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Optimizing influenza vaccine allocation by age using cost-effectiveness analysis: A comparison of 6720 vaccination program scenarios in children and adults in Belgium

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ABSTRACT

Background: Many European countries prioritize groups for annual influenza vaccination based on risk of severe disease and death. This has resulted in relatively high influenza vaccination coverage in older adults in Belgium. However, coverage is much lower in younger adults and negligible in children. Children and young adults are known to play a major role in the transmission dynamics of influenza. Thus, an important policy question is how influenza vaccines can be optimally allocated across age groups, taking indirect effects into account.
Methods: We adapted a dynamic transmission model to reproduce influenza seasonality in Belgium comparing 6720 mutually exclusive vaccination options, including current practice. Vaccination options were defined by different combinations of coverage level changes in nine age groups. We performed an economic evaluation comparing all options from a healthcare payer perspective. Quality-adjusted life-years (QALYs) were the primary health outcome. We expressed parametric uncertainty using the Incremental Net Monetary Benefits (INMB) approach.
Results: Of all the vaccination options considered, over 90 % dominated the current Belgian vaccination strategy in terms of cost-effectiveness. Children were estimated to contribute a substantial indirect protective effect to the overall population. The most cost-effective program increases vaccination coverage rates for children to 90 %, 50–64 years old to 48 %, and 65–74 years old to 75 %.
Discussion: Overall QALY gains can be maximized in seasonal influenza vaccination programs at acceptable costs by achieving high vaccination coverage in childhood age groups. Programmatic and ethical concerns towards such an implementation in the Belgian context need to be separately considered.

1. Introduction

Influenza is an acute respiratory illness that manifests with varying severity, ranging from relatively mild illness to severe disease requiring hospitalization, and death. For many years, vaccination has been a widely accepted and practiced method to prevent influenza morbidity and mortality. This is achieved with varying degrees of success as the ever-changing nature of the virus requires annual vaccine reformulations to match concurrently circulating virus strains and vaccine uptake depends on willingness to be vaccinated, which in turn is influenced by perceptions of the severity of influenza and of vaccine associated adverse events (Verelst et al., 2018; Kim et al., 2018a). As influenza affects people of all ages, and its vaccination requires important annual investments, policy makers seek to optimize influenza vaccine allocation over different age groups given their budget constraints.

Three standard-dose quadrivalent influenza vaccines (SD-QIV) and one high dose quadrivalent influenza vaccine (HD-QIV) have been approved for use in persons over 6 months and in high risk groups, respectively, in Belgium (Belgisch Centrum, 2024). The Belgian Superior Health Council's guidelines prioritize vaccination for people with a

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higher risk of severe illness due to influenza infection, such as older adults, persons living in institutions, and patients with underlying diseases. In addition to the priority group, Belgian governmental organizations subsidize vaccination for healthcare workers, pregnant women, older, healthy adults, and farmers (Hanquet et al., 2011). A 2018 national household survey (Berete et al., 2019) found no significant differences in self-reported influenza vaccine uptake between men and women in Belgium, but uptake increased with age, from less than 10 % in 15–24 year-olds, rising gradually up to about 50 % in 65–74 year-olds and 70 % in the 75-year-olds and older.

Priority groups differ globally. As of 2018, 118 World Health Organization (WHO) member countries had a national influenza immunization policy in place, targeting all persons older than 6 months (Morales et al., 2021). Of the 118 WHO countries, 29 countries recommend vaccination for everyone over 6 months of age while 76 countries included children as a priority group (Morales et al., 2021). Children and the general adult population have been shown to play an important role in the propagation and circulation of the pathogen, resulting in an increased interest in the benefits of vaccinating children, adolescents, and young adults (Fisman and Bogoch, 2017). The United States Advisory Committee on Immunization Practices has recommended universal influenza vaccination in the US for basically everyone over 6 months since 2010 (CDC, 2024a), and the United Kingdom's (UK) influenza vaccination program has been extended to include healthy children and adolescents aged 2 to <17 years from 2013 onwards (Sinnathamby et al., 2023). In the 2018–19 season in Belgium, over 92 % of GP visits due to influenza-like illness were patients under the age of 65 years (Sciensano, 2023), but the estimated vaccine uptake for that age group remains low in comparison to those in the high-risk group (Demarest and Charafeddine, 2013).

Cost-effectiveness analyses (CEA) are widely used to inform decision makers on the health and monetary benefits of alternative targeted influenza vaccination campaigns (Drummond et al., 2015). However, many previous analyses of influenza vaccination evaluate only a single target group. To determine the optimal universal vaccination strategy, it's essential to simultaneously compare various vaccination options for all age groups in a single analysis. The analysis of a wide variety of vaccination programs using a dynamic transmission model that accounts for herd immunity, while accounting for uncertainty in a probabilistic way, presents computational challenges that have not been addressed in existing literature. With the overall aim to develop and demonstrate a workable approach to allow such extensive analyses more swiftly in future, we evaluate simultaneously over 6000 influenza vaccination programs, each reflecting different coverage rate increases in one or more age groups, and/or stopping vaccination in working adults.

2. Materials and methods

We employ a dynamic transmission model fitted to Belgian surveillance data to estimate the age-specific number of influenza cases seeking ambulatory care in Belgium for 6720 influenza vaccination options. The results of the dynamic model are combined with data on health care use, treatment and vaccination costs, loss in quality of life and mortality due to influenza, to estimate the effectiveness and cost-effectiveness of each of the vaccination options against the current vaccination strategy and against each other.

2.1. Dynamic disease transmission model

We adapted the dynamic transmission model from a study commissioned by the Belgian Health Care Knowledge Centre (KCE) reported in Beutels et al. (2013). and with modeling details reported in Goeyvaerts

Table 1
Parameters for Economic Evaluation (€2023 price level).

Parameter	Value		Reference
Baseline scenario vaccination coverage by age	Less than 6 months	0 %	(Beutels et al., 2013; Hanquet et al., 2011)
	6 months to 17 years	0.066 %	
	18–49 years	11 %	
	50–64 years	28 %	
	65–74 years	50 %	
	75 + years	71 %	
QALY Loss for Hospitalized Patient[αβ]	0.009 (0.008) [0.003–0.017] (SD=0.0036)		(Bilcke et al., 2014; Mao et al., 2022)
QALY Loss for Patients Seeking Medical Care[αβ]	age< =60: 0.005 (0.005) [0–0.032] (SD=0.0082)		
	age> 60: 0.011 (SD=0.0123)		
QALY Loss for Patients Not Seeking Medical Care[αβ]	age< =60: 0.005 (0.004) [0–0.047] (SD=0.012)		
	age> 60: 0.009 (SD=0.0113)		
Cost of Quadrivalent Vaccine Dose	€17.02		(RIZIV, 2023a)
Cost of Vaccine Administration (assumed equivalent to cost of a GP visit in Belgium)	€30.00		(RIZIV, 2023b)
Cost of Influenza-related Hospitalization (in €)[γ]	6 months to 1 year: 3254.67		(Beutels et al., 2013; Bilcke et al., 2014)
	2–5 years: 2733.51		
	6–15 years: 2136.24		
	16–35 years: 2324.58		
	36–55 years: 3453.62		
	56–69 years: 5347.05		
	70–79 years: 6451.29		
	80 + years: 7728.39		
Cost of Ambulatory Care for Hospitalized Patients[αγ]	Highest Costs: N(mean = 180.52, sd = 20.19)		
	Lowest Costs: N(mean = 154.35, sd = 17.69)		
Cost of Ambulatory Care[αγ]	Highest Costs: N(mean = 82.3, sd = 1.34)		
	Lowest Costs: N(mean = 65.84, sd = 1.18)		
Cost of Non-Medically Attended Influenza[αγ]	Highest Costs: N(mean = 9.25, sd = 0.37)		
	Lowest Costs: N(mean = 4.37, sd = 0.21)		
Discount Rate (QALY Loss)	0.015		(Cleemput, 2012)

