Factors Influencing Infant and Adolescent Vaccine Uptake in Flanders, Belgium

H. Theeten, E. Lefevere, C. Vandermeulen, P. Van Damme, and N. Hens

Abstract This chapter focuses on the determinants of a number of immunization programme outcomes in Flanders (Belgium), such as vaccine initiation and uptake, completion of the vaccination schedule and compliance to official validity criteria. These were assessed in both infant and adolescent age groups. Three main groups of potential influencing factors are looked at: (1) individual background variables; (2) family level variables; (3) external factors such as the governmental vaccination programme and other initiatives to promote vaccination. Data on parental willingness to pay for and willingness to accept multiple concomitant injections and their determinants are discussed as well. Exploring relationships between vaccination programme outcomes and influencing factors can give important information to optimize vaccination programme performance.

H. Theeten (✉) • P. Van Damme
Centre for the Evaluation of Vaccinations, Vaccine and Infectious Disease Institute, University of Antwerp, Universiteitsplein 1, 2610 Wilrijk, Belgium
e-mail: heidi.theeten@ua.ac.be; pierre.vandamme@ua.ac.be

E. Lefevere,
Herman Deleeck Centre for Social Policy, University of Antwerp, St Jacobstraat 2, 2000 Antwerp, Belgium
e-mail: eva.lefevere@ua.ac.be

C. Vandermeulen
Department of Youth Health Care, KU Leuven, Kapucijnenvoer 35, 3000 Leuven, Belgium
e-mail: corinne.vandermeulen@uzleuven.be

N. Hens
Center for Statistics, Hasselt University, Agoralaan 1, 3590 Diepenbeek, Belgium

Centre for Health Economic Research and Modeling Infectious Diseases, University of Antwerp, Universiteitsplein 1, 2610 Wilrijk, Belgium
e-mail: niel.hens@uhasselt.be

P. Manfredi and A. d'Onofrio (eds.), *Modeling the Interplay Between Human Behavior and the Spread of Infectious Diseases*, DOI 10.1007/978-1-4614-5474-8_3,

1 Introduction

During the previous century, highly effective vaccines have been developed and vaccination programmes have been implemented. Together, these have allowed for primary prevention of infectious diseases that once disabled or killed large numbers of adults and children, such as measles, polio and diphtheria. However, continued and extensive surveillance of diseases, vaccines and vaccination programmes is necessary since any of these diseases can be reintroduced, as has happened in the past. Such reintroduction of diseases can be induced by, among others, vaccine failure or failure to vaccinate for reasons such as programme performance regression or changes in people's attitudes and perceptions towards vaccinations. Accurate information on vaccine uptake, disease susceptibility in the target groups, disease epidemiology and changes in people's attitudes and preferences towards vaccines and vaccination programmes is highly needed to evaluate the performance of recommended vaccination programmes. This information can also be used to guide decisions on adaptation of the existing programmes or on the introduction of new vaccines.

This chapter summarizes findings from studies on infant and adolescent vaccination in Flanders, the northern region of Belgium, representing about 2/3 of the Belgian population. The studies explored various indicators of vaccine uptake (vaccination initiation, vaccination completion), compliance with the recommended validity criteria and attitudes and preferences towards vaccinations. In order to understand the setting of these studies some background information on the organization of the vaccination programme in Belgium seems appropriate.

Belgium is governed both by a national and sub-national (regional) governments. Vaccination policy is a shared responsibility of the national and the regional Ministries of Health. A national schedule of recommended vaccines is provided and regularly updated by the national Superior Health Council (SHC). The regional authorities are responsible for the organization and promotion of the immunization programmes in their respective regions. The way the vaccination programme is organized in each region (supply of vaccines via the public and the private health setting vs via the private health setting only) as well as the price of the vaccine (free of charge, partially or not reimbursed) are jointly decided by the national and the regional governments. With regard to the organization of the vaccination programme, for most vaccines recommended by the SHC, parents can choose to have their child vaccinated in a public or in a private health care setting. In the case of infant vaccinations, the public health setting consists of well-baby clinics. These clinics systematically offer vaccines to all children between 0 and 3 years of age through regular preventive consultations. Most of these vaccines are free of charge, while for some of them an out-of-pocket cost is required. In the case of school-aged children, the public health setting consists of free of charge preventive consultations by school health services. Throughout the school career of a child, the vaccination status is checked at regular points in time and recommended vaccines are offered systematically to children at specific ages. All vaccines offered by these school health services are currently (situation April 2012) free of charge.

The private health care setting for both infant and school-aged children consists of general practitioners and paediatricians, who can order and administer free of charge vaccines as well. Nevertheless, they charge a fee for the consultation.

In practice, many vaccines, once the SHC recommends them, are first available only via the private health care setting during some time, prior to an agreement on financing between the national and the regional governments. This was the case for, e.g., the hepatitis B vaccine, the *Haemophilus influenzae* type b vaccine, pneumococcal vaccines and human papilloma virus (HPV) vaccines. If no final agreement is reached between the national and the regional government on a specific vaccine, this vaccine can still be obtained via the private health setting, but the initiative for vaccination lies entirely with the parents or with the physicians, and there is no systematic offer of these vaccines to the eligible children. Partial reimbursement is in some cases provided by the national government or by private, non-profit sickness funds.

2 Studies

The results described in this section can be divided into two subsections. In the first subsection, indicators of vaccine uptake and its determinants are described. In the second subsection, we look at other indicators relevant for the surveillance and monitoring of the vaccination programme, namely parental attitudes with regard to the administration of concomitant vaccines and willingness to pay to avoid an extra injection. Table 1 gives an overview of the different studies that are summarized below.

