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# The public health impact of vaccination programmes in the Netherlands

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# THE PUBLIC HEALTH IMPACT OF VACCINATION PROGRAMMES IN THE NETHERLANDS

A HISTORICAL ANALYSIS OF  
MORTALITY, MORBIDITY, AND COSTS

MAARTEN VAN WIJHE

# **The public health impact of vaccination programmes in the Netherlands**

A historical analysis of mortality, morbidity, and costs

Maarten van Wijhe

The work described in this thesis was carried out at the unit of Infectious Disease Modelling, Centre for Infectious Disease Control, National Institute for Public Health and the Environment (RIVM), the Netherlands, in collaboration with the unit of PharamcoTherapy, -Epidemiology and -Economics, Faculty of Science and Engineering, University of Groningen, the Netherlands.

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groningen

# The public health impact of vaccination programmes in the Netherlands

A historical analysis of mortality, morbidity, and costs

## PhD thesis

to obtain the degree of PhD at the  
University of Groningen  
on the authority of the  
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the decision by the College of Deans.

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# **Chapter 1**

## **General introduction**

*"Every friend of humanity must look with pleasure on this discovery, by which one more evil is withdrawn from the condition of man; and must contemplate the possibility, that future improvements and discoveries may still more and more lessen the catalogue of evils."*

— Thomas Jefferson in a letter to Benjamin Waterhouse on smallpox vaccination, 1801

## Overview

Mass vaccinations are considered one of the greatest medical health interventions devised by man. In a letter to Edward Jenner, who can be considered the founder of modern vaccinations, Thomas Jefferson (United States president from 1801 to 1809) even goes as far as to note that "*Medicine has never before produced any single improvement of such utility*". Since Jenner's discovery of cow's pox inoculation against smallpox in 1797, vaccines have effectively eradicated smallpox and eliminated poliomyelitis from most part of the world. The occurrence of many other vaccine-preventable diseases has declined in most high-income countries, some still occur rarely, such as diphtheria and tetanus, while others, like measles and mumps still cause occasional outbreaks.

The late 19<sup>th</sup> and early 20<sup>th</sup> century saw dramatic declines in childhood mortality and rapid increases in life expectancy (Wolleswinkel-van den Bosch et al., 1997; Tulapurkar et al., 2000). While there is a general consensus that vaccination programmes were at least in part responsible for the decline of infectious diseases in the 20<sup>th</sup> century, for many long-standing vaccination programmes it is unclear how much they actually have contributed to lowering mortality and morbidity. Vaccines are not the only factor that contributed to the decline in infectious diseases. Other developments in medicine, the availability of better medical care, the development of antibiotics, improvement in nutrition, hygiene, housing conditions, maternal care, and increasing economic welfare have all likely contributed. Considering these factors, the impact of vaccination programmes is not easily quantified.

This thesis provides an overview of the impact of long-standing childhood vaccination programmes in the Netherlands. We take a step back and describe to what degree vaccination programmes have contributed to the prevention of infectious disease mortality and morbidity in the Netherlands. To do so, we ask the somewhat obvious question: "What would have happened had vaccination programmes not been introduced?".

While obvious, this question is important because it lets us directly estimate what the benefits of vaccination programmes have been. It is also a unique question as it is rarely posed and investigated as such. Answering this question provides a more accurate picture of the impact of vaccination programmes than previous research has revealed.

To get a grip on what would have happened had a vaccination programme not been introduced, long time series of both cause-specific mortality and morbidity are needed, covering the period before and after the start of vaccinations. The Netherlands is uniquely suited to this end as detailed records have been kept on infectious diseases mortality and morbidity over the 20<sup>th</sup> century. For a large part, the data used in the following chapters spans most of the 20<sup>th</sup> century. These data were previously unavailable and were collected and digitised by hand from various archived sources.

We mainly focus on vaccination programmes against diphtheria, pertussis, tetanus, poliomyelitis, measles, mumps, and rubella. There are several reasons for focussing on these diseases. First, they were among the first infectious diseases against which mass vaccination programmes were implemented in the Dutch National Immunisation Programme. In a sense, vaccines against these diseases form the core of most vaccination programmes against childhood infections around the world. Secondly, few studies have evaluated the impact of these long-standing vaccination programmes and their impact and effectiveness are often taken for granted. Finally, for most of these infectious diseases ample data were available before and after the start of vaccination, allowing us to estimate their impact.

The following sections of this chapter provide background on development of the Dutch National Immunisation Programme, the various effects of vaccination and how the population-level impact of vaccination programmes can be estimated.

## Development of mass vaccination programmes

### *Public health context*

The concept of public health as we know it today did not exist until the 19<sup>th</sup> century. In the 19<sup>th</sup> century, a new movement arose that thought of disease as a consequence of environmental influences, and thus susceptible to public

interventions. This also meant that one could study disease in the population using quantitative research to devise interventions, and that combating disease was an affair of both the general public as well as the government who had the means to implement broad scale measures. This new movement, also referred to as the *sanitary movement* ('hygiénisten' in Dutch), was dedicated to changing the then poor health status of people in larger cities, mainly through public health interventions such as improvements in sanitation through clean drinking water and sewage disposal (Houwaart, 1991). They aimed to achieve this by professionalising public health with a strong scientific and political view. In the Netherlands this movement found increasing traction since 1850 and political support around 1865. It was at that time the precursor to the Dutch Health and Youth Care Inspectorate ('Inspectie Gezondheidszorg en Jeugd' in Dutch) was founded and tasked with advising national and local governments on public health. To do so, they would collect statistics on public health in the population, such as cause-specific mortality and notifications of the occurrence of infectious diseases. This first health surveillance system would eventually evolve to the systems we still use today.