[α]Indicates sampled parameters.
[β]mean (median) [minimum-maximum] (standard deviation).
[γ]2012 value adjusted for inflation using 2023 Belgium Health Price Index.
[δ]Costs with high and low estimates were sampled with equal probability.

et al. (2015). This model simulated influenza spread in Belgium from the beginning of the 2003 influenza season to the end of 2010. For computational efficiency, in the current analysis we limited the time frame to a single representative season based on initial model parameters (Supp. Table 1) derived from the average incidence of the aforementioned 7 influenza seasons, such as rates of infection and recovery, and waning immunity for infections and vaccinations (Goeyvaerts et al., 2015). The model employs a time independent social contact matrix from the 2006 Belgian POLYMOD contact survey (Mossong et al., 2008; Hens et al., 2009; Goeyvaerts et al., 2010) to allow for age-specific infection dynamics. Contacts were limited to conversational contact lasting longer than 15 minutes that involved skin-to-skin touching. Initial population size and age-specific all-cause mortality rates (Supp. Figure 1) were updated to Belgian figures from the Eurostat 2021 census (Lahti et al., 2017). In the current analysis we assume that future influenza seasons exhibit similar characteristics as those studied in depth in Belgium in the period 2003–2010, including any lasting changes on seasonal influenza transmission dynamics under the influence of the pandemic emergence of 2009 H1N1 influenza and 2019 SARS-CoV-2. Probabilistic sensitivity analysis was carried out throughout the analysis. A single simulation represents an independent set of model input parameters consisting of fixed parameters, single sampled values from the five randomized parameters (Appendix 1.1, Supp. Table 1), single cost and QALY loss values sampled from the distributions in Table 1, and a single set of age-specific vaccine efficacy estimates sampled from a multivariate normal distribution (Appendix 1.3.2). The dynamic model was initialized for each set of input parameters and scenarios and ran for 6 seasons to allow dynamics to stabilize. An evaluation of optimal simulation counts (Appendix 1.1.1) deemed 600 simulations per scenario sufficient to obtain stable results.

2.2. Vaccination program options

Alternative vaccination programs were defined with respect to age group and coverage rate. Coverage rates for children were adjusted from a baseline value of 0.066% to 90% coverage in 10 % increments for the following 5 age groups: <1 year, 1 year, 2–4 years, 5–11 years, and 12–17 years, based on the Belgian school system. Coverage for children in the less than 1 year age group was held fixed at 0.033 % to account for the ineligibility for influenza vaccination of children under 6 months old (Table 1), taken to represent half of the cohort size of infants <1 year old. Adult coverage rates were adjusted following recommendations from stakeholders (Hanquet et al., 2011). For the 50–64 year old age group coverage rate changes were investigated in 10 % increments from 28 % up to 48 %. For the age group of 65 years and older, coverage rate changes from the baseline values (50 % for 65–74 years; 71 % for 75+ years) are explored to 75%. Furthermore, a vaccination coverage decrease is investigated in the 18–49 year age group from a baseline of 11% to 0%. As no dramatic changes in seasonal influenza vaccination coverage by age have been reported since then (Berete et al., 2019), the age-specific vaccination coverage estimated by Hanquet et al. (2011) was set as the standard of care and served as the baseline program. Including this baseline scenario, 6720 programs were considered based on 280 possible combinations of childhood vaccination (Supp. Table 3) and 24 combinations of adult vaccination (Supp. Table 4).

2.3. Vaccine efficacy

Age-specific vaccine efficacy was sampled from a multivariate normal distribution with 3 dimensions for 3 age groups - 6–35 months, 18–64 years, and >65 years (Appendix 1.3.2). The marginal distributions of vaccine efficacy for 6–35 month olds were estimated from a meta-analysis of the three corresponding QIVs currently used in Belgium (Claeys et al., 2018; Colombo et al., 2024; Esposito et al., 2022; Pepin et al., 2019; EudraCT Identifier: 2016-004904-74; ClinicalTrials.gov identifier: NCT01439360) (Appendix 1.3.1). One vaccine brand reported a 61.6 % efficacy rate for 18–64 years for the equivalent trivalent formulation (Beran et al., 2009; EudraCT Identifier: 2012-001230-34) and a trial reported that the added strain in the QIV formulation resulted in comparable vaccine efficacy (Kieninger et al., 2013; ClinicalTrials.gov identifier: NCT01204671) thus was applied to the respective age groups. Linear interpolation of vaccine efficacy estimates for 6–35 month olds and 18–64 year olds was used to estimate vaccine efficacy for the 4–17 year age group.

In the latest Cochrane review on elderly influenza vaccination, trivalent influenza vaccines (TIV) were estimated to have a mean efficacy of 58% (34%-73%) against influenza based on 9 randomized and controlled clinical trials (Demicheli et al., 2018). Several studies (Gaglani et al., 2021; Kim et al., 2018b) have consistently reported that QIVs have demonstrated comparable, if not improved, effectiveness compared to the previously available TIVs. For the purposes of the current analysis, we adopted a pragmatic conservative approach, by applying the TIV vaccine efficacy estimate produced by the most recent Cochrane review for age groups 65 years and up (Demicheli et al., 2018).

2.4. Economic evaluation

In line with Belgian guidelines for economic evaluation (Cleemput, 2012), the analysis was conducted from a healthcare payer perspective. Since the time horizon for vaccinations and infections was limited to a single influenza season, discounting of direct intervention and medical costs and acute non-fatal health outcomes was not needed. However, a discount rate of 1.5 % was applied to future life-years lost due to influenza-related mortality, in accordance with Belgian guidelines (Cleemput, 2012).

The number of ambulatory influenza infections was estimated from the number of new influenza-like illness (ILI) cases generated by the dynamic model, using the “no medical care fraction” (0.492) estimated from a survey in Belgium (Beutels et al., 2013; Bilcke et al., 2014) (Supp. Figure 4). This estimate of influenza infections along with the total number of vaccinations by age group, over time, for each vaccination scenario were used to generate incremental direct costs and incremental health outcomes, including the number of influenza cases (ambulatory and no medical care), hospitalizations and deaths averted, Quality-Adjusted Life Years (QALYs) gained, and Incremental Net Monetary Benefits (INMB).

The input parameters of the economic evaluation are summarized in Table 1. As reported in Hanquet et al. (2011), hospitalization and case-fatality ratios (Supp. Figure 5) were calculated based on regression analyses of reported lab-confirmed influenza cases and influenza and pneumonia-related hospitalizations and deaths over the 2000–2009 seasons using Belgium’s national hospital database and death certificate registry. Direct health care costs for ambulatory, hospitalized, and no medical care patients consist of hospital stay, diagnostics, medication and consultation costs borne by the public National Institute for Health and Disability Insurance (NIHDI), the patients, and their private insurers. The age-specific hospitalization costs for patients with a primary diagnosis of influenza was estimated by coupling the national hospital and financial administrative databases as described in Beutels et al. (2013). Ambulatory costs for hospitalized and non-hospitalized patients and ILI related costs for patients who did not seek medical care were obtained from Bilcke et al. (2014) (Table 1). All costs were adjusted to the 2023 price level using Statbel’s Health Index (STATBEL) (Appendix 1.4.1).

