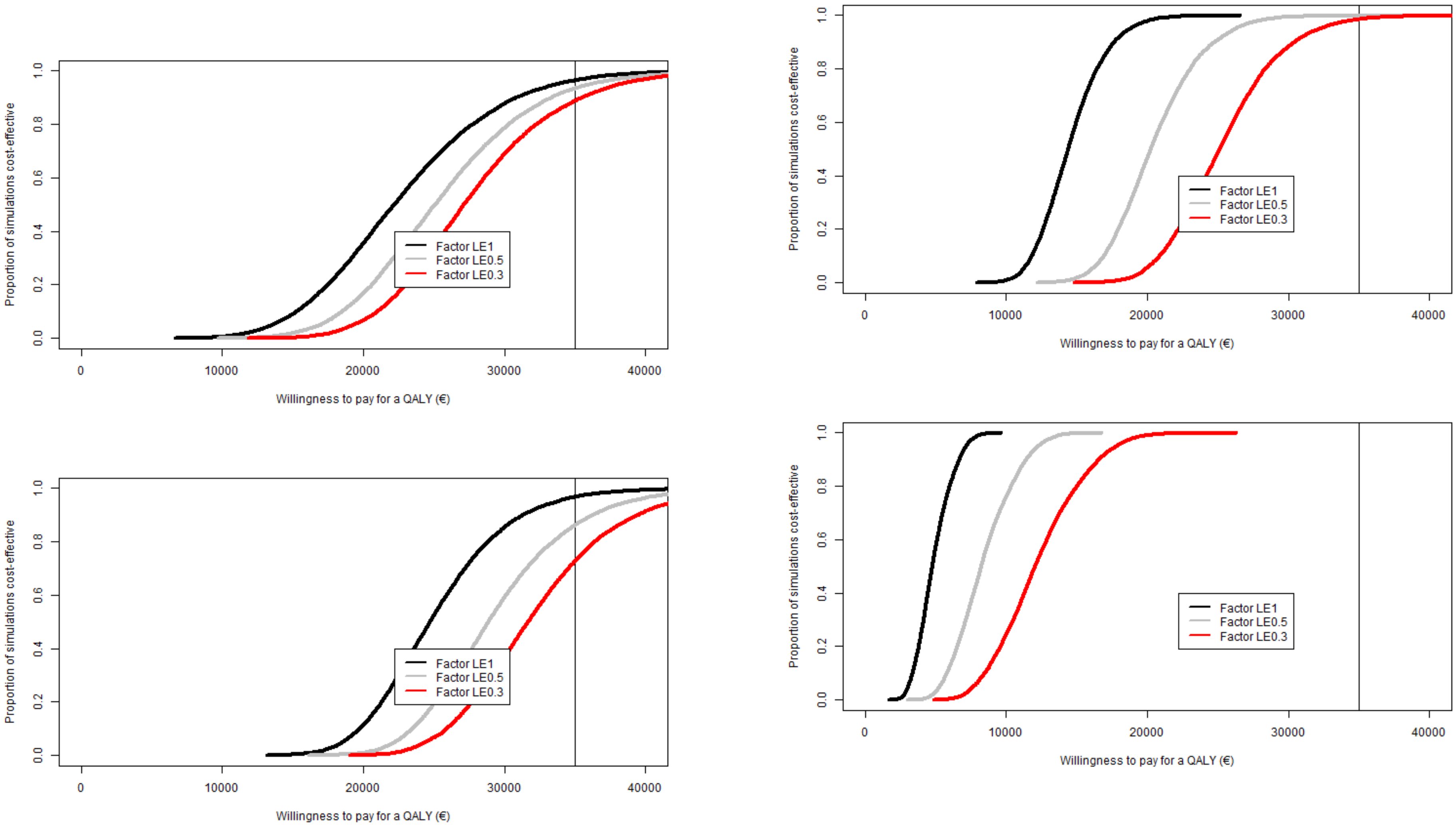




6.2.3.3 Scenario analyses

In these scenario analyses, we investigate the impact of changes in the factor by which life-expectancy is lower than the average for people with comorbidities at a given age.