Over time the focus of public health shifted to the prevention of childhood mortality and the control of infectious diseases. To this end, the Municipal Health Services were installed in the first decades of the 20<sup>th</sup> century. Their focus was, amongst others, on maternal and neonatal care and care for young children. Core among their instruments would be vaccines. The development of vaccines was booming in the early 20<sup>th</sup> century. Based on the foundations laid by individuals as Robert Koch, Emile von Behring, Shibasaburo Kitasato, and Louis Pasteur, vaccines were developed against diphtheria (1923), tetanus (1926), tuberculosis (1927), yellow-fever (1935), influenza (1936) typhus (1938), and pertussis (1923–1942) (for a more complete overview of the history of vaccines see Plotkin and Plotkin (2013)).

By the mid-20<sup>th</sup> century, mortality due to infectious diseases had declined drastically and life expectancy had increased: where in the mid-19<sup>th</sup> century life expectancy was around 45 years, by the mid-20<sup>th</sup> century this had increased to well over 70 years (Oeppen and Vaupel, 2002). Slowly, chronic diseases started to emerge as the next public health threat. The transition, from high incidence of infectious diseases in the 19<sup>th</sup> century to chronic diseases in the 20<sup>th</sup> century is generally referred to as the epidemiologic transition (Omran, 1971; Wolleswinkel-van den Bosch et al., 1997).

### *The Dutch National Immunisation Programme*

In the Netherlands, mass vaccinations against diphtheria, pertussis, and tetanus started in the early 1950s, see (Table 1.1). The toxoid vaccine against diphtheria was already widely available before that time, but there was no official integration in the health care system and no formal nationwide vaccination programmes existed (Hoogendoorn, 1954). Vaccines were administered mainly by general practitioners and municipal health services of their own volition. They were locally organised on a relatively small scale and financed by local private and collective funds. After World War 2, and with the development of vaccines against pertussis and tetanus, vaccination efforts increased.

To increase vaccination uptake, a more coordinated approach was needed. Starting in 1951 and under the guidance of the Dutch Health Care Inspectorate ('Inspectie voor de Gezondheidszorg' in Dutch), a concerted effort of healthcare workers, including general practitioners, municipalities, infant consultation clinics, and local Health Organisations ('Kruisverenigingen' in Dutch) laid down the organisational structure needed for a successful infant vaccination programme, wherein each of these parties would collaborate (Vos and Richardus, 2004a). To further stimulate vaccination efforts, the government provided financial support through the so-called Praeventie fund ('Praeventiefonds' in Dutch) which provided a small fee for each registered vaccination. In addition, the vaccines, produced or bought by the National Institute for Public Health, were made available for free through the Health Care Inspectorate since 1953.

It was recognised that a successful vaccination programme required a uniform registration system. Such a system was developed and built upon the already existing registration for smallpox vaccination (in place since 1823). All parents received a booklet in which each vaccine was registered. Since 1959 a second registration card was kept by the local government and updated with each administered vaccination.

When the first polio vaccines became available in the mid-1950s, the developments towards a National Immunisation Programme (NIP) accelerated. Polio was a major public health threat at that time with large epidemics every few years causing many infant deaths and leaving even more paralysed. The Netherlands was struck again by a polio epidemic in 1956 and the Minister of Public Health tasked the Health Care Inspectorate to formulate a plan for mass vaccinations against

polio. Together with the National Organisation of Municipalities, directors of municipal health services, and the Royal Dutch Medical Association a plan was formed to install 'immunisation organisations' ('Entgemeenschappen' in Dutch) supervised by the Health Care Inspectorate. These immunisation organisations built upon the collaboration set up in prior years and would be responsible for allowing every child to be vaccinated. Municipalities were to make a register with all children eligible for vaccination, medical doctors and general practitioners were responsible for the vaccinations themselves, and Health Organisations and municipal health services were responsible for the coordination (including sending personal invitations to parents and organising the necessary equipment), as well as registration of vaccinations (Vos and Richardus, 2004b). In 1957 mass vaccinations against poliomyelitis started, and within five years everyone born since 1945 was invited to be vaccinated.

The start of mass vaccinations against polio is generally seen as the official start of the Dutch NIP. Over time, many more vaccines were added to the childhood immunisation programme Table 1.1. Besides the childhood vaccinations, other vaccination programmes were implemented as well, such as the influenza vaccinations for people over 65 years of age- and risk-groups in 1995 (extended to include everyone over 60 years of age in 2008), vaccinations against tuberculosis with the BCG-vaccine for risk groups, vaccinations for military forces, and traveller's vaccinations.