Average QALY loss incurred by non-medically attended ILI cases for all age groups, by ambulatory influenza cases under 60 years of age, and by hospitalized cases under 60 years of age were obtained from a 2012 survey on influenza burden in Belgium (Bilcke et al., 2014). Average QALY loss due to influenza related healthcare seeking (GP consultation or hospitalization) for over 60 year olds was based on a prospective study by Mao et al.(2022). The QIV cost was set to €17.02, which is the 2023 public price for individuals not in the high risk groups as reported

by NIHDI (RIZIV, 2023a). Vaccines were assumed to be administered by a GP for all age groups and therefore vaccine administration costs were age independent and based on primary care consultation tariffs (RIZIV, 2023b).

Uncertainty around the input parameters of the economic evaluation was accounted for with probabilistic sensitivity analysis. Cost estimates consist of an equal number of values, randomly ordered, drawn from the highest and lowest cost estimates, which were assumed normally distributed. The uncertainty around the mean QALY loss was assumed to follow a beta distribution, with distinct alpha and beta parameters

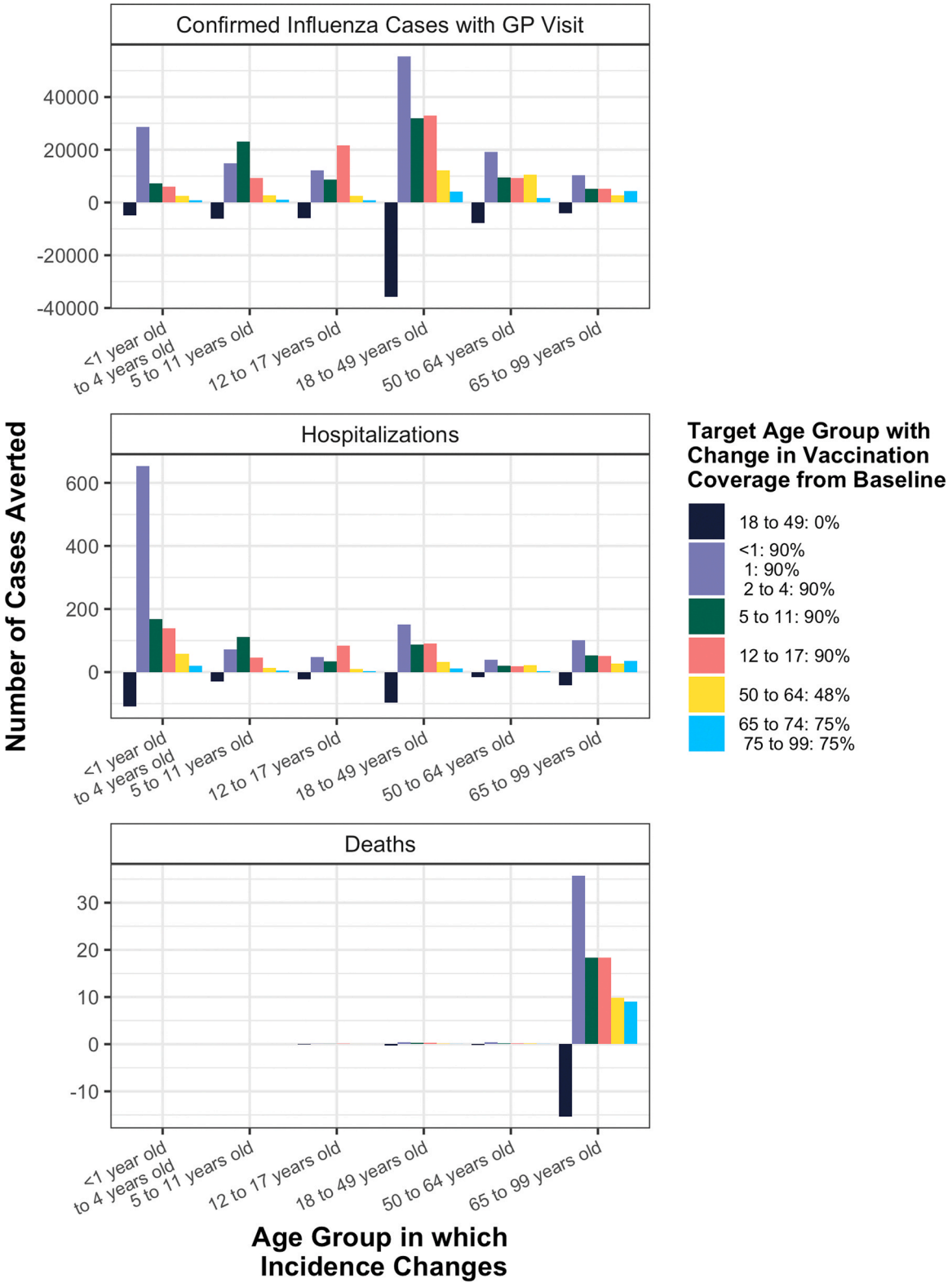

Fig. 1. Age-stratified impact of adjusted target age group vaccination coverage on cases, hospitalizations and deaths*
*Results based on 600 simulations (Appendix 1.1.1)

derived from reported mean and standard deviations for hospitalized [*Beta*(6.285, 691.96)], ambulatory care [<= 60 years old: *Beta*(0.37, 73.29); >60 years old: *Beta*(0.79, 70.21)], and no medical care [<= 60 years old: *Beta*(0.17, 33.44); >60 years old: *Beta*(0.68, 71.31)] individuals among certain age groups.

The main measure of cost-effectiveness was INMB (Appendix 1.3.2), which assesses the monetary impact of implementing one vaccination program by comparing its additional costs and outcomes against standard of care, given a single willingness-to-pay value (k) of €35,000 per QALY gained.

3. Results

3.1. Costs and effects of all alternative vaccination programs

Out of the 6719 alternative vaccination programs considered, 6047 (90 %) resulted in fewer cases, 6294 (94 %) resulted in fewer hospitalizations, 6287 (94 %) resulted in fewer deaths, and 6137 (91 %) resulted in a gain in QALYs when compared to the baseline program (Supp. Table 5). The most effective vaccination program assumed increased coverage to the predetermined age-specific maxima and averted 297,742 cases, 1856 hospitalizations, 81 deaths, and resulted in 4594 QALYs gained per year (Supp. Table 8).

There were 582 programs that resulted in QALY losses, 46 of which were costlier compared to the baseline. These consist of programs with minimal or non-existent increases in coverage rates among childhood age groups and decreased vaccination coverage for 18–49 year olds. Overall, 341 programs resulted in a higher disease burden in all its aspects (i.e. more cases, hospitalizations, deaths, and QALY losses). These programs stop vaccinating 18–49 year olds and achieve only low coverage improvements in other age groups (Supp. Table 10).

From the health care payer's perspective, there were 1620 cost-saving programs when compared to the baseline. Of these, 772 (48 %) reduced only treatment costs, 535 (33 %) reduced only vaccination costs, and 313 (19 %) reduced both vaccination and treatment costs (Supp. Table 11). Programs with lower treatment and vaccination costs than baseline predominantly reduced vaccination coverage rates for adults 18–49 years old to 0 %.