Figure 65 – CEACs by life expectancy factor, top to bottom: age group 0-14, 15-49, 50-64 and 65+ years



Virtually all scenarios in all age groups, except the youngest age categories 0-14 and 15-49 years, fall below a €35 000 threshold. For these latter categories, we investigate in Table 68 how low the total vaccination costs need to be in order to achieve that the 95th percentile of the ICER distribution (P95) falls below a €35 000 theoretical threshold. For the age group 0-14 years, P95 falls below the threshold at a life expectancy equal to the general population. For this age category with a life expectancy of 50% or 30% of the general population, we need the vaccination costs per dose to be below €20.44 or €7.57 respectively, to achieve P95 below €35 000.

For the age group 15-49, we cannot lower total vaccination costs to achieve P95 below the threshold when the life expectancy is only 50% of the general population of the same age class. With an equal life expectancy, P95 falls below the threshold.

If we also include administration costs in the threshold analysis, we can calculate the thresholds shown in Table 68.

Table 68 – Total vaccination costs per dose for which P95 of the ICER is below a €35 000 threshold, only for age groups 0-14 years and 15-49 since older age groups have P95 below this threshold

Age group	Scenario	Maximum total vaccination cost
0-14	factor LE 1	Cost effective at current vaccination costs
	factor LE 0.5	€20.44
	factor LE 0.3	€7.57
15-49	factor LE 1	Cost effective at current vaccination costs
	factor LE 0.5	Not CE with €0 vaccination costs
	factor LE 0.3	Not CE with €0 vaccination costs

LE: Life expectancy.

7 SUMMARY AND DISCUSSION

This Belgian study collected and analyzed an extensive range of Belgian data and developed refined modeling tools, which were applied to a very wide range of vaccination options. However, there are two main obstacles impeding simple, clear-cut specific advice on influenza vaccination for policy making. On the one hand, the absence of information on how influenza vaccine would be added to the regional vaccination programmes in Belgium, required modeling a wide range of age targets (including in children) and vaccine uptake options (5667 options were considered, which in turn multiplied when different assumptions on the costs of vaccine administration needed to be made). On the other hand, there are still many uncertainties on the influenza virus and its interaction with human hosts. Additionally, the clinical picture associated with influenza infection is not highly typical, which could lead to misdiagnosis, implying specific estimates of the disease burden of influenza are subject to substantial uncertainty, in terms of health outcomes, health care costs and health-related quality of life. Nonetheless, this elaborated study allows drawing a number of general conclusions, which are likely to aid decision-making. Indeed, the findings show that a large variety of influenza vaccination options for children and adults could be considered cost-effective, and some of these would even be cost-saving versus the current situation.

7.1 Vaccinating children

Under the base case assumptions, i.e. rapid waning of immunity, vaccines administration through GP visits and current retail price for vaccine purchase, influenza vaccination of children would not be cost-saving and would unlikely be considered a cost-effective way of allocating scarce resources, as the median ICERs are all above €40 000/QALY gained. An interesting finding is that the ICER does not depend much on the vaccination coverage achieved, mainly because of the high vaccination costs in the base case.