As of 2017, there are vaccines against 14 diseases in the Dutch National Immunisation Programme, see Table 1.2. In the Netherlands the national vaccination coverage has consistently been high for decades with a coverage of around 96%. However, across the Netherlands regions exist with suboptimal coverage, due to the clustering of communities who partially refuse vaccination based on religious believes. This region, known as the Bible-belt, spans from the South-West to the North-East of the Netherlands. Epidemics of vaccine-preventable diseases occasionally occur in these regions (Oostvogel et al., 1994; Hahne et al., 2009; Knol et al., 2013).

In recent years the national vaccination coverage in the Netherlands has declined steadily. Reasons for this decline are still unclear but are cause for concern with public health officials. Large outbreaks of measles have occurred across Europe in 2017, with more than 20 000 cases reported and 35 deaths, partially due to lowered uptake of vaccinations (European Centre for Disease Prevention and

**Table 1.1:** Short history of the Dutch National Immunisation Programme (a more extensive table can be found in Chapter 6, Table 6.1).

Year	Vaccine added	Remarks
1799	Smallpox <sup>1</sup>	
1951		Start financial support of Child Welfare Centers by the Praeventiefonds.
1953	Diphtheria	Government starts providing vaccines free of charge.
1954	Tetanus, Pertussis	Combined diphtheria-tetanus-pertussis vaccine (DTP).
1955		Start first 'Entgemeenschap'.
1957	Poliomyelitis	Poliomyelitis vaccine catch-up for everyone born after 1945. Official start of the Dutch National Immunisation Programme (NIP).
1962		DTP combined with poliomyelitis in DTP-IPV for newborns.
1963		Complete funding of the NIP provided by the government.
1965		Diphtheria-tetanus-poliomyelitis vaccine (DT-IPV) as re-vaccination at 4 and 9 years of age.
1974	Rubella	For 11-year-old girls. Smallpox vaccination discontinued.
1976	Measles	
1987	Rubella, mumps	Combined measles-mumps-rubella vaccine (MMR) for both boys and girls of 14 months of age MMR catch-up for everyone born since 1978.
1993	<i>Haemophilus influenzae</i> serotype b (Hib).	
1995	Influenza	Start of nationally organised influenza vaccination for risk-groups. <sup>2</sup>
1996		Influenza vaccination extended to 65-year-olds and over.
2001	Acellular pertussis (aP)	Acellular pertussis vaccine for 4-year-olds.
2002	Meningococcal C (MenC)	MenC catch-up for everyone aged 1-18.
2003	Hepatitis B (HepB)	For children with parents from risk countries and children from mothers who carry hepatitis B-virus. Hib combined with DTP-IPV in DTP-IPV-Hib.
2005		DTaP-IPV-Hib replaced with DTaP-IPV-Hib.
2006	7-valent pneumococcal conjugate vaccine (PCV-7)	HepB combined with DTaP-IPV-Hib for risk groups. Acellular pertussis for 4-year-olds now combined in DTaP-IPV.
2008		DTaP-IPV-Hib-HepB for children with down syndrome. Target age for influenza vaccination lowered to 60 years from 65.
2009		Human papillomavirus vaccine (HPV) catch-up for girls born in 1993-1996.
2010	HPV	For 12-year-old girls.
2011		Change from PCV-7 to PCV-10. DTaP-IPV-Hib-HepB now as a combination vaccine for all children.
2013		Change from four to three doses of PCV-10, at 2, 4, and 11 months.
2014		Change from three to two doses of HPV.
2018		MenACWY replaces MenC.

NIP: National Immunisation Programme. Vaccine key: aP, acellular-pertussis; DTP, diphtheria-tetanus-pertussis; IPV, Inactivated poliomyelitis vaccine; Hib, *Haemophilus influenzae* serotype b; HepB, hepatitis B; MenC, meningococcal serotype C; MenACWY, meningococcal serotype A, C, W, and Y; MMR, measles-mumps-rubella; PCV, pneumococcal conjugate vaccine; HPV, human papillomavirus.

<sup>1</sup> In the Netherlands, mandatory smallpox vaccination for school-going children started in 1823 and was abolished in 1928; it was however still incentivised to be vaccinated.

<sup>2</sup> Risk groups for influenza vaccinations were defined by the Health Council of the Netherlands.

Control (ECDC), 2017-2018). Should this trend continue, some infectious diseases that have long been controlled by vaccinations might become common again.

These developments also highlight the importance of monitoring and regularly evaluating the effectiveness and impact of vaccination programmes, not just to keep track of the diseases, but also in an effort to direct interventions and resources, help sustain awareness, and identify problems in the implementation of the programme (Schuchat and Bell, 2008).

**Table 1.2:** Dutch National Immunisation Programme as of June 2018.

Age	First vaccine	Second vaccine
6 - 9 weeks	DTaP-IPV, Hib, HBV	PCV-10
3 months	DTaP-IPV, Hib, HBV	
4 months	DTaP-IPV, Hib, HBV	PCV-10
11 months	DTaP-IPV, Hib, HBV	PCV-10
14 months	MMR	MenACWY <sup>1</sup>
4 years	DTaP-IPC	
9 years	DT-IPV	
12 years (girls only)	HPV	HPV (6 months later)

Vaccine key: DTaP, diphtheria-tetanus-acellular-pertussis; IPV, Inactivated poliomyelitis vaccine; Hib, *Haemophilus influenza* serotype b; HepB, hepatitis B; PCV, pneumococcal conjugate vaccine; MMR, measles-mumps-rubella; MenACWY, meningococcal serotype A, C, W, and Y; HPV, human papillomavirus.