The program with the greatest overall reduction in vaccination coverage compared to the baseline scenario saved €11.2 million in vaccination costs on average, but incurred an additional €6.7 million in direct treatment costs. In contrast, the program with decreased vaccination coverage for 18–49 year olds (11% to 0%) and increased coverage for children under 2 years old to 60 % resulted in the most vaccination cost savings while also saving treatment costs, but ranks 5595 among all programs based on INMB. A similar program but with 90 % coverage for children under 2 resulted in the most overall cost savings (Supp. Table 9). Alternatively, the program with the maximum considered vaccination coverage for all age groups saved an average of €30.6 million in direct treatment costs, despite an average of €60.4 million added vaccination costs.

3.2. Herd Immunity

Widespread influenza vaccination will yield indirect benefits to unvaccinated persons due to herd immunity. By studying individual strategies' ability to reduce the overall number of cases, we can assess these indirect impacts over the season. Based on age-stratified results from 600 simulations (Appendix 1.1.1), the program that increases vaccination coverage in school-aged children alone seemed to show the greatest overall impact on caseload, averting 146,501 ambulatory influenza cases. Following closely was the program that increases vaccination for children under 5 (140,471 cases averted). Further breakdown of school-age children showed that bringing vaccination coverage up to 90 % in 5–11 year olds averted only marginally more cases (85,896) than achieving 90 % uptake in 12–17 year olds (84,746 cases averted). For comparative cost-effectiveness, it is important to remember that the 5–11 year target group contains one more age cohort to vaccinate than the 12–17 year target group. A comparably smaller increase in vaccination coverage for older, working adults (33,168 cases averted) and elderly (12,860 cases averted) yielded marginal protective benefits for other adult age groups, with much less discernible impact observed for children under 18.

The program that increases vaccination coverage for children under 5 had the greatest number of influenza cases averted beyond the target age groups compared to programs that target other age groups (Fig. 1). The program that increases vaccination coverage for 5–11 year olds had better protective effects on children under 5 and adults aged 50–74 years, while the program that increases coverage for 12–17 year olds had better protective effects on 18–49 year olds and the elderly aged 75+ (Supp. Table 14). Increasing vaccination coverage for all children and adults aged 50–74 years old as in the most cost-effective program (Table 2) averted an average 284,681 influenza cases in one season, 43 % of which were among age groups where vaccination coverage was kept at baseline (Supp. Table 14).

3.3. Cost-effectiveness

There were 6191 (92 %) cost-effective vaccination programs based on INMB (INMB > 0) when compared to the baseline program. Among all considered vaccination programs, the most cost-effective at a willingness-to-pay threshold of €35,000 is the program that increases vaccination coverage for all children to 90 % and for adults aged 50–64 years to 48 % and aged 65–74 years to 75 %, with an INMB of €131,047,736. The cumulative herd effects from increased vaccination of these age groups maximizes protection for all target groups (Supp. Table 14). The program that increases vaccination coverage for all children to 80 % dominates the programs which increase vaccination coverage for all but one childhood age group up to 90 % (Supp. Table 6). Among adults, the program in which vaccination coverage is increased to the largest considered values for all adult age groups dominates all other programs (Supp. Table 7). Table 2 lists only the top 10 programs in terms of INMB for illustrative purposes. The full table of results, with

Table 2
Top 10 (i.e. top 0.15 %) programs based on Incremental Net Monetary Benefit given a willingness-to-pay value of €35,000 per QALY gained.

Assumed vaccination coverage by age group									Incremental QALY Gain	Incremental Cost	Incremental Net Monetary Benefit
<1	1	2–4	5–11	12–17	18–49	50–64	65–74	75–99			
90 %	90 %	90 %	90 %	90 %	11 %	48 %	75 %	71 %	4,586	€29,445,042.70	€131,047,736
90 %	90 %	90 %	90 %	90 %	11 %	48 %	75 %	75 %	4,594	€29,834,381.68	€130,971,948
90 %	90 %	90 %	90 %	90 %	11 %	48 %	50 %	71 %	4,472	€26,249,771.13	€130,264,271
90 %	90 %	90 %	90 %	90 %	11 %	48 %	50 %	75 %	4,482	€26,636,688.07	€130,216,257
90 %	90 %	90 %	90 %	90 %	11 %	38 %	75 %	71 %	4,454	€26,365,203.48	€129,533,655
90 %	90 %	90 %	90 %	90 %	11 %	38 %	75 %	75 %	4,464	€26,751,973.25	€129,487,478
90 %	90 %	90 %	90 %	90 %	11 %	38 %	50 %	71 %	4,331	€23,222,362.38	€128,354,359
90 %	90 %	90 %	90 %	90 %	11 %	38 %	50 %	75 %	4,341	€23,606,526.43	€128,338,162
90 %	90 %	90 %	90 %	90 %	11 %	28 %	75 %	71 %	4,311	€23,355,037.31	€127,540,008
90 %	90 %	90 %	90 %	90 %	11 %	28 %	75 %	75 %	4,322	€23,739,047.14	€127,525,826

uncertainty, is available in the accompanying web application.

Among the top 1 % programs based on INMB, less than a fifth (18 %) reduce vaccination coverage for the young adults (18–49 years) to 0 %. Programs that reduce overall vaccination coverage compared to baseline have an average rank of 6068. The program with the maximum considered vaccination coverage for all age groups ranks 2nd among all programs. The program with the lowest possible INMB that remains cost-effective compared to baseline increases coverage for 1–4 and 12–17 year olds to 10 %, decreases 18–49 year old coverage to 0 %, increases 50–64 year old coverage to 38 %, and increases coverage for 65 and older to 75 %.

4. Discussion

We developed and demonstrated an approach to allow many imaginable scenarios to be compared based on effectiveness and cost-effectiveness in a single analysis, and found this approach to be feasible, yet challenging when it comes to summarizing the results of such elaborate analyses. In future work we will develop further automation in the execution of these comparisons, include aspects that will substantially increase the number of scenarios (like ranges of willingness to pay for a QALY with associated cost-effectiveness acceptability, value of information and net loss analyses (Bilcke and Beutels, 2022), an additional societal perspective, and more differential coverage options across child age groups) and focus on parallel sub-analyses using selections of scenarios policy makers may want to focus on. The joint consideration of different outcome criteria such as cost-effectiveness, budget-impact, effectiveness on morbidity and mortality outcomes under uncertainty will further guide our work in this area. We chose influenza as the topic of application since it requires consideration of all ages, and is a highly topical and a complex subject for policy makers.

The results of this analysis show that the most cost-effective programs are characterized by achieving high vaccination coverage in all children (up to 90 % from 0.07 % current uptake). Our findings on the benefits of including universal childhood vaccination in influenza vaccination programs are broadly in line with other literature (Boccalini et al., 2021). It is well aligned with the 2013 study for Belgium by Beutels et al. (2013). on which the current analysis was built, and a 2021 study for The Netherlands by de Boer et al. (2021) using 50 % coverage to compare three overlapping childhood age groups (2–6, 2–12, and 2–17 years) with vaccination costs per dose of €16.74 and a willingness to pay per QALY of €20,000, de Boer et al. (2021) concluded that increasing QIV/Q-LAIV vaccination coverage in children aged 2–17 years old was cost-effective from a healthcare payer's perspective.