2.1 Determinants of Vaccine Uptake

We first describe the indicators of vaccine uptake and its determinants for various vaccines supplied via both the public and the private setting, and subsequently indicators for one specific vaccine (HPV vaccine) during the period it was only supplied via the private health care setting (partly reimbursed). For all vaccines we identified low-uptake risk groups. Identification of low-uptake risk groups allows for targeted strategies that can enhance the uptake of vaccines, overall or in certain risk groups.

2.1.1 Vaccines Offered Both via the Public and the Private Health Care Setting

A first series of studies [1, 4, 7, 8] investigated indicators of vaccine uptake for vaccines offered free of charge to infants and school children both via the public and the private health care setting. Information was obtained through two immunization

Table 1 Overview of selected studies in Flanders, Belgium

	Reference	Study population	Main outcome	Factors studied	Design
t9.2	[4]	1,349 infants (°2003, interviewed 2005)	Coverage per vaccine dose recommended in infancy, full series coverage, validity of the schedule	Socio-demographic background (child/family/parent level), vaccinator types involved, side effects of vaccination, frequency of illness of the child, use of day care	Random cluster sample, interview at home, written documentation of recommended vaccine doses at home, supplemented with vaccination data from medical files, survey regression analysis for association between factors and outcome
t9.3	[1]	915 infants (°2006, interviewed 2008)			
t9.4	[8]	1,344 adolescents (°1991, interviewed 2005)	Coverage per recommended vaccine dose for measles-mumps-rubella, hepatitis B, diphtheria-tetanus-polio[1] and meningococcal C[2] vaccines up to 13 years of age, validity of the schedule	Socio-demographic background (child/family/parent level), vaccinator types involved[2], side effects of vaccination, school career of the adolescent	(see above)
t9.5	[1]	1,319 adolescents (°1994, interviewed 2008)			
t9.6	[7]	792 children (7–8 years of age) (°1997, interviewed 2005)	Coverage per vaccine dose recommended up to 6 years of age, full series coverage, validity of the schedule	Socio-demographic background (child/family/parent level), degree of urbanization	(see above)

t10.1	[6]	cfr. [4] and [8]	Willingness to pay to avoid a concomitant injection, number of concomitant injections parents would allow during one visit	cfr. [4] and [8], each outcome variable as a factor in the analysis of the other outcome variable	(see above)
t10.2	[2]	117,151 girls (12–18 years of age) (°1989–1996, analysed 2010)	HPV vaccination initiation	Age, socio-economic background (family level), place of residence, reimbursement regime, information campaign	Analysis of reimbursement claims[c] Cox regression model for factors predicting HPV vaccination initiation
t10.3	[3]	127,854 girls (12–18 years of age) (°1989–1996, analysed 2010)	HPV vaccination initiation	Age, socio-economic background (family level), place of residence, cervical cancer screening by mother	Analysis of reimbursement claims[c], generalized linear mixed model for association between mother's cervical cancer screening and daughter's HPV vaccination initiation

Legend: infants were 18–24 months of age, adolescents were 13–14 years of age

[1]Administration of the tetanus-diphtheria-polio booster doses recommended at 6 years of age was not assessed in adolescents in 2005

[2]A once-only meningococcal C conjugate vaccine catch-up campaign in 2002–2004 targeted both cohorts of adolescents

[3]Limited to reimbursement claims made at the National Alliance of Christian Mutualities

coverage surveys performed in 2005 and 2008, both ordered by the Flemish Ministry of Health. Their principal aim was to assess coverage of the following infant and adolescent vaccines: poliomyelitis (polio), diphtheria-tetanus-pertussis (DTP), H. *influenzae* type b (Hib), hepatitis B (HBV), measles-mumps-rubella (MMR) and meningococcal C (MenC) vaccines. The survey comprised samples of 18–24-month-old infants (°2003 and °2006), 7–8-year-old school-aged children (°1997) and 13–14-year-old adolescents (°1991 and °1994) (Table 1). Two-step random cluster samples were selected as recommended by the Expanded Programme on Immunization (EPI) of the World Health Organization. Families were interviewed at home. The obtained vaccination data were updated from medical files of private physicians or public health services (if necessary and if possible), as well as from the child's individual record in Vaccinnet, Flanders' online vaccine ordering and registration system. The main results with regard to vaccine uptake are summarized in Table 2.

Vaccine coverage in Flanders was found to be higher at infant age (where it surpassed 90 % for all assessed vaccines) than at later age (where the coverage of most recommended vaccines was below 90 %). Note that non-availability of vaccination documents at home was also more frequent at later age and can thus have biased the findings. First dose coverage (limited to multi-dose vaccines), an indicator of vaccination initiation, ranged from 96.9 to 99.0 % in infants and from 80.6 to 83.3 % in adolescents in 2005. In 2008, vaccination initiation levels of close to 100 % and between 86.4 and 92.5 % were noted in infants and adolescents, respectively. Full series coverage (vaccination completion) per vaccine in infants ranged from 92.2 to 94.1 % in 2005 and from 95.1 to 96.6 % in 2008. In adolescents, full series were assessed for HBV and MMR vaccines only. Full series coverage for MMR in this age group rose from 74.6 in 2005 to 83.5 % in 2008; for HBV a rise from 75.7 to 89.3 % was noted. Age-appropriate vaccination rate (full series of all recommended vaccines) in infants was stable at 89.5 and 89.6 % in 2005 and 2008, respectively, whereas in adolescents it increased from 58.1 to 72.8 %. Excluding invalid doses (as based on official criteria for minimal age at administration and minimal interval between doses) resulted in a reduction of full series coverage only in infants. Valid series coverage per vaccine in that age group ranged from 85.6 to 90.1 % in 2005 and from 88.4 to 93.4 % in 2008. Several predictors of the vaccination coverage per vaccine and per dose in each surveyed age cohort were studied, using parametric and non-parametric methods (Table 2). The most important predictor of lower vaccination coverage in infants was the main vaccinator, with children vaccinated in the private health care setting having a higher risk of undervaccination than children vaccinated in the public health care setting. In adolescents an atypical school career was a consistent risk factor, but several socio-economic factors were found to be significant as well, with, e.g., children from families with a lower family income or children whose parents or grandparents were born outside the EU having a higher risk of undervaccination. For a lot of factors the association with coverage of specific vaccines was significant in one birth cohort and borderline or non-significant in another, but in general similar trends could be seen.