<sup>1</sup> Since May 1 2018. Before that only MenC was given.

## Defining the various effects of vaccines

When someone is vaccinated, he or she is administered a weakened version of the pathogen, or parts thereof, to build immunity without suffering full-blown infection. The individual's immune system is thus trained to recognise a particular pathogen. On an individual level, vaccines can exert their protective effect in several ways. A vaccine may reduce the individual's susceptibility to infection by an infectious agent, thus reducing their chance to become infected by a certain factor. In mathematical models, this reduced susceptibility factor is often incorporated in one of three ways: (i) the chance of infection is reduced by a factor  $p$  for everyone who is vaccinated (a so called 'leaky' vaccine as some who are vaccinated will get infected anyway); (ii) a proportion  $p$  of everyone vaccinated is fully protected while the rest is not (often called the 'all-or-nothing' vaccine); or (iii) something in between. A vaccine may also

reduce the chance to develop symptoms, the severity or duration when someone is infected, or it may reduce the degree or duration of infectiousness (Preziosi and Halloran, 2003).

### *Direct, indirect, total, and overall effects*

Halloran and Struchiner (1991), described the various effects of vaccination programmes on a population level and they distinguish between the direct, indirect, total, and overall effects.

The *direct effects* of a vaccine are the direct benefits of the vaccine for those vaccinated. The direct effectiveness can be seen as the difference in infections or disease between vaccinated individuals and unvaccinated individuals in a population with an established vaccination programme, assuming a homogeneous and constant hazard rate of infection for all individuals. It can also be described as the added benefit of being vaccinated compared to not being vaccinated given a certain level of vaccination coverage in the population (Haber, 1999; Shim and Galvani, 2012). This is often measured in trial settings.

*Indirect effects* result from the reduction in circulation of a pathogen. As more people are vaccinated, the circulation of that pathogen is hampered as there are fewer individuals that can be infected and that can transmit the disease to others. As a consequence, unvaccinated individuals may benefit from others who are vaccinated. This *herd protection* is an important feature of vaccines and distinguishes them from most other public health interventions (Halloran and Struchiner, 1991; Haber, 1997). If the proportion of immune individuals in the population due to vaccination is high enough, an infectious disease cannot propagate itself and will be eliminated. This is also referred to as *herd immunity* (Fine et al., 2011; Metcalf et al., 2015). Maintaining a high coverage is therefore important in order to eliminate vaccine-preventable diseases and to prevent their re-emergence. Not all indirect effects of vaccination programmes are favourable. When transmission is reduced by mass vaccination, the average age of infection increases as it will take longer for someone to encounter the pathogen. This poses a problem for generally mild childhood diseases that can cause serious complications when acquired later in life, such as varicella and rubella (Guzzetta et al., 2016; Panagiotopoulos et al., 1999).

The *total effects* of a vaccination programme can be seen as the difference in outcomes in vaccinated individuals in a population with a vaccination programme compared to unvaccinated individuals in a population without a vaccination programme. In this case both direct and indirect effects are taken into account. Such a comparison can be done for example by comparing the number of disease notifications in the pre-vaccination period with those among vaccinated individuals in the period following the implementation of vaccination programmes.

*Overall effects* reflect the difference in outcomes between an average individual in a population with a vaccination programme and an average individual in a population without a vaccination programme. This differs from the total effects in that it does not require detailed information on who is vaccinated and who is not and takes both direct and indirect effects of vaccinated and unvaccinated individuals into account. The overall effects of a vaccination programme are the most accurate representation of the population impact of a vaccination programme as a whole.

## **The impact of vaccination programmes**

The potential impact of vaccination programmes is perhaps best illustrated by the eradication of smallpox in 1980 and the ongoing polio eradication initiative. The World Health Organisation (WHO) commenced a programme to eradicate smallpox in 1959 which was intensified in 1967. Their programme of surveillance and containment consisted mainly of finding and isolating infected individuals and vaccinating everyone with whom they had contact (ring vaccinations). The strategy proved successful and one of the most feared infectious diseases was finally declared eradicated nearly two centuries after Edward Jenner's first publication on smallpox vaccination (Fenner et al., 1988).

After the development of the polio vaccines and the start of mass vaccination programmes, the number of polio cases dropped dramatically in many countries. However, polio remained endemic in countries that could not support extended vaccination programmes. In 1988, the Global Polio Eradication Initiative (GPEI) was launched with the purpose to eradicate polio by vaccinating as many at risk children as possible. GPEI is supported by the WHO, Rotary International, UNICEF, the CDC, and the Gates Foundation amongst many other contributors and spends around one billion USD each year to eradicate polio. Thanks to this initiative, over 2.5 billion

children have been vaccinated and the cases of polio have declined by over 99%; only 3 countries still had endemic polio in 2016.