Our work further subdivided pediatric age groups and included healthy children aged 6 months to 2 years, for whom the SD-QIVs have also been deemed safe and efficacious (Belgisch Centrum, 2024; OECD, 2024). This allows for more detailed evaluation of variations in age-specific vaccination coverage within the pediatric population than in de Boer et al. (2021) and Pitman et al. (2012). Pitman et al.'s modeling work focusing on health outcomes of the live attenuated influenza vaccine (LAIV) only, considered two childhood age groups (2–4 or 2–18 years) with varying coverage rates and found improvements in clinical outcomes with increasing coverage rates (Pitman et al., 2012). Their suggestion that expanding vaccination among 2–18 year olds by 10 % can have similar population-wide effects as expanding vaccination among 2–4 year olds by 80 % is noteworthy. Our results showed that a program that only increases vaccination for 2–4 year olds to 80 % is more effective and cost-effective, with 356 more QALYs gained and €896,265 saved, than a program that expands vaccination coverage to 10 % for 2–17 year olds, all else being equal. Increasing coverage to 50 % in 2–17 year olds substantially improves health outcomes compared to the aforementioned programs, but still ranks 2384 among all programs based on INMB due to limited herd effects we estimate when coverage remains low in children under 2 years and only moderate in all other children.

The benefits of herd immunity are evident in the age-stratified analysis of a subset of the vaccination programs considered (Fig. 1). Comparisons of the number of ambulatory influenza cases averted for programs which increase vaccination coverage for selected target age groups to the maximum considered rates show substantial differences. Increased vaccination in children led to most reductions in influenza incidence beyond the target group. We found that the program increasing coverage rates for all children alone to 60 % fell within the top 5 % based on cost-effectiveness. Programs that concurrently increase vaccination coverage for some children and for older adults still dominate, thus increased vaccination for older age groups can amplify the additional protection conferred by vaccinating children. Herd immunity implications, however, are sensitive to the contact patterns and their interpretation for use in a dynamic transmission model. The disproportionate protection conferred by children aged 4 and younger seems to stem predominantly from the social contact matrix used, and perhaps also to some extent from potential overreporting of ILI in younger children (Goeyvaerts et al., 2015; Loedy et al., 2027) (Supp. Figure 3).

The subsequent programs in our top 25 cost-effective results increase coverage in at least one of the adult target groups - 21 programs increased coverage for 50–64 year olds, 16 increased coverage for 65–74 year olds, 13 increased coverage for 75 years and up. Despite the substantial increase in coverage rates for children and the high baseline coverage rates considered for the 65 and older group, the second and fourth most cost-effective programs from this analysis further increased vaccination coverage for those aged 75 and up by 4 %. Cost-effectiveness studies for influenza vaccination for the elderly and other risk groups are ubiquitous as influenza-related mortality is highest amongst this group (Hanquet et al., 2011; Dilokthornsakul et al., 2022), but few explore coverage changes in other age groups. Ting et al., (2017) found only two studies deemed of high quality that considered the overall population; however, they did not review official HTA government advisory reports such as Beutels et al. (2013) for Belgium.

Our model accounts for seasonal, age-specific variations in vaccine efficacy in an average influenza season in Belgium, but assumes the same vaccine efficacy for different clinical outcomes. This assumption can lead to an overestimation of the benefits conferred by the vaccination programs we considered as vaccine efficacy against severe outcomes (e.g. hospitalizations and deaths) may vary from vaccine efficacy against infection (Ainslie et al., 2019). A 2009 randomized trial in Canada found that immunizing children and adolescents with the TIV resulted in 61 % indirect protective effectiveness (Loeb et al., 2010). A 2024 study quantifying vaccine effectiveness against onward infections during the 2017–2020 influenza seasons among US households, however, estimated 5% [−22.3%, 26.3%] vaccine effectiveness against influenza A, 56.4% [30.1%, 72.8%] against influenza B, and 21% [1.4%, 36.7%] overall (Grijalva et al., 2024). Quantifying the effects of QIV efficacy on onward influenza transmission requires further investigation. We also assumed QIV efficacy for the adults is equivalent to that of the TIVs due to limited data from clinical trials (Pitkala and Strandberg, 2022). Moreover, our model did not account for changes in exposure-related immunity over multiple seasons. Vaccine effectiveness is susceptible to factors such as waning immunity and changes in circulating virus strains. Backer et al. (2019). modeled high childhood vaccination coverage rates over multiple seasons and found reductions over time in mean influenza attack rates (IAR) and increased variation in IAR and epidemic size by age, which affects age-specific morbidity and mortality.

Numerous studies have determined season-specific vaccine effectiveness (Stuurman et al., 2020, 2021, 2023), but such estimates remain rare for QIVs. Our reference vaccine efficacy estimates were ascertained from laboratory-confirmed influenza caused by any influenza subtype when applicable. The sensitivity of our results to a potential mismatch between the predominantly circulating influenza subtype and vaccine strains was not separately considered. Tricco et al. determined that TIVs

reduced the risk of laboratory-confirmed influenza in seasons where vaccines were mismatched from the circulating virus strains by 56% (Tricco et al., 2013), but an influenza lineage B mismatch is less likely to result in decreased effectiveness with a QIV than with a TIV (Carregaro et al., 2023). Additionally, some studies (de Boer et al., 2016; Zeevat et al., 2021) assuming higher efficacy for QIVs against influenza B strains, found QIVs to have better cost-effectiveness than TIVs, although this also depends on assumed price differences.

Vaccine cost and administration costs were assumed uniform across all age groups, though alternative vaccine delivery approaches could be elaborated, such as administration via pharmacies, school-based programs for children under 18 (WHO, 2024) or expanded workplace vaccination for the working-age population. Workplace vaccination has been found to have a protective effect beyond the workplace and can address barriers to access that could limit vaccination coverage in that age group (Verelst et al., 2021). Consideration of such costs requires detailed numeration of relevant variables such as employment and school-attendance but also a different payer perspective than considered here. The HD-QIV has been approved for use in high risk groups and individuals over 65 in Belgium since the 2022–23 season (Hoge Gezondheidsraad, 2022). It was not included in this analysis, but cost €40.87 per dose during the 2023–24 season (Belgisch Centrum, 2024).

There is little heterogeneity in the childhood vaccination strategies we considered. Vaccination coverage rates follow an either-or approach, which may not be representative of real-life situations. Surveys conducted by the Centers for Disease Control (CDC) on vaccination coverage estimates in 7 consecutive influenza seasons in the United States (Santibanez et al., 2020; Srivastav et al., 2014) show that childhood coverages follow a downward trajectory as age increases. Backer et al. suggest that high childhood vaccination coverage rates can cause shifts in susceptible groups in future influenza seasons and an increased reliance on vaccines due to fewer exposures stimulating natural immunity (Backer et al., 2019). There is conflicting evidence to suggest that repeated vaccination of the same persons may (Ohmit et al., 2014; Skowronski et al., 2017; Kwong et al., 2020) or may not (Valenciano et al., 2018; Domínguez et al., 2017) reduce per-person vaccine efficacy in subsequent seasons. We did not address this issue with our approach. This question, however, warrants further scrutiny from the biomedical research community, so that it could unequivocally inform future simulation models.