Table 2 Factors significantly ($p<0.05$) associated with incomplete vaccination[1] , non-vaccination[2] or invalid vaccination[3]

			Category with	Vaccine						
t11.1	Factor[a]		higher risk	DTP (+Hib)[d]	Polio[d]	DT-IPV	HBV[d]	MMR	MenC	HPV
t11.2	Individual level	Age	Younger girls (vs. older)							Adolescent girls[2]
t11.3		School career	Delay or special education			Adolescents °1994[2]	Adolescents[1]	Adolescents[1]	Adolescents[2]	
t11.4	Family level	Employment of the mother	Non-working (vs. working full-time)	Infants °2003[1,3]	Infants °2003[3]		Infants °2003[3]			
t11.5			Full-time (vs. part-time)				Adolescents °1991[1]	Adolescents °1991[1]	Adolescents °1991[2]	
t11.6		Family income[b]	Lowest category	Children[1,3]	Infants °2003[1] Children[1]	Children[2,3] Adolescents °1994[2]	Children[1] Adolescents °1994[1]	Children[2,3]	Children[2,3]	Adolescent girls[2]
t11.7		Birth order	4th or higher	Infants °2006[1]	Infants °2006[1]		Infants °2006[1]	Infants °2006[2]	Infants °2006[2]	
t11.8		Family type	Single or divorced	Infants °2006[1]	Infants °2006[1]	Adolescents °1994[2]		Adolescents °1991[1]		
t11.9			Foster parents[e]			Adolescents °1994[2]		Adolescents °1994[1]		
t11.10		Origin of the mother	Non-European			Adolescents °1994[2]	Adolescents[1]	Adolescents[1]	Adolescents °1991[2]	

(continued)

Table 2 (continued)

			Category with	Vaccine						
	Factor[a]		higher risk	DTP (+Hib)[d]	Polio[d]	DT-IPV	HBV[d]	MMR	MenC	HPV
t12.2			Non-Belgian	Infants °2006[1]	Infants °2006[1]		Infants °2006[1]		Adolescents °1994[2]	
t12.3		Educational level of the mother	Primary school (vs. higher)			Children[2,3]	Children[1,3]		Adolescents °1991[2]	
t12.4			University (vs. primary school)			Adolescents °1994[2]		Adolescents °1994[1]		
t12.5		Age of the mother	Younger	Infants °2006[1]	Infants °2006[1]		Infants °2006[1]	Infants °2006[2]	Infants °2006[2]	
t12.6		Employment of the father	Part-time/unemployed (vs. full-time)[f]					Adolescents °1991[1]	Adolescents °1991[2]	
t12.7		Cervical cancer screening mother	Non-screening mother (vs. screening mother)							Adolescent girls[2]
t12.8	External factors[a]	Main vaccinator[c]	Paediatrician or family physician (vs. public health setting)	Infants[1,3] Children[1,3]	Infants[1,3] Children[1,3]		Infants[1,3] Children[1,3]	Infants[2,3] Children[1,3]	Infants[2,3]	

t13.1	Degree of urbanization	City	Children[3]	Children[2,3]	
t13.2	Reimbursement rules	Higher co-payment, less media advertising			Adolescent girls[2]
t13.3	Information campaign	Personal information, letter not sent			Adolescent girls[2]

DTP diphtheria-tetanus-pertussis combined vaccine, *Hib* H. *influenzae* type b vaccine, *DT-IPV* diphtheria-tetanus-inactivated poliomyelitis vaccine, given as a school-age booster dose, *HBV* hepatitis B vaccine, *MMR* measles-mumps-rubella vaccine, *polio* poliomyelitis vaccine, *MenC* conjugated meningococcal group C vaccine, *HPV* human papillomavirus vaccine

Note: predictors for invalid vaccination were only assessed in infants °2003; incomplete vaccination was not assessed for HPV vaccination

Oral live polio vaccine was given to children °1997, whereas the inactivated vaccine was used for infants °2005/2008. Whole cell pertussis vaccines were used for children °1997, whereas acellullar vaccines were used for infants °2005/2008. Administration of Hib vaccines was not assessed in children °1997. Administration of DT-IPV vaccines was not assessed in adolescents °1991. Infants were surveyed at 18–24 months of age; children were 7–8 years of age; adolescents were 13–14 years of age; adolescent girls were 12–18 years of age. Birth year is mentioned if results were restricted to a specific birth cohort

[a]Note that the studies on HPV vaccination assessed uptake in a setting where the vaccines were only offered to eligible girls via private health care, whereas the other studies assessed vaccine uptake in a setting where vaccines were available both via public and private health care

[b]Note that family income was a predictor of valid MMR vaccination in infants °2003, but only the unknown income category was significantly different from the lowest income category

[c]Note that having several vaccinators involved was a significant predictor of being vaccinated with MMR vaccine for infants born in 2006 only

[d]In infants born in 2006, combined DTP-Hib-IPV-HBV vaccines were used

[e]Foster parents were only assessed separately in the analysis of adolescents born in 1994