The attractiveness of the programme however hinges on two pivotal factors: the vaccination costs per dose and the duration of immunity. First, vaccinating children would become a more attractive intervention if vaccination costs can be reduced by 25-75%, which was explored in our analyses, e.g. by vaccinating through school health services and well-baby clinics and by reducing vaccine prices through large purchases. Clearly, all

efforts to reduce the vaccination costs would greatly benefit the programme and vaccine programme managers should consider how they could best organize childhood influenza vaccination in Belgium. Second, the waning immunity, or the speed at which the immunity induced by the vaccine or by natural infection wanes, is important for two reasons. On the one hand, it has a big impact on the incremental cost-effectiveness per se, as the shorter the duration of immunity provided by the vaccine, the worse the cost-effectiveness. On the other hand, it has an impact on the ranking of preferred strategies: the shorter the duration of immunity, the more interesting it is to first vaccinate the "oldest" children, followed sequentially by the other age groups down to the youngest ones. Conversely, when we assume a longer duration of immunity (e.g. 6 years), influenza vaccination of the youngest children (<2 years) would be the most cost-effective option, followed by vaccination of older age groups in children under 18 years. In this study, we adhered to a short duration of immunity in the main analysis because it was estimated (and not assumed) by fitting to Belgian data. It is also more in line with recent vaccine effectiveness findings for any strain, while the immunity of 6 years, where it has been used in the literature, referred to one circulating strain. Under that assumption, we found that vaccinating older children 5-17 years of age is marginally preferential to vaccinating the younger ones.

Our analyses also systematically show that LAIV is more cost-effective than TIV under our assumption of price parity. This is easily explained by the higher and more stable vaccine effectiveness of LAIV across seasons compared to TIV, for the same age. As LAIV is not yet available in Belgium, its future price – and whether prices will be similar for both vaccines – is still unknown. In the UK, the private market (non-tendered) price is however higher for LAIV than for TIV (£14.0 vs. £12.5 for TIV) but the tendered prices are unknown.

A very important finding from this study is that childhood vaccination cannot replace adult vaccination. Although some herd immunity effects can be achieved by childhood vaccination, especially if we assume a long duration of immunity, it would not be sufficient to replace adult vaccination options. Even under the most effective scenario of childhood vaccination, i.e. vaccinating all children <18 years at 80% (using LAIV except in the <2 years), a mean of ~300 additional admissions and ~70 additional deaths would be prevented in the elderly above 64 years. However, the same strategy would prevent >400 admissions in children <5 years. Conversely by increasing vaccination coverage of all adults ≥50 years of age, a mean of around 350 admissions and around 60 deaths would be prevented. At the same token, a reduction in vaccination coverage in adult age groups (e.g. stopping vaccination at ages 18-50 years and above 85 years, and introducing childhood vaccination) could lead to direct net savings at no decrease in QALYs, but this choice would create excess mortality and net losses in life years versus current practice, and would thus seem unacceptable for ethical reasons.

The cost-effectiveness study on which the UK decision was based to introduce universal childhood vaccination found that childhood vaccination was a highly cost-effective intervention (<£506/QALY gained), and that vaccinating children 2-4 years of age was even cost-saving.[123] That UK study made use of a similarly structured dynamic transmission model (Vynnycky et al) and it may thus be surprising that our findings are different. Although this discrepancy may be due to health care system and contact pattern differences, we found that many parameters in the UK study were very optimistic while our study ended up with more conservative parameters, while acknowledging as much as possible uncertainties related to model and parameter choices (see box below). However, a number of general findings of our study were also reported by other cost-effectiveness or modelling studies. For instance Vynnicky et al also found that the predicted reduction in the incidence resulting from vaccination decreased slightly as the assumed duration of protection to the circulating strain decreased.[125] Weycker in the US also found that even relatively low rates of vaccine coverage can yield important public health benefits.[14]

Comparison of key parameters between the UK and our analysis

- All efficacy estimates were assumed to be higher (50-75% for TIV), without uncertainty and constant across seasons for the UK.
- The quality of life loss due to influenza disease was three times higher than the one we estimated from the literature.
- The cost of ambulatory care (£80 or €93) was 46% higher than the highest estimate from our cost survey.

- The cost of vaccine purchase was assumed to be 42% lower than our base case estimates.
- Immunity was assumed to wane much more slowly at a rate of 1/6-1/12 years for a circulating strain in the UK.