While the effectiveness of vaccines have been studied extensively in vaccine trials and outbreak situations, surprisingly few studies have quantified the public health impact of long-standing vaccination programmes on the population-level. There are several reasons for this. First, to assess the impact of a vaccination programme long time series of reliable historical data on cause-specific mortality, case notifications or hospitalisations, and vaccination coverage are required (Rohani and King, 2010). These data are often difficult to find or lacking altogether, especially when a vaccination programme was implemented more than half a century ago. Second, there is a lack of standardised methods to evaluate the historical impact of vaccination programmes (Lipsitch et al., 2016) as these programmes were implemented on a large scale and control groups are difficult to identify. Ideally one would like to compare two or more ‘identical’ populations, similar in all regards except the presence of a vaccination programme. It is difficult to imagine such control populations exist, especially since vaccination programmes are often implemented on a large scale. Alternatively, the pre-vaccination period could be compared with the period following vaccine implementation, or the effect of vaccinations could be modelled explicitly using mathematical or statistical models.

In one of the most cited articles on the impact of vaccination programmes, Roush and Murphy (2007) evaluated the impact of vaccinations on disease and mortality in the United States by comparing the number of cases and deaths in the pre-vaccination period with the then most recent numbers. In their analysis they compared 13 vaccine-preventable diseases, all of which showed an overwhelming decline between 80% and 100% (Roush and Murphy, 2007). Such comparisons are also often found on the websites of many government institutions.

In a more recent effort to estimate the impact of mass vaccinations, Van Panhuis et al. (2013) estimated, for the United States, that around 100 million cases of polio, measles, rubella, mumps, pertussis, hepatitis A, and diphtheria were averted by vaccinations (Van Panhuis et al., 2013). To do so they collected and digitised all weekly notified cases of infectious diseases from the Morbidity and Mortality Weekly Reports (MMWR) since 1888 at the city, county, and state level and compiled

them in a database called Project Tycho. In their analysis they assumed that the pre-vaccination average incidence rate of notified cases of vaccine-preventable diseases would remain constant.

Both Roush and Murphy (2007) and Van Panhuis et al. (2013) are landmark papers regarding the population level impact of vaccination programmes. Although valuable, their analyses do not account for pre-existing declining trends in infectious disease incidence. This omission will bias the outcome towards a higher effectiveness.

In a rare paper that considered the impact of both vaccination and demographics, Merler and Ajelli (2014) used a mathematical transmission model informed with long time series of measles cases, births rates, demographic information, and vaccination coverage, to estimate the impact of vaccination against measles in Italy. They convincingly showed that the decline in measles incidence in the pre-vaccination era was mainly driven by decreasing birth rates. When taking demographic changes into account, measles vaccination still had a strong impact on disease notifications. This analysis showed that the inclusion of demographic changes can provide valuable insights and provide a more robust and thorough investigation of the impact of vaccinations.

## This thesis

Estimating the impact of vaccination programmes requires insight into what would have happened had these programmes not been implemented. This in turn requires long time series of mortality, morbidity, and vaccination coverage. Changes in mortality and morbidity, unrelated to vaccinations, will have an impact on the presumed impact of these vaccination programmes and need to be accounted for. Often, the impact of long-standing vaccination programmes is taken for granted and not the subject of in-depth studies.

In this thesis, we provide new insights into the impact of vaccination on mortality and morbidity in the Netherlands. We start off in Chapter 2 by investigating the impact of long-standing vaccination programmes on mortality in the Netherlands. Using methods borrowed from demographic studies and combining them with survival analysis we estimate the mortality burden and number of deaths averted by vaccination programmes. In Chapter 3 we expand on these results and estimate

the overall effectiveness and derive the direct and indirect effects. In Chapter 4 we show that the methods from Chapter 1 can also be applied to other settings such as influenza vaccinations. We show the importance of accounting for competing risks when evaluating the cause-specific mortality burden.

In Chapter 5 we construct a database of monthly notified cases of infectious diseases over the 20<sup>th</sup> century in the Netherlands. With this database we estimate the number of averted cases and the overall effectiveness in the first years of mass vaccinations using a time series regression-based approach. To round out the story of vaccination programmes in the Netherlands, Chapter 6 goes into detail on the history of and developments in the government expenditure on vaccination programmes. The insights derived from these chapters may help inform policy makers, health care professionals, and parents alike in a time of increasing vaccine hesitancy. Our approach highlights the value and need for historical epidemiological research of public health interventions, providing new insights to provide context for today's debates on current vaccine impact and future vaccine candidates (Chapter 7). As a whole, this thesis provides an overview of the public health benefit of long-standing childhood vaccination programmes over the 20<sup>th</sup> century in the Netherlands.

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## Chapter 1

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## Chapter 1

Wolleswinkel-van den Bosch, J.H., Loosman, C.W., Van Poppel, F.W., et al. Cause-specific mortality trends in The Netherlands, 1875-1992: a formal analysis of the epidemiologic transition. *Int J Epidemiol*, 1997. **26**(4):772–781. [DOI: 10.1093/ije/26.4.772].





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## **Chapter 2**

### **Effect of vaccination programmes on mortality burden among children and young adults in the Netherlands during the 20<sup>th</sup> century: a historical analysis**

The contents of this chapter have been published in *The Lancet Infectious Diseases*:

**Effect of vaccination programmes on mortality burden among children and young adults in the  
Netherlands during the 20<sup>th</sup> century: a historical analysis**  
Maarten van Wijhe, Scott A. McDonald, Hester E. de Melker, Maarten J. Postma, Jacco Wallinga  
*Lancet Infectious Diseases*, Feb 9 2016, 16(5):592–598.