[f]A part-time working father was a risk factor for meningococcal C vaccination, whereas an unemployed father was a risk for HBV vaccination

2.1.2 Vaccines Offered Only via a Private Health Care Setting

The second series of studies [5, 6] investigated predictors of vaccine uptake for one specific vaccine, namely the HPV vaccine, in the period it was recommended to adolescent girls by the SHC but offered only via the private health care setting with partial reimbursement (2007–2009). Information was obtained through analyses of HPV vaccine reimbursement claims of the National Alliance of Christian Mutualities (NACM), the largest sickness fund in Flanders. All female members aged 12–18 (°1989–1996; N=117 151 in [2], N = 127 854 in [3]) and living in Flanders were selected from the membership files of the NACM. Initiation of HPV vaccination between January 2007 and June 2009 varied between 20 and 80 % depending on the year of birth (age) of the girls. These differences in vaccination coverage were mainly due to two factors. First, there were differences in the reimbursement rules (during certain periods of time and for certain birth cohorts the out-of-pocket cost for the vaccines was much lower, and eligibility rules were more advertised in the media). Second, the vaccine was partly reimbursed up until the age of 15 or later 18 years, so for the youngest girls in the study (born in 1995 and 1996) there was still a lot of time left after June 2009 to start vaccination. Besides these two main factors a higher probability of initiation of HPV vaccination was found for girls coming from families with higher incomes and for girls who were personally informed about their eligibility for reimbursement. Furthermore, the probability of initiation of HPV vaccination was found to be positively associated with cervical cancer screening of the mother in the years prior to the launch of HPV vaccines (factors affecting the probability of vaccination initiation are summarized in Table 2).

2.2 Parental Attitudes and Willingness to Pay

The main results with regard to parental attitudes are summarized in Table 3.

In the vaccination coverage study of 2005 additional questions were added to the questionnaires of both infants and adolescents to obtain information on parental attitudes and preferences with respect to multiple vaccine injections [5, 7]. The results were analysed separately for parents of infants and parents of adolescents. Willingness to pay (amount in euro) to avoid a concomitant injection and the maximum number of concomitant injections parents would allow during the same visit were used as a proxy of parental acceptance of concomitant injections. Parents of young children as well as those of adolescents gave preference to a maximum of two separate vaccine injections to be given at the same immunization visit. Parents also shared common attitudes on the amount of money they would pay to avoid concomitant injections. A significant proportion of parents of both infants and adolescents, 41.0 % and 38.8 %, respectively, were not willing to pay anything, whereas in both age groups the remaining parents mentioned a median amount of 20 euro to avoid a concomitant injection. However, extensive analysis using several regression methods to identify predictors of the attributed value and the allowed

Table 3 Predictors of different proxies for parental acceptance of concomitant vaccine injections (not vaccine specific). Being willing to pay to avoid a concomitant injection (WTP); amount (in euro) caregivers are willing to pay (amount WTP); number of concomitant injections caregivers would allow (number allowed); as assessed in parents of infants and adolescents in 2005

Predictor	Category with lower outcome	WTP Yes	Amount WTP	Number allowed	
Educational level of the mother	Lowest (vs. secondary school)	Infants			t14.2
Employment of the father	Part-time or freelance (vs. full-time)	Infants			t14.3
	Not working (vs. full-time)	Adolescents			t14.4
Number of siblings	Lower number			Infants	t14.5
Origin of the mother	Belgian vs. other European country		Infants		t14.6
	Non-European vs. Belgian			Infants	t14.7
Main vaccinator	Well-baby clinic (vs. paediatrician)		Infants		t14.8
Number of concomitant injections parents would allow	Lower number	Adolescents			t14.9
WTP	Being willing to pay			Infants	t14.10
Respondent's relation to the child	Mother vs grandparent[1]			Infants[2]	t14.11
Child's vaccination status	Complete			Infants[2]	t14.12
	Incomplete			Adolescents[3]	t14.13

Note: Only factors and categories with significant odds ratios were plotted. Family income was a significant predictor of WTP in infants, but only if the unknown income category was compared to the categories with known income

[1] Grandparents accounted for less than 2 % of the respondents

[2]Comparing respondents who would allow an unlimited number of injections to those who would allow a limited number

[3]Comparing respondents who would allow more than two concomitant injections to respondents who would allow not more than two

number of concomitant injections (Table 3) explained only a small part of the variability in the answering behaviour and yielded some conflicting information; this suggests that the proxies we used are only rough indicators of parental attitudes on concomitant vaccines.

3 Discussion

In this chapter we summarized studies on predictors of infants' and adolescents' vaccine uptake and attitudes of parents towards vaccination in Flanders (Belgium). First, individual level characteristics, such as age and school career

were found to significantly affect vaccination coverage. Second, various family level characteristics such as family income, parental educational level or screening behaviour by the mother, were also significantly associated with vaccine uptake. A final set of predictors of vaccine uptake consisted of external factors such as main vaccinator, information campaigns or the reimbursement rules. Exploring relationships between vaccine uptake and these predictors can help to identify subgroups with higher risk of undervaccination who merit special attention. It can also be used to monitor existing vaccination programmes and to guide decisions on changes in these vaccination programmes. Information on parental attitudes towards different aspects of vaccination and vaccination programmes can further optimize these decisions. The results of the presented analyses suggest, in general, a need to monitor and support vaccinating activities of private vaccinators (paediatricians and family physicians) and to develop specific strategies for families in an unfavourable socio-economic situation, as well as for children in special education programmes. Interventions to increase vaccine uptake in infants should address the importance both of timely administration and of completion of the schedule, since similar risk factors were found for invalid and for incomplete vaccination. Apart from the socio-economical and individual predictors of vaccine uptake, documentation of vaccination is a major hurdle in the assessment of vaccination coverage, especially in older age groups, when vaccination is less an issue and is often scattered over different vaccine providers. A cornerstone for good documentation and vaccination practices throughout life is a centralized registration database, which is easily accessible for all vaccine providers and which takes into account safety and privacy issues.