It is clear that the vaccination of age groups that are currently less targeted by other routine vaccines, such as healthy children >2 years of age, is a substantial challenge that would entice organizational changes implying a wide range of actors. On one side, vaccination of children through private practices would require a high motivation on the parent side and imply an additional burden. A US study has estimated that 60% to 80% of children aged 5 to 8 years would need 2 unscheduled extra physician visits in the first year to be fully vaccinated, and 20% would need 1 extra visit, even if every medical visit was used to provide a vaccination. Among children aged 9 to 18 years, at least 75% would need 1 extra visit.[315, 316] Authors also stated that school-based vaccination programs might offer the most effective strategy for school-aged children. In Belgium, existing services such as Kind&Gezin, the clinics from the Office National de l'Enfance (ONE) and school health services have shown to be effective in providing vaccination to (pre)school children, such as HPV and hepatitis B vaccine. However, administering an annual influenza vaccination to entire cohorts of children would add a high burden to their current workload, involve additional costs and organizational challenges.

7.2 Changing coverage in adults with or without childhood vaccination

The most cost-effective strategies for adult vaccination consist in increasing the coverage among various age groups ≥50 years while reducing or even stopping the vaccination of younger healthy adults 15-49 years of age, who are currently not a target group. Although these scenarios result in attractive ICER below €20 000/QALY gained, they are detrimental to the young adults by inducing an increased morbidity in this group. The next most cost-effective option is to keep the current coverage in young adults and increase it in all elderly over 75 years up to 75% (ICER around €20 000/QALY gained). Savings would occur if the vaccination of the old elderly (≥85-95 years) and/or young healthy adults is stopped and resources are used to vaccinate children. However again, life years would be lost in the elderly which make them detrimental and unethical options. The assumption of longer duration of immunity would slightly change the hierarchy of options.

The most effective intervention overall would be to vaccinate all children and increase the coverage in all adults ≥50 years. At a 80% coverage in children, this intervention could prevent nearly half of the current number of influenza hospitalisations and deaths, but would only be cost-effective if we assume a slower waning of immunity and/or a substantially lower price.

We also explored the impact of improving uptake in the other target groups for influenza vaccines, in separate analyses (static models). We showed that vaccination of pregnant women, health care workers and persons with comorbidities can all be considered as relatively cost-effective, especially – but not necessarily – if marginal administration costs can be kept low. For pregnant women, it should be clear that the cost-effectiveness improves when the vaccine can be administered earlier in the season.

7.3 Limitations of the study

Although the use of a model by definition implies that we cannot predict with certainty what would happen in the real world, the models we applied here were appropriately structured and parameterised to tackle the research questions, and deal with uncertainty to the best of our ability. We are not aware of a "better" model structure to apply to this problem, or a better approach to deal with uncertainty inherent in these types of evaluations.

Instead of assuming infectious disease parameters (as was done in all previous analyses known to us), we fitted our transmission model to the available Belgian data to estimate the best set of infectious disease parameters. This is a major strength of the analysis. The main limitation of our analysis is related to the available surveillance data as the dataset on reported cases of ILI and laboratory confirmed cases of ILI+ was not sufficient to allow us to distinguish influenza A (the most common in our country) from influenza B (much rarer in our country, and hardly picked up in the surveillance data we could use for this study) in our model. We therefore were forced to model all influenza as a single strain, although modeling influenza A and B separately would allow for more realistic estimates through the fitting process. However, we allowed several parameters to vary by season to capture part of the influenza type

variability and the impact of this limitation on the results and conclusions should be minor.

A further limitation is that, due to the unspecific nature of influenza and the inaccuracy of related coding practices, we had to use regression analysis to derive the fractions of ILI hospitalizations and deaths that are attributable to influenza. We used the data for pneumonia and influenza coded hospitalizations, because the regression results presented a poor fit when we selected other data to regress against (such as all respiratory coded hospitalizations). The fractions that we obtained from these analyses were lower than what has been found in a number of other countries, possibly due to differences in database systems, hospitalization practices, and seasonal circulation. However, hospitalization and death rates were close to those found in other studies using similar parameters during similar seasons with low to moderate intensity.