## Abstract

### *Background*

In the 20<sup>th</sup> century childhood mortality burden declined rapidly, and vaccination programmes are frequently suggested as contributing factor. However, quantification of this contribution is subject to debate or absent. We present historical data from the Netherlands that allow us to quantify the reduction in childhood mortality burden for vaccine-preventable diseases as a function of vaccination coverage.

### *Methods*

We retrieved cause-specific and age-specific historical mortality data from Statistics Netherlands from 1903 to 2012 (for Dutch birth cohorts born from 1903 to 1992) and data on vaccination coverage since the start of vaccination programmes from the Dutch Health Care Inspectorate and the Dutch National Institute for Public Health and the Environment. We also obtained birth and migration data from Statistics Netherlands. We used a restricted mean lifetime method to estimate cause-specific mortality burden among children and young adults for each birth cohort as the years of life lost up to age 20 years, excluding migration as a variable because this did not affect the results. To correct for long-term trends, we calculated the cause-specific contribution to the total childhood mortality burden.

### *Findings*

In the pre-vaccination era, the contribution to mortality burden was fairly constant for diphtheria (1.4%), pertussis (3.8%), and tetanus (0.1%). Around the start of mass vaccinations, these contributions to the mortality burden decreased rapidly to near zero. We noted similar patterns for poliomyelitis, mumps, and rubella. The number of deaths due to measles around the start of vaccination in the Netherlands were too few to detect an accelerated rate of decrease after mass vaccinations were started. We estimate that mass vaccination programmes averted 148 000 years of life lost up to age 20 years [95% prediction interval: 110 000, 201 000] among children born before 1992. This corresponds to about 9 thousand deaths averted [95% prediction interval: 6, 12].

### *Interpretation*

Our historical time series analysis of mortality and vaccination coverage shows a strong association between increasing vaccination coverage and diminishing contribution of vaccine-preventable diseases to overall mortality. This analysis provides further evidence that mass vaccination programmes contributed to lowering childhood mortality burden.

## Introduction

The 20<sup>th</sup> century showed rapid decreases in childhood mortality and a resultant increase in life expectancy around the world. A large part of the reduction in childhood mortality is attributed to the successful prevention of infectious diseases (Armstrong et al., 1999; Tulapurkar et al., 2000; Breiman et al., 2004). One of the foremost preventive measures has been the introduction of mass vaccination programmes (Breiman et al., 2004; Roush and Murphy, 2007; Centers for Disease Control and Prevention (CDC), 2011; Hinman et al., 2011; Van Panhuis et al., 2013; Greenwood, 2014). However, a precise quantification of the contribution of vaccinations to the fall in childhood mortality burden is not available. Such a quantitative assessment of the effect of vaccination programmes would help parents to reach an informed decision about vaccinating their children, and would inform the debate about the effectiveness of such programmes (Kata, 2010).

An assessment of the contribution of vaccination programmes to the decrease in mortality is challenging, because it needs reliable historical data about both vaccination coverage and mortality for infectious diseases. A second difficulty is that mortality was falling well before the introduction of mass vaccination; hence, care should be taken before attributing any change in mortality rates solely to the introduction of mass vaccination (Armstrong et al., 1999; DiLiberti and Jackson, 1999; Tulapurkar et al., 2000).

Here, we present an analysis of historical data from the Netherlands that allowed us to quantify the reduction in the childhood mortality burden for vaccine-preventable diseases as a function of vaccination coverage.

## Materials and methods

### *Mortality data*

We obtained detailed cause-specific mortality data for the Netherlands from 1903 to 2012 (for Dutch birth cohorts born from 1903 to 1992). For the first part of this period, 1903–1940, we transcribed the data from archived annual reports of the national census bureau (Statistics Netherlands). For the second part of this period, 1941–2012, we decoded the data from a database, provided by Statistics Netherlands, with individual mortality records where the cause of death was coded

according to the International Classification of Diseases (ICD). The mortality records over this period covered six ICD revisions, which were implemented in 1941 (ICD-5), 1950 (ICD-6), 1958 (ICD-7), 1969 (ICD-8), 1979 (ICD-9), and 1996 (ICD-10). For each revision, we validated the code lists against previous studies (Supplementary Table 2.2) (Wolleswinkel-van Den Bosch et al., 1996).

We extracted data about the number of deaths from all causes, and the number of deaths due to diphtheria, pertussis, tetanus, poliomyelitis, measles, mumps, rubella, varicella, and diarrhoea (combined with dysentery and enteritis). Both varicella and diarrhoea served as negative control groups (ie, diseases or disorders for which no mass vaccination campaigns have been introduced in the Netherlands). For most of these causes, mortality data were available from 1903 to 2012; the exceptions were poliomyelitis and mumps, which were included as causes of death since 1920, rubella since 1941, and varicella since 1936. Cause-specific deaths were available by year and age-group (for 1903–1920, data were available for the age-groups <1 year, 1–4, 5–13, 14–19, 20–29, 30–39, 40–49, 50–79, and ≥80 years; for 1920–1940, data were available for the same age-groups as for 1903–1920, except for 5–14 and 15–19 years [rather than 5–13 and 14–19 years]; and for 1941–2012, data were available by 5-year age-groups, with separate groups for <1 year and ≥80 years). Central mortality rates were calculated as the number of deaths per year divided by the mid-year population size for each age-group.