Regular reassessment of vaccine coverage in different settings would provide the opportunity to detect and interpret trends over time. Targeted research (e.g. using a qualitative design) in known subgroups of undervaccinated children could add information on more specific hurdles for vaccination, out of which tailored strategies could be inferred. Ideally data on vaccination coverage should be complemented by studies designed to estimate the serological level of immunity in the target population, which is the indicator we are ultimately interested in when evaluating the performance of vaccination programmes. To have a better insight in parents' preferences regarding concomitant vaccine injections, sensitive quantifications using a more appropriate design (e.g. discrete choice experiments) would confer important additional insights.

Acknowledgements We thank all the families who participated in the vaccine coverage studies, the physicians who supplied information and all other collaborators. The vaccine coverage studies were funded by the Flemish government. For the studies on HPV vaccination initiation we thank the NACM for its fruitful cooperation. Both studies on uptake of the HPV vaccine were financed by the Research Foundation Flanders (FWO).

References

1. Hoppenbrouwers, K., Vandermeulen, C., Roelants, M., Boonen, M., Van Damme, P., Theeten, H., Depoorter, A.: Studie van de vaccinatiegraad bij jonge kinderen en adolescenten in Vlaanderen in 2008. Technical report, 2009. URL http://www.zorg-en-gezondheid.be/cijfersinfectieziekten_en_vaccinaties.aspx
2. Lefevere, E., Hens, N., De Smet, F., Van Damme, P.: BMC Public Health **11**, 470 (2011). doi: 10.1186/1471-2458-11-470. URL http://dx.doi.org/10.1186/1471-2458-11-470
3. Lefevere, E., Hens, N., Theeten, H., Van den Bosch, K., Beutels, P., De Smet, F., Van Damme, P.: Vaccine **29**, 8390–8396 (2011). doi: 10.1016/j.vaccine.2011.08.039. URL http://dx.doi.org/10.1016/j.vaccine.2011.08.039
4. Theeten, H., Hens, N., Vandermeulen, C., Depoorter, A.-M., Roelants, M., Aerts, M., Hoppenbrouwers, K., Damme, P.V.: Vaccine **25**, 4940–4948 (2007). doi: 10.1016/j.vaccine.2007.03.032. URL http://dx.doi.org/10.1016/j.vaccine.2007.03.032
5. Theeten, H., Hens, N., Aerts, N., Vandermeulen, C., Roelants, M., Hoppenbrouwers, K., Damme, P.V., Beutels, P.: Pediatr. Infect. Dis. J. **28**, 61–63 (2009). doi: 10.1097/INF.0b013e318184eea3. URL http://dx.doi.org/10.1097/INF.0b013e318184eea3
6. Theeten, H., Hens, N., Aerts, M., Vandermeulen, C., Roelants, M., Hoppenbrouwers, K., Damme, P.V., Beutels, P.: Vaccine **27**, 1964–1969 (2009). doi: 10.1016/j.vaccine.2009.01.096. URL http://dx.doi.org/10.1016/j.vaccine.2009.01.096
7. Theeten, H., Vandermeulen, C., Roelants, M., Hoppenbrouwers, K., Depoorter, A.-M., Van Damme, P.: Acta Paediatr. **98**, 1307–1312 (2009). doi: 10.1111/j.1651-2227.2009.01331.x. URL http://dx.doi.org/10.1111/j.1651-2227.2009.01331.x
8. Vandermeulen, C., Roelants, M., Theeten, H., Depoorter, A.-M., Van Damme, P., Hoppenbrouwers, K.: Pediatrics **121**, e428–e434 (2008). doi: 10.1542/peds.2007-1415. URL http://dx.doi.org/10.1542/peds.2007-1415

Part II
Modeling Behaviour Change in Response to Epidemic Threats

Modeling the Impact of Behavior Changes on the Spread of Pandemic Influenza

Sara Y. Del Valle, Susan M. Mniszewski, and James M. Hyman

Abstract We use mathematical models to assess the impact of behavioral changes in response to an emerging epidemic. Evaluating the quantitative and qualitative impact of public health interventions on the spread of infectious diseases is a crucial public health objective. The recent avian influenza (H5N1) outbreaks and the 2009 H1N1 pandemic have raised significant global concerns about the emergence of a deadly influenza virus causing a pandemic of catastrophic proportions. Mitigation strategies based on behavior changes are some of the only options available in the early stages of an emerging epidemic when vaccines are unlikely to be available and there are only limited stockpiles of antiviral medications. Mathematical models that capture these behavior changes can quantify the relative impact of different mitigation strategies, such as closing schools, in slowing the spread of an infectious disease. Including behavior changes in mathematical models increases complexity and is often left out of the analysis. We present a simple differential equation model which allows for people changing their behavior to decrease their probability of infection. We also describe a large-scale agent-based model that can be used to analyze the impact of isolation scenarios such as school closures and fear-based home isolation during a pandemic. The agent-based model captures realistic individual-level mixing patterns and coordinated reactive changes in human behavior in order to better predict the transmission dynamics of an epidemic. Both models confirm that changes in behavior can be effective in reducing the spread of disease. For example, our model predicts that if school closures are implemented for the

S.Y. Del Valle (✉) • S.M. Mniszewski
Los Alamos National Laboratory, West Jemez Road, Los Alamos, NM 87545, USA
e-mail: sdelvall@lanl.gov;smm@lanl.gov

J.M. Hyman
Tulane University, St Charles Avenue, New Orleans, LA, USA
e-mail: mhyman@tulane.edu

P. Manfredi and A. d'Onofrio (eds.), *Modeling the Interplay Between Human Behavior and the Spread of Infectious Diseases*, DOI 10.1007/978-1-4614-5474-8_4,

duration of the pandemic, the clinical attack rate could be reduced by more than 50%. We also verify that when interventions are stopped too soon, a second wave of infection can occur.