To our knowledge, this work is one of the first that evaluates the cost-effectiveness of national influenza vaccination policy, considering all target age groups at varying coverage rates. This underscores the potential in economic evaluations of influenza vaccine optimization. Our results demonstrate the significant role children can play in the cost-effective design of influenza vaccination programs. Influenza vaccination coverage among childhood age groups averaged 50 % in the United Kingdom (UK Health Security Agency, 2023) and 56 % in the United States for the 2023–24 season (CDC, 2024b). A program with similar childhood coverage considered under our approach is within the top 10 % based on cost-effectiveness. Nonetheless, these coverage rates are markedly lower than the coverage rates in our top results. Achieving high coverage rates among children is a task that extends beyond the children themselves and relies on cooperation among a wider group of stakeholders such as parents, educators, and healthcare providers. Such an undertaking can be influenced by factors, such as access to and attitudes towards vaccination, in a decision context involving ethics and preferences for interventions in childhood (Verelst et al., 2018; Luyten and Beutels, 2016) that exceed effectiveness and cost-effectiveness, and were beyond the scope of the current paper.

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Ethics declarations

Not applicable. We do not report individual patient data.

Role of the Funder

The publication of study results was not contingent on the sponsors' approval or censorship. We confirm that this work has not been submitted or accepted for publication elsewhere. We confirm that all authors of this manuscript have contributed significantly to the work. This manuscript has been read and approved by all authors.

CRediT authorship contribution statement

Beutels Philippe: Writing – review & editing, Supervision, Resources, Funding acquisition, Conceptualization. **Willem Lander:** Writing – review & editing, Software, Resources, Methodology. **Bilcke Joke:** Writing – review & editing, Supervision, Resources, Conceptualization. **Hens Niel:** Writing – review & editing, Supervision, Resources, Funding acquisition. **Manansala Regina:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

All other authors report no potential conflicts of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.epidem.2025.100826.

Data Availability

Data will be made available on request.

References

A Phase III, Observer-Blind, Randomized, Non-Influenza Vaccine Comparator-Controlled, Parallel-Group, Multi-Country Study in Children Aged 6-35 Months to Assess the Safety and Efficacy of Abbott's Candidate Quadrivalent Influenza Vaccine. Health Products Regulatory Authority. EudraCT Identifier: 2016-004904-74 . Accessed January 17, 2024.⟨https://www.clinicaltrialsregister.eu/ctr-search/trial/2016-004904-74/results⟩.

A Phase III, Open-Label, Multicentre Study to Evaluate the Immunogenicity, Safety and Reactogenicity of a Revaccination Dose of the GlaxoSmithKline Biologicals' Quadrivalent Seasonal Influenza Candidate Vaccine GSK2321138A, Administered to Children Who Previously Participated in Study 115345 (FLU D-QIV-004 PRI).; EudraCT Identifier: 2012-001230-34. June 5, 2013. Accessed January 17, 2024. ⟨https://www.clinicaltrialsregister.eu/ctr-search/trial/2012-001230-34/CZ⟩.

Ainslie, K.E.C., Haber, M., Orenstein, W.A., 2019. Challenges in estimating influenza vaccine effectiveness. Expert Rev. Vaccin. 18 (6), 615–628. https://doi.org/10.1080/14760584.2019.1622419.

An Efficacy Study of GSK Biologicals' Quadrivalent Influenza Vaccine GSK2321138A (FLU D-QIV) When Administered in Children. ClinicalTrials.gov identifier: NCT01439360. 2018. Accessed January 1, 2024. ⟨https://clinicaltrials.gov/study/NCT01439360⟩.

Backer, J.A., van Boven, M., van der Hoek, W., Wallinga, J., 2019. Vaccinating children against influenza increases variability in epidemic size. Epidemics 26, 95–103. https://doi.org/10.1016/j.epidem.2018.10.003.

Belgisch Centrum voor Farmacotherapeutische Informatie, 2024. Vaccin tegen influenza. BCFI. Accessed February 9, 2024. http://www.bcfi.be/nl/chapters/13?frag=11304.

Beran, J., Vesikari, T., Wertzova, V., et al., 2009. Efficacy of inactivated split-virus influenza vaccine against culture-confirmed influenza in healthy adults: a prospective, randomized, placebo-controlled trial. J. Infect. Dis. 200 (12), 1861–1869. https://doi.org/10.1086/648406.

Berete F., Tafforeau J., Demarest S., Drieskens S. Gezondheidsenquête 2018: Vaccinatie. Sciensano; 2019.

Beutels, P., Vandendijck, Y., Willem, L., et al., 2013. Seasonal Influenza Vaccination: Prioritizing Children or Other Target Groups? - Part II. Health Technology Assessment (HTA) (KCE). Belgian Health Care Knowledge Centre.

Bilcke, J., Beutels, P., 2022. Generating, presenting, and interpreting cost-effectiveness results in the context of uncertainty: a tutorial for deeper knowledge and better practice. Med Decis. Mak. 42 (4), 421–435. https://doi.org/10.1177/0272989X211045070.

Bilcke, J., Coenen, S., Beutels, P., 2014. Influenza-like-illness and clinically diagnosed flu: disease burden, costs and quality of life for patients seeking ambulatory care or no professional care at all. PLoS One 9 (7), e102634. https://doi.org/10.1371/journal.pone.0102634.

Boccalini, S., Bechini, A., Moscadelli, A., Paoli, S., Schirripa, A., Bonanni, P., 2021. Cost-effectiveness of childhood influenza vaccination in Europe: results from a systematic review. Expert Rev. Pharm. Outcomes Res 21 (5), 911–922. https://doi.org/10.1080/14737167.2021.1925110.

Carregaro, R.L., Roscani, A.N.C.P., Raimundo, A.C.S., et al., 2023. Immunogenicity and safety of inactivated quadrivalent influenza vaccine compared with the trivalent vaccine for influenza infection: an overview of systematic reviews. BMC Infect. Dis. 23, 563. https://doi.org/10.1186/s12879-023-08541-0.

Centers for Disease Control and Prevention. Influenza Vaccination: A Summary for Clinicians | CDC. March 22, 2024a. Accessed July 30, 2024. ⟨https://www.cdc.gov/flu/professionals/vaccination/vax-summary.htm⟩.

Centers for Disease Control and Prevention, 2024b. Weekly Flu Vaccination Dashboard. Influenza (Flu). June 21. Accessed August 27, 2024. ⟨https://www.cdc.gov/flu/fluvaxview/dashboard/vaccination-dashboard.html⟩.

Claeys, C., Zaman, K., Dbaibo, G., et al., 2018. Prevention of vaccine-matched and mismatched influenza in children aged 6–35 months: a multinational randomised trial across five influenza seasons. Lancet Child Adolesc. Health 2 (5), 338–349. https://doi.org/10.1016/S2352-4642(18)30062-2.

Cleemput, Irina, 2012. Neyt Mattias, Van De Sande Stefaan, Thiry Nancy. Belgian Guidelines for Economic Evaluations and Budget Impact Analyses: Second Edition. Health Technology Assessment (HTA). Belgian Health Care Knowledge Centre (KCE). https://doi.org/10.57598/R183C.

Colombo, L., Hadigal, S., Nauta, J., Kondratenko, A., Rogoll, J., van de Witte, S., 2024. Influvac Tetra: clinical experience on safety, efficacy, and immunogenicity. Expert Rev. Vaccin. 23 (1), 88–101. https://doi.org/10.1080/14760584.2023.2293241.

de Boer, P.T., Crépey, P., Pitman, R.J., Macabeo, B., Chit, A., Postma, M.J., 2016. Cost-effectiveness of quadrivalent versus trivalent influenza vaccine in the United States. Value Health 19 (8), 964–975. https://doi.org/10.1016/j.jval.2016.05.012.

de Boer, P.T., Nagy, L., Dolk, F.C.K., Wilschut, J.C., Pitman, R., Postma, M.J., 2021. Cost-effectiveness of pediatric influenza vaccination in The Netherlands. Value Health 24 (1), 19–31. https://doi.org/10.1016/j.jval.2020.10.011.