#### *Data for population sizes and vaccination coverage*

We obtained age-specific national population estimates for 1903–2012 from Statistics Netherlands (Supplementary Figure 2.1). For 1903–1949, we transcribed the estimated population size by 5-year age-groups from compiled periodic reports. For 1950–2012, we used an existing database containing age-specific population estimates. We obtained a database containing the number of births for 1903–2012 and migration data from Statistics Netherlands (Supplementary Figure 2.3). We transcribed historical vaccination coverage data by birth cohort from annual reports by the Dutch Health Care Inspectorate for the 1952–1969 birth cohorts. For the birth cohorts 1970–2012, data for coverage were obtained from records held by the Dutch National Institute for Public Health and the Environment. For each birth cohort, we used the national vaccination coverage at age 11 months (the age at which babies should have completed the primary series and received a first booster)

for diphtheria, pertussis, tetanus, and poliomyelitis, and the national coverage at age 14 months (the first vaccination) for measles, mumps, and rubella. For birth cohorts with missing coverage data for these two ages (1953 and 1958–1961), we interpolated the coverage from adjacent birth cohorts. The coverage does not include unregistered administration of vaccines and therefore slightly underestimated the actual vaccination coverage.

Mass vaccination started in the Netherlands in 1953, when children aged 1–10 years could be vaccinated against diphtheria at the expense of the government. In 1954, the diphtheria vaccine was combined with vaccines for pertussis and tetanus. In 1957, poliomyelitis vaccination was added to the programme, with a catch-up campaign for all born since 1945. Rubella vaccination started in 1974 for girls aged 11 years. Measles vaccination started in 1976 for children aged 14 months. Since 1987, all children aged 14 months and 9 years were given a combined vaccination against measles, mumps, and rubella, with a catch-up campaign for children aged 9 years born in 1978–1982 and children aged 4 years born in 1983–1985.

### *Outcomes*

The main outcomes of our study were cause-specific mortality burden among children and young adults for each birth cohort, cause-specific contributions to the total childhood mortality burden, and the mortality burden averted because of vaccination programmes.

### *Statistics*

We used the restricted mean lifetime method (Andersen et al., 2013; Andersen, 2013) to calculate cause-specific mortality burden among children and young adults for each birth cohort as the number of years of life lost up to age 20 years (YLL20; Supplementary Figure 2.2). (Andersen, 2013) We chose the cut-off age of 20 years to enable a fair comparison of mortality burden between birth cohorts born between 1903 and 1992, and excluded migration because it had no effect on the results (migration in this context means the difference between individuals moving into the Netherlands and moving out; Supplementary Figure 2.4).

The age-specific, all-cause mortality rates fell throughout the 20<sup>th</sup> century, and this decreasing trend is also noted with many cause-specific mortality rates(Wolleswinkel-van den Bosch et al., 1997; Taylor et al., 1998b; Armstrong et al., 1999; Tulapurkar et al., 2000). To correct for this long-term trend, we focused on the cause-specific contributions to the all-cause number of years of life lost (ie, total childhood mortality burden). For each birth cohort and each infectious disease, we calculated these contributions as the ratio of cause-specific years of life lost before age 20 to all-cause years of life lost before age 20. We restricted the analysis to birth cohorts for which we have complete data on cause-specific mortality rates for all age ranges. This means that for poliomyelitis and mumps we restricted the analysis to cohorts born since 1920, for rubella to cohorts born since 1941, and for varicella to cohorts born since 1936. For all other infections the analyses covered all cohorts born since 1903. The mortality burden averted because of vaccination was obtained by extrapolating the pre-vaccination mortality burden and subtracting the actual mortality burden over the vaccination period (Supplementary Figure 2.5).