1 Introduction

Pandemics are global epidemics and are often associated with a high morbidity and mortality burden. There have been three pandemic influenza outbreaks in the 20th history: the Spanish flu (1918–19), the Asian flu (1957–58), and the Hong Kong flu (1968–69) [32]. The 1918–1919 influenza pandemic (known as the Spanish flu) was the most devastating in recent history, where at least 20 million died [30]. In the United States, about 675,000 lives were lost to the Spanish flu with an estimated mean case fatality rate of 2% [52]. This case fatality rate is an order of magnitude larger than the case fatality rates observed in seasonal flu epidemics in normal years. Recurrent outbreaks of H5N1 around the world and the most recent pandemic (H1N1) 2009 suggest that a deadly pandemic is eminent.

Nearly half of the world's population resides in urban areas [50]. Air travel connects these urban centers in a global network where a new influenza strain can spread around the world in a few weeks, as recently experienced with pandemic (H1N1) 2009. In addition, influenza's short incubation period and the lack of a universal vaccine can increase the spread of influenza, posing a significant global challenge to public health officials. Mathematical models can help in meeting this challenge, if the model includes the most significant properties of the transmission dynamics. In particular, the model most include how people change their behavior in response to an epidemic threat.

Evidence suggests that in the presence of a deadly disease and lack of pharmaceutical interventions, people will change their behavior to avoid infection [15, 19, 42]. Recent studies have evaluated the impact that non-pharmaceutical interventions, such as school closures, social distancing, and travel restrictions, could have on the spread of the next influenza pandemic [13, 14, 21, 24]. However, none of these studies have incorporated intentional changes in individual behavior, such as avoiding gatherings, increasing hygiene, or staying home. Furthermore, these studies have assumed that these non-pharmaceutical interventions would remain in effect for the duration of the pandemic. Typically, people resume their normal behaviors due to lack of resources or as the perceived risk declines [27]. Recent studies on the impact of basic public health measures implemented during the 1918 pandemic [6, 27] indicate that non-pharmaceutical interventions did not last for the duration of the pandemic.

Mathematical models for the spread of infectious diseases have been extensively used to gain insights into the transmission dynamics of infectious diseases. Several approaches have been used for these studies including simple compartmental models [31, 44], network models [35], and agent-based models [18, 24, 34, 48].

These models have provided new insights on important issues such as the effects of drug resistance [5, 46], treatment [34, 40], vaccination [3, 45], non-pharmaceutical interventions [11, 15] and on the overall dynamics of infectious diseases [28].

Diseases often spread through person-to-person contacts; therefore, realistic mixing patterns can be crucial to accurately predicting the path and severity of the disease [16]. The course of an epidemic through a population is determined by the interactions among individuals and the process of transmitting a pathogen is a stochastic (random) process based on the length of time the individuals are in contact with each other and the strength of the contact. Agent-based models can capture this realistic contact structure and allow the simulation to explore how contact networks and different demographic characteristics affect disease transmission.

Several studies have shown the importance of population structure when modeling disease spread [20], but only a few studies have incorporated realistic mixing populations [18, 24]. The accurate representation of population heterogeneity is one of the greatest challenges of epidemic modeling. While substantial progress has been made over the years with the introduction of different mixing functions [29] and mixing matrices [2] for compartmental models, they are still far from achieving a good approximation to real world scenarios. In recent years, new approaches that incorporate more realistic contact structures have been developed to allow for nonrandom interactions among populations [4, 22, 48, 54]. For example, Zaric [54] compared random and nonrandom mixing patterns for network epidemic models and showed that different mixing assumptions led to different epidemic outcomes. In particular, they found that random mixing generally results in a greater number of new infections than nonrandom mixing. Similarly, Bansal et al. [4] used several real and simulated datasets of human contact networks to analyze their impact on disease spread. They concluded that homogeneous-mixing models are appropriate for host populations that are nearly homogeneous. However, network models are more appropriate to better capture and predict disease spread through heterogeneous host populations. Furthermore, Fukś et al. [22] used an agent-based model of Southern and Central Ontario to investigate the spatial correlations of disease spread. They concluded that spatial correlations were difficult to destroy if neighborhood sizes were inhomogeneous. Finally, Stroud et al. [48] showed a strong correlation between local demographic characteristics and pandemic severity. This study used an agent-based model of Southern California with a heterogeneously mixing population and concluded that the average household size in a census tract was strongly correlated with the clinical attack rate.

Here, we use a simple mathematical model to show how behavioral changes can be easily introduced into epidemiological models. In addition, we use a large-scale agent-based model to assess the potential impact of temporary and permanent behavioral changes including school closures in containing a pandemic influenza and analyze how these changes affect the contact structure and transmission dynamics.

2 Methods

We will consider two approaches to incorporate behavior changes in a mathematical model. We first describe a simple system of five ordinary differential equations (ODEs) to describe disease dynamics based on the Kermack–McKendrick susceptible-infected-recovered model (SIR) [31]. We extended this model by using the approaches introduced in Del Valle et al. (2005) [15]. The second approach is based on a stochastic agent-based model, object-oriented platform for people in infectious epidemics (OPPIE). This is an extension of the Los Alamos Epidemic Simulation System (EpiSimS) [16, 18, 48] and includes dynamic behavior changes.