Demarest, S., Charafeddine, R., 2013. GEZONDHEIDSENQUETE 2013. Rapport 5: Preventie. Wetenschappelijk Instituut Volksgezondheid.

Demicheli, V., Jefferson, T., Pietrantonj, C.D., et al., 2018. Vaccines for preventing influenza in the elderly. Cochrane Database Syst. Rev. 2. https://doi.org/10.1002/14651858.CD004876.pub4.

Dilokthornsakul, P., Lan, L.M., Thakkinstian, A., Hutubessy, R., Lambach, P., Chaiyakunapruk, N., 2022. Economic evaluation of seasonal influenza vaccination in elderly and health workers: a systematic review and meta-analysis. eClinicalMedicine 47. https://doi.org/10.1016/j.eclinm.2022.101410.

Domínguez, A., Soldevila, N., Toledo, D., et al., 2017. The effectiveness of influenza vaccination in preventing hospitalisations of elderly individuals in two influenza seasons: a multicentre case–control study, Spain, 2013/14 and 2014/15. Eurosurveillance 22 (34), 30602. https://doi.org/10.2807/1560-7917.ES.2017.22.34.30602.

Drummond, M.F., Sculpher, M.J., Claxton, K., Stoddart, G.L., Torrance, G.W., 2015. Methods for the Economic Evaluation of Health Care Programmes, 4th edition. Oxford University Press.

Esposito, S., Nauta, J., Lapini, G., Montomoli, E., van de Witte, S., 2022. Efficacy and safety of a quadrivalent influenza vaccine in children aged 6–35 months: a global, multiseasonal, controlled, randomized Phase III study. Vaccine 40 (18), 2626–2634. https://doi.org/10.1016/j.vaccine.2022.02.088.

Fisman, D.N., Bogoch, I.I., 2017. Have you herd? Indirect flu vaccine effects are critically important. Lancet Public Health 2 (2), e57–e58. https://doi.org/10.1016/S2468-2667(17)30004-X.

Gaglani, M., Vasudevan, A., Raiyani, C., et al., 2021. Effectiveness of trivalent and quadrivalent inactivated vaccines against Influenza B in the United States, 2011–2012 to 2016–2017. Clin. Infect. Dis. 72 (7), 1147–1157. https://doi.org/10.1093/cid/ciaa102.

Gezondheidsraad, Hoge, 2022. Vaccinatie Tegen Seizoensgebonden Griep. Winterseizoen 2022-2023. Hoge Gezondheidsraad.

Goeyvaerts, N., Hens, N., Ogunjimi, B., et al., 2010. Estimating infectious disease parameters from data on social contacts and serological status. J. R. Stat. Soc. Ser. C Appl. Stat. 59 (2), 255–277. https://doi.org/10.1111/j.1467-9876.2009.00693.x.

Goeyvaerts, N., Willem, L., Van Kerckhove, K., et al., 2015. Estimating dynamic transmission model parameters for seasonal influenza by fitting to age and season-specific influenza-like illness incidence. Epidemics 13, 1–9. https://doi.org/10.1016/j.epidem.2015.04.002.

Grijalva, C.G., Nguyen, H.Q., Zhu, Y., et al., 2024. Estimated effectiveness of influenza vaccines in preventing secondary infections in households. JAMA Netw. Open 7 (11), e2446814. https://doi.org/10.1001/jamanetworkopen.2024.46814.

Hanquet, G., Jonckheer, P., Vlayen, J., Vrijens, F., Thiry, N., Beutels, P., 2011. Seasonal Influenza Vaccination: Priority Target Groups – Part I. Good Clinical Practice (GCP). Belgian Health Care Knowledge Centre (KCE).

Hens, N., Goeyvaerts, N., Aerts, M., Shkedy, Z., Van Damme, P., Beutels, P., 2009. Mining social mixing patterns for infectious disease models based on a two-day population survey in Belgium. BMC Infect. Dis. 9 (1), 5. https://doi.org/10.1186/1471-2334-9-5.

Kieninger, D., Sheldon, E., Lin, W.Y., et al., 2013. Immunogenicity, reactogenicity and safety of an inactivated quadrivalent influenza vaccine candidate versus inactivated trivalent influenza vaccine: a phase III, randomized trial in adults aged ≥18 years. BMC Infect. Dis. 13, 343. https://doi.org/10.1186/1471-2334-13-343.

Kim, Y.K., Song, J.Y., Jang, H., et al., 2018b. Cost effectiveness of quadrivalent influenza vaccines compared with trivalent influenza vaccines in young children and older adults in korea. PharmacoEconomics 36 (12), 1475–1490. https://doi.org/10.1007/s40273-018-0715-5.

Kim, H., Webster, R.G., Webby, R.J., 2018a. Influenza virus: dealing with a drifting and shifting pathogen. Viral Immunol. 31 (2), 174–183. https://doi.org/10.1089/vim.2017.0141.

Kwong, J.C., Chung, H., Jung, J.K., et al., 2020. The impact of repeated vaccination using 10-year vaccination history on protection against influenza in older adults: a test-negative design study across the 2010/11 to 2015/16 influenza seasons in Ontario, Canada. Eurosurveillance 25 (1), 1900245. https://doi.org/10.2807/1560-7917.ES.2020.25.1.1900245.

Lahti, L., Huovari, J., Kainu, M., Biecek, P., 2017. Retrieval and analysis of Eurostat open data with the eurostat Package. R. J. 9 (1), 385. https://doi.org/10.32614/RJ-2017-019.

Loeb, M., Russell, M.L., Moss, L., et al., 2010. Effect of influenza vaccination of children on infection rates in hutterite communities: a randomized trial. JAMA 303 (10), 943–950. https://doi.org/10.1001/jama.2010.250.

Loedy N., Wallinga J., Hens N., Torneri A. Repetition in social contacts: implications in modelling the transmission of respiratory infectious diseases in pre-pandemic and pandemic settings. Proc. R. Soc. B. Biol. Sci. 291(2027):20241296. doi:10.1098/rspb.2024.1296.

Luyten, J., Beutels, P., 2016. The social value of vaccination programs: beyond cost-effectiveness. Health Aff. (Millwood) 35 (2), 212–218. https://doi.org/10.1377/hlthaff.2015.1088.

Mao, Z., Li, X., Korsten, K., et al., 2022. Economic burden and health-related quality of life of respiratory syncytial virus and influenza infection in European Community-dwelling older adults. J. Infect. Dis. 226 (ement_1), S87–S94. https://doi.org/10.1093/infdis/jiac069.

Morales, K.F., Brown, D.W., Dumolard, L., et al., 2021. Seasonal influenza vaccination policies in the 194 WHO Member States: the evolution of global influenza pandemic preparedness and the challenge of sustaining equitable vaccine access. Vaccin. X 8, 100097. https://doi.org/10.1016/j.jvacx.2021.100097.

Mossong, J., Hens, N., Jit, M., et al., 2008. Social contacts and mixing patterns relevant to the spread of infectious diseases. PLoS Med. 5 (3), e74. https://doi.org/10.1371/journal.pmed.0050074.

OECD. PF3.2: Enrolment in Childcare and Pre-School. Organisation for Economic Co-operation and Development Accessed February 15, 2024. ⟨https://www.oecd.org/els/soc/PF3_2_Enrolment_childcare_preschool.pdf⟩.