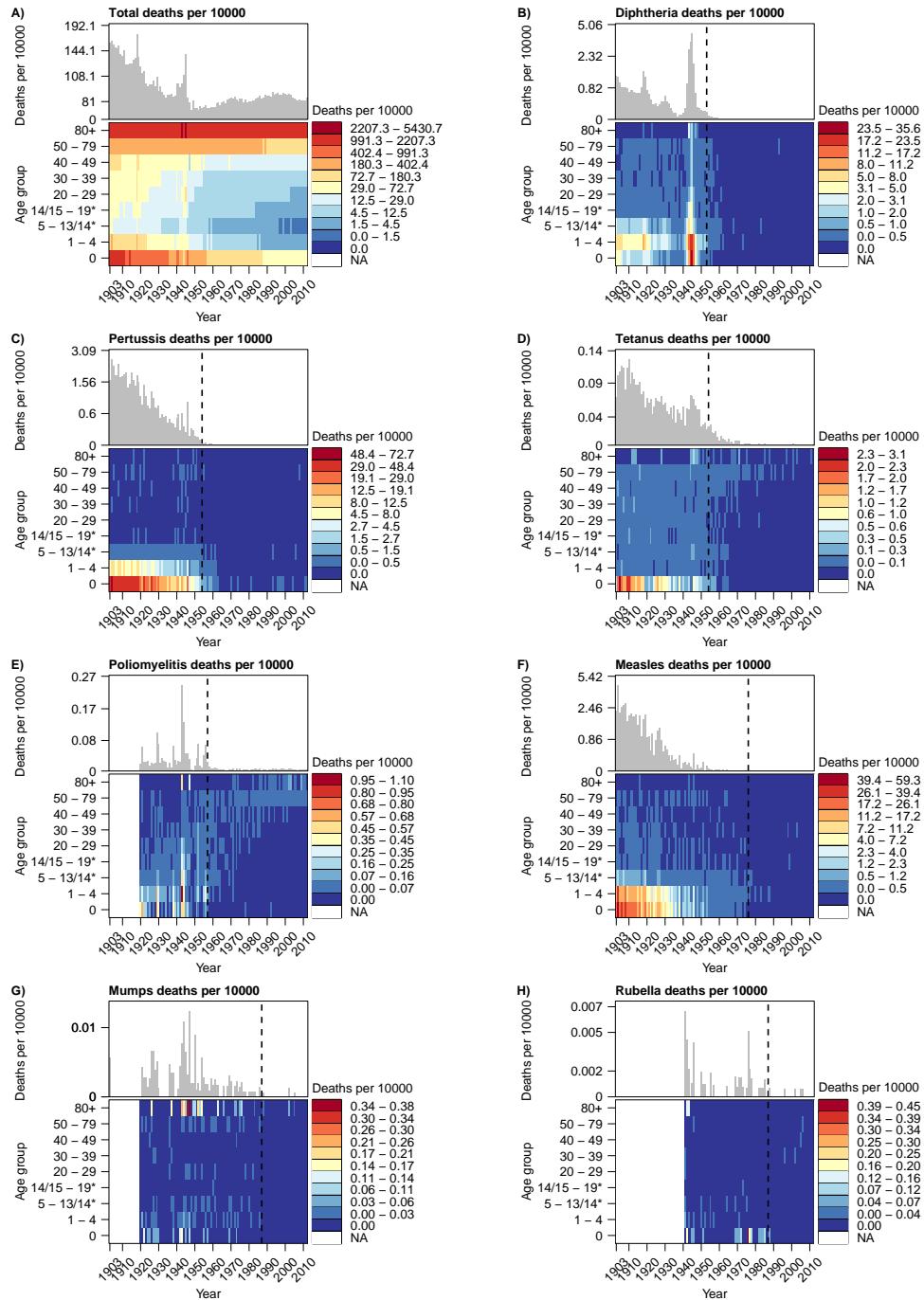
### *Role of the funding source*

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and MvW, MJP, and JW had final responsibility for the decision to submit for publication.

## **Results**

### *Mortality rates*

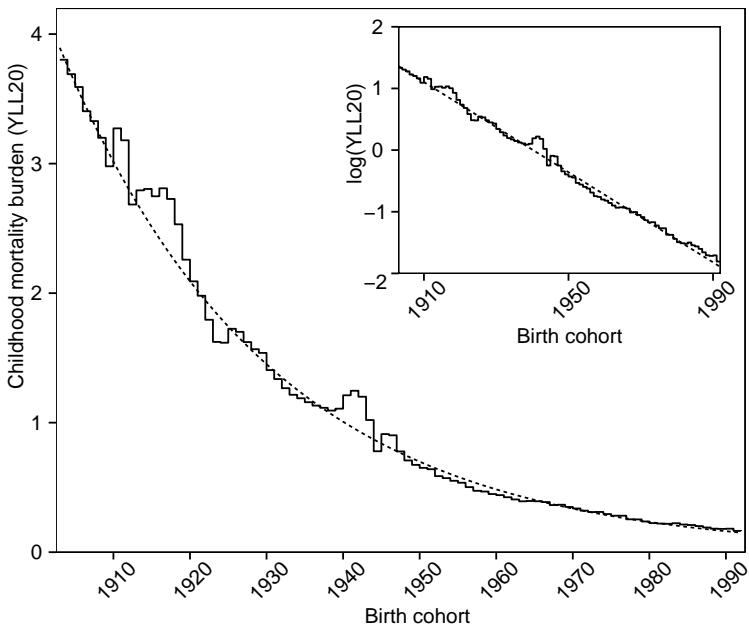
From 1903 to 2012, all-cause mortality rates showed a strong and persistent reduction in most age-groups, especially in children aged 0–4 years (Figure 2.1). All-cause mortality decreased from 156 deaths per 10 000 individuals per year in 1903 to 84 deaths per 10 000 individuals per year in 2012. This trend of decreases was interrupted during World War 1 (1914–1918) and World War 2 (1939–1945). Cause-specific mortality for each of the specific childhood infections shows a decreasing trend among the youngest age-groups and fell to near zero after the launch of mass vaccination programmes (lower panels in Figure 2.1; Supplementary Figure 2.6).



**Figure 2.1: All-cause and cause-specific mortality rates, the Netherlands 1903–2012.** Figure shows mortality rates for all