Another limitation is that in the absence of implementation plans for seasonal influenza vaccination, we had to model a wide range of possible scenarios. This may have led to an excessive number of options to prioritize, and the inclusion of options that may not be realistic (although these were deliberated first with Belgian experts). Clearly, when more specific information is available on the options towards implementation in Belgium, we can make a more specific analysis using more specific estimates for vaccination costs, and draw yet more specific conclusions.

Further limitations are related to the exclusion of indirect costs of productivity losses for adult flu patients and for parents of child flu patients. This relates to the generally preferred approach to cost-effectiveness analysis (as also outlined in KCE guidelines for HTA). It seems very likely that if indirect costs of productivity losses had been considered, the various influenza vaccination options would become more attractive to the point where they may have shown net savings. This was also pointed out in the review section of this report.

Direct treatment costs in ambulatory care or self-care were derived from a prospective population-based survey during the mild 2011-2012 season, which may not be representative of the distribution of seasons used in our model simulations. We believe however that our estimates of the costs per case are representative, as a mild season would only affect the frequency of cases not their severity, compared to more intensive seasons. Further, from this survey, ILI costs rather than influenza costs were used for estimating the out of hospital costs for a hospitalised patient, as the number of hospitalized influenza patients was too small. However, the survey also showed that ambulatory costs did not differ substantially between patients who were diagnosed by their physician with ILI and patients who were diagnosed by their physician with influenza.

In addition to vaccine efficacy, the quality of life estimates were the main parameters that were sourced from international studies, rather than estimated from the best available Belgian data.

For the analyses related to pregnant women and health care workers, a limitation is that we can only show the impact of different assumptions regarding secondary infections in newborns or other patients, but there are insufficient data to quantify the uncertainty reliably. We managed to show though, that the main conclusions from these analyses remained relatively robust under varying assumptions.

Another limitation is that there are no LAIV efficacy data in children above 6 years. We thus assumed that LAIV efficacy in the 6-17 years of age was equal to the efficacy in the 2-5 years. This is supported by effectiveness data from US observational studies in older children.

7.4 Future perspectives

Quadrivalent LAIV and TIV vaccines are expected in a near future, and would contain an additional B strain compared to trivalent vaccines. However, as B strains are much rarer in Belgium, the expected gain would mainly be an slightly increased efficacy. Some data claim for a longer immunity of these quadrivalent vaccines but these are up to now only speculative. The impact on the selection of optimal strategies and the estimates of the median ICERs would be very low. For instance, a quadrivalent vaccine given at the same costs but with a 10% higher effectiveness (compared to LAIV in the current study) would only slightly decrease the median ICER of vaccinating children 2-17 years versus the current situation, from €44 280 to €38 845 (95%CI €24 882–60 567) per QALY gained. This indicates that the analyses of this report are also valid for the upcoming quadrivalent vaccines. This also suggests that the quadrivalent vaccination options should have similar costs as the trivalent options we modeled.

Any decision on vaccination strategies must take into account that influenza viruses are a moving target and that the variability of influenza

seasons makes it impossible to predict the future impact of preventive strategies with certainty and accuracy. It is thus essential that the long-term impact of any change in the influenza vaccination of target groups be monitored.

On the research agenda, there is a need for effective vaccines indicated in children <2 years of age. The reviews of literature highlighted that TIV efficacy is lower in children compared to adults and varies by season. LAIV showed very high efficacy in this group in clinical trials but is not indicated in children <2 years due to an increased rate of wheezing after vaccination in clinical trials. However, this group bears the highest burden of disease especially in terms of hospitalisation rates (together with the elderly) and needs an effective protection against influenza.

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