Ohmit, S.E., Thompson, M.G., Petrie, J.G., et al., 2014. Influenza vaccine effectiveness in the 2011–2012 season: protection against each circulating virus and the effect of prior vaccination on estimates. Clin. Infect. Dis. 58 (3), 319–327. https://doi.org/10.1093/cid/cit736.

Pepin, S., Dupuy, M., Borja-Tabora, C.F.C., et al., 2019. Efficacy, immunogenicity, and safety of a quadrivalent inactivated influenza vaccine in children aged 6–35 months: a multi-season randomised placebo-controlled trial in the Northern and Southern Hemispheres. Vaccine 37 (13), 1876–1884. https://doi.org/10.1016/j.vaccine.2018.11.074.

Pitkala, K.H., Strandberg, T.E., 2022. Clinical trials in older people. Age Ageing 51 (5), afab282. https://doi.org/10.1093/ageing/afab282.

Pitman, R.J., White, L.J., Sculpher, M., 2012. Estimating the clinical impact of introducing paediatric influenza vaccination in England and Wales. Vaccine 30 (6), 1208–1224. https://doi.org/10.1016/j.vaccine.2011.11.106.

Rijksinstituut voor ziekte- en invaliditeitsverzekering (RIZIV). Tarieven van artsen vanaf 01-08-2023. Honoraria, prijzen en tegemoetkomingen van artsen - Raadplegingen en bezoeken. 2023b. Accessed November 14, 2023, https://www.riziv.fgov.be/SiteCollectionDocuments/tarief_artsen_deel01_20230801.pdf.

Rijksinstituut voor ziekte- en invaliditeitsverzekering (RIZIV). Terugbetaling van het vaccin tegen de seizoensgriep. 2023a. Accessed November 14, 2023. ⟨https://www.riziv.fgov.be/nl/thema-s/verzorging-kosten-en-terugbetaling/wat-het-ziekenfonds-terugbetaalt/geneesmiddelen/geneesmiddel-terugbetalen/terugbetaling-van-het-vaccin-tegen-de-seizoensgriep⟩.

Safety and Immunogenicity Study of GSK Biologicals' Seasonal Influenza Candidate Vaccine (GSK2321138A). Bethesda (MD): National Library of Medicine (US). ClinicalTrials.gov identifier: NCT01204671. September 24, 2018. Accessed July 30, 2024. ⟨https://clinicaltrials.gov/study/NCT01204671⟩.

Santibanez, T.A., Srivastav, A., Zhai, Y., Singleton, J.A., 2020. Trends in childhood influenza vaccination coverage, United States, 2012-2019. Public Health Rep. 135 (5), 640–649. https://doi.org/10.1177/0033354920944867.

Sciensano. Influenza and influenza-like illness. For a Healthy Belgium. December 1, 2022. Accessed March 24, 2023. ⟨https://www.healthybelgium.be/en/health-status/communicable-diseases/influenza-and-influenza-like-illness#ili-season-2018-19⟩.

Sinnathamby, M.A., Warburton, F., Reynolds, A.J., et al., 2023. An intercountry comparison of the impact of the paediatric live attenuated influenza vaccine (LAIV) programme across the UK and the Republic of Ireland (ROI), 2010 to 2017. Influenza Other Respir. Virus 17 (2), e13099. https://doi.org/10.1111/irv.13099.

Skowronski, D.M., Chambers, C., De Serres, G., et al., 2017. Serial vaccination and the antigenic distance hypothesis: effects on influenza vaccine effectiveness during A (H3N2) epidemics in Canada, 2010–2011 to 2014–2015. J. Infect. Dis. 215 (7), 1059–1099. https://doi.org/10.1093/infdis/jix074.

Srivastav A., Santibanez T.A., Kahn K.E., et al. National Early Season Flu Vaccination Coverage, United States, November 2014. Centers for Disease Control and Prevention; 2014.

STATBEL. Consumer price index and health index. Directorate-general Statistics - Statistics Belgium. Accessed July 24, 2023. ⟨https://statbel.fgov.be/en/open-data/consumer-price-index-and-health-index⟩.

Stuurman, A.L., Biccler, J., Carmona, A., et al., 2021. Brand-specific influenza vaccine effectiveness estimates during 2019/20 season in Europe – Results from the DRIVE EU study platform. Vaccine 39 (29), 3964–3973. https://doi.org/10.1016/j.vaccine.2021.05.059.

Stuurman, A.L., Bollaerts, K., Alexandridou, M., et al., 2020. Vaccine effectiveness against laboratory-confirmed influenza in Europe – Results from the DRIVE network during season 2018/19. Vaccine 38 (41), 6455–6463. https://doi.org/10.1016/j.vaccine.2020.07.063.

Stuurman, A.L., Carmona, A., Biccler, J., et al., 2023. Brand-specific estimates of influenza vaccine effectiveness for the 2021–2022 season in Europe: results from the DRIVE multi-stakeholder study platform. Front Public Health 11, 1195409. https://doi.org/10.3389/fpubh.2023.1195409.

Ting, E.E.K., Sander, B., Ungar, W.J., 2017. Systematic review of the cost-effectiveness of influenza immunization programs. Vaccine 35 (15), 1828–1843. https://doi.org/10.1016/j.vaccine.2017.02.044.

Tricco, A.C., Chit, A., Soobiah, C., Hallett, D., Meier, G., Chen, M.H., Tashkandi, M., Bauch, C.T., Loeb, M., 2013. Comparing influenza vaccine efficacy against mismatched and matched strains: a systematic review and meta-analysis. BMC medicine 11, 1–9.

UK Health Security Agency, 2023. Surveillance of influenza and other seasonal respiratory viruses in the UK, winter 2022 to 2023. GOV.UK. Accessed July 3, 2023. ⟨https://www.gov.uk/government/statistics/annual-flu-reports/surveillance-of-influenza-and-other-seasonal-respiratory-viruses-in-the-uk-winter-2022-to-2023⟩.

Valenciano, M., Kissling, E., Larrauri, A., et al., 2018. Exploring the effect of previous inactivated influenza vaccination on seasonal influenza vaccine effectiveness against medically attended influenza: results of the European I-MOVE multicentre test-negative case-control study, 2011/2012-2016/2017. Influenza Other Respir. Virus 12 (5), 567–581. https://doi.org/10.1111/irv.12562.

Verelst, F., Beutels, P., Hens, N., Willem, L., 2021. Workplace influenza vaccination to reduce employee absenteeism: An economic analysis from the employers' perspective. Vaccine 39 (14), 2005–2015. https://doi.org/10.1016/j.vaccine.2021.02.020.

Verelst, F., Willem, L., Kessels, R., Beutels, P., 2018. Individual decisions to vaccinate one's child or oneself: a discrete choice experiment rejecting free-riding motives. Soc. Sci. Med. 207, 106–116. https://doi.org/10.1016/j.socscimed.2018.04.038.

World Health Organization. School vaccination. WHO Immunization Data. Accessed February 21, 2024. ⟨https://immunizationdata.who.int/global/wiise-detail-page/school-vaccination?ISO_3_CODE=BEL&YEAR⟩=.

Zeevat, F., Crépey, P., Dolk, F.C.K., Postma, A.J., Breeveld-Dwarkasing, V.N.A., Postma, M.J., 2021. Cost-effectiveness of quadrivalent versus trivalent influenza vaccination in the Dutch National Influenza Prevention Program. Value Health 24 (1), 3–10. https://doi.org/10.1016/j.jval.2020.11.002.