2.1 Ordinary Differential Equation Model

In our ODE model, the population is divided into two subgroups: a group that does not change its behavior or has *normal* behavior (subscript n) and a group that modifies its *behavior* in response to an outbreak (subscript b). People move back and forth between the two groups (reducing susceptibility or infectivity) depending on the behavior adopted. Individuals in each activity group are characterized by their epidemiological status: susceptible, S_n and S_b and infectious individuals, I_n and I_b; the transfers are shown diagrammatically in Fig. 4. Because we are primarily interested in the effectiveness of changes in behavior for a single outbreak, we use a closed system with no migration in or out of the population, and births and natural deaths are not included in the model.

We define t_0 as the beginning of the epidemic. Movement of individuals between the two groups depends upon disease incidence in the population. It is assumed that a certain fraction of the population will change their behavior to protect themselves against infection or reduce their chances of spreading the disease. Let $\varphi_{S_b} S_n$ and $\varphi_{I_b} I_n$ be the transfer rates from the S_n and I_n classes to the S_b and I_b classes, respectively, and $\varphi_{S_n} S_b$ and $\varphi_{I_n} I_b$ be the transfer rates from the S_b, and I_b classes to the S_n and I_n classes, respectively. The rate coefficients are modeled by step functions given by:

$$\varphi_i = \begin{cases} 0, \, t < \tau \\ c_i, \, \tau < t < \tau_{max} \\ 0 \; t > \tau_{max} \end{cases} \tag{134}$$

for i $= S_n, I_n, S_b$, and I_b, where the parameter c is a positive constant that determines the rate of movement and τ is the time that determines when the new behavior is adopted.

Using the transfer diagrams in Fig. 1, we obtain the following system of differential equations:

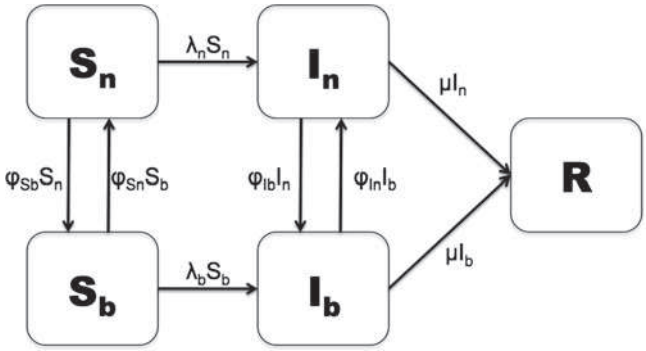

Fig. 1 Schematic relationship between people who adopt a new behavior in response to an epidemic and people who do not change their behavior. The arrows that connect the boxed groups represent movement of individuals from one group to an adjacent one. Susceptible individuals (S_n or S_b) can become infected (I_n or I_b) at rates λ_n or λ_b; infected individuals recover at a rate μ; and people change their behavior based on the transfer rates φ_{S_b}, φ_{I_b}, φ_{S_n}, or φ_{I_n}

$$\begin{aligned}
\frac{dS_n}{dt} &= -(\varphi_{S_b} + \lambda_n)S_n + \varphi_{S_n} S_b \\
\frac{dI_n}{dt} &= -(\varphi_{I_b} + \mu)I_n + \varphi_{I_n} I_b + \lambda_n S_n \\
\frac{dS_b}{dt} &= -(\varphi_{S_n} + \lambda_b)S_b + \varphi_{S_b} S_n \\
\frac{dI_b}{dt} &= -(\varphi_{I_n} + \mu)I_b + \varphi_{I_b} I_n + \lambda S_b \\
\frac{dR}{dt} &= \mu(I_n + I_b)
\end{aligned} \tag{1}$$

where λ_n (for normal behavior) and λ_b (for modified behavior) are the forces of infection. λ_n and λ_b incorporate the probability of transmission per contact, β, the reduced number of contacts because of symptomatic infection, θ, and $1 - \eta_j$ (j = s or i), which accounts for the effectiveness of the behavior in reducing either susceptibility (η_s) or infectivity (η_i). β is defined as the susceptibility of the population multiplied by the infectivity of the disease multiplied by the average number of contacts an individual has per day. The forces of infection for both groups are shown by:

$$\begin{aligned}
\lambda_n &= \beta\left[\left(\frac{\theta I_n}{\rho}\right) + (1-\eta_i)\left(\frac{\theta I_b}{\rho}\right)\right] \\
\lambda_b &= \beta\left[(1-\eta_s)\left(\frac{\theta I_n}{\rho}\right) + (1-\eta_i)(1-\eta_s)\left(\frac{\theta I_b}{\rho}\right)\right]
\end{aligned} \tag{2}$$

where $\rho = N - (1-\theta)(I_n + I_b)$ and N is the total population $(S_n + S_b + I_n + I_b + R)$. In the forces of infection, η_i is incorporated into the $\theta I_b/\rho$ infectious fractions because individuals in the I_b class have adopted a new behavior and η_s is incorporated into the infectious fractions in λ_b because individuals in the susceptible class (S_b) have also adopted a new behavior. These forces of infection and appropriate initial conditions complete our model formulation.

2.2 The Agent-Based Model

The OPPIE simulation platform is an agent-based model that combines the demographic-based population of a region, a network of specific business and home locations, and the movement of individuals between locations with daily itineraries. We simulated the spread of an influenza epidemic using a synthetic population constructed to statistically match the 2000 US Census population demographics of Southern California at the census tract level. There are 20 million individuals living in six million households, with an additional one million locations representing actual schools, businesses, shops, and social recreation addresses. This synthetic population only represents individuals reported as household residents; thus, visiting tourists, guests in hotels, and travelers in airports are not explicitly included.

Each individual has a schedule of activities based on the National Household Transportation Survey (NHTS) [37]. A schedule specifies the type of activity, the starting and ending time, and the location of each assigned activity. There are six types of activities: *home*, *work*, *shopping*, *social recreation*, *school*, and *other*. The time, duration, and location of activities determine which individuals mix together at the same location at the same time, which is relevant for airborne transmission.

Each location is geographically located using the Dun & Bradstreet commercial database. Each building is subdivided based on the number of activities available at that location. There are one or more buildings per activity that are further subdivided into rooms or mixing places. Schools have classrooms, workplaces have workrooms or offices, and shopping malls have shops. Typical room sizes can be specified; for example, for workplaces the mean workgroup size varies by standard industry classification (SIC) code. The number of rooms in each building is computed by dividing the peak occupancy by the appropriate mixing group size. We used two data sources to estimate the mean workgroup by SIC including a study on employment density [53] and a study on commercial building usage from the Department of Energy [36]. Based on these two data sources workgroup sizes range from 3.1 for transportation workers to 25.4 for health service workers. The average workgroup size over all types of work is 15.3. For the analyses presented here, the average mixing group sizes are 8.5 at a school, 4.4 at a shop, and 3.5 at a social recreation venue.

2.2.1 Disease Progression Model

Airborne diseases spread primarily from person to person during close proximity through contact, sneezing, coughing, or via fomites. In OPPIE, an opportunity for disease spread between two individuals occurs when they occupy a mixing location together. Whether or not a susceptible individual becomes infected is based on how long they co-occupy within a mixing place, the presence of infectious individuals, a high-level description of the activity they are engaged in, and their age.

A location represents a street address, and a room or mixing place represents a specific place where people have face-to-face interactions. When an infectious person is in one of these mixing locations with a susceptible person for some time, we estimate a probability of disease transmission, which depends on the variables identified above.

A susceptible person j has a dimensionless susceptibility multiplier S_j and an infectious person i has an infectious multiplier I_i. The probability that the susceptible individual j becomes infected during an activity is computed as:

$$P_j = 1 - e^{-\sum_i T S_j I_i t_{ij}} \tag{3}$$

where T is the average transmissibility per unit time, t_{ij} is the duration of contact, and the sum extends over all infectious people that occupied the room with individual j.

Disease progression of the epidemic is modeled as a Markov chain consisting of five main epidemiological stages: uninfected, latent (non-infectious), incubation (partially infectious), infectious, and recovered. Infected individuals start in the incubation stage and remain there for a period of between 0 and 0.5 days, 0.5 or 1.0 day, before transitioning to the symptomatic or recovered stages, respectively. The average incubation time is 1.9 days and average duration of the symptomatic stage is 4.1 [34]. The disease model assumes that 50% of adults and seniors, 75% of students, and 80% of preschoolers will stay home within 12 hours of the onset of influenza symptoms. These people can then transmit disease only to household members or visitors. Based on previous studies [34], 33.3% of infections are assumed to be subclinical. Individuals in the subclinical stage are only half as infectious as those in the symptomatic stages and continue their normal activities as if they were not infected. The infection rate for children is assumed to be double than for adults. All scenarios were analyzed for the same set of transmission parameters where the population was initially seeded with 100 people infected, all in the incubation stage.

2.2.2 Baseline Assumptions

The Homeland Security Council released the National Strategy for Pandemic Influenza for the United States, which suggests that the emergence of a new influenza virus could have a clinical disease attack rate of 30% in the overall

population [49]. Based on this attack rate, we constructed a baseline scenario under the assumption of no specific intervention to contain the pandemic and an infection attack rate of 45% with a clinical attack rate of 30%.

2.2.3 School Closure Assumptions

Protecting children during an influenza pandemic is important since illness rates are typically highest among school-aged children [38]. Closing schools limits students' contacts and has the potential to block paths of spread between families and neighborhoods [1]. Several studies have analyzed the impact of school closures [8,21,24]; however, these studies only investigated the impact of sustaining a school closed during the entire epidemic. School closures in OPPIE are implemented as a general closure of selected activity locations. Based on the Center for Disease Control and Prevention pandemic guidelines [9], closures in OPPIE follow a steplike function and are specified with a start and stop time; the activity to close; and a single location or a fraction of all locations of the specified activity type that will be closed. During the time a closure is in effect, anyone whose activity schedule would have taken them to one of the closed locations will stay home during that time instead. Scheduled after-school activities are not affected by a school closure.

2.2.4 Fear-Based Home Isolation Assumptions

Fear-based home isolation consists of people staying home as a reaction to an epidemic crisis. Some of these people may be considered the "worried well". The news of increasing numbers of people becoming ill, or seeing friends and family fall ill, is strong motivation to avoid potential infectious situations. Surprisingly, none of the recent studies on pandemic influenza have incorporated the impact of this type of behavioral change. We assume that people isolate due to fear at a level that follows the pattern of the epidemic [6, 27]. This is implemented with a specification of start, peak, and end times with corresponding fractions of the population that will be isolating at those times, along with a minimum and maximum contiguous duration per individual. We assume that people who choose to stay home will only self-isolate for 7–14 days at a time. People isolate on an individual basis, not on a household basis, so there might be households in which some members of the family are isolating due to fear and others are going about their normal activities. Fear-based home isolation begins when a percentage of the population is symptomatic (e.g., 0.1%). The number of people self-isolating increases linearly until reaching a maximum near the epidemic peak day. After this day, the stay-home rate begins to drop linearly with time, until no fear-based home isolation is occurring by a selected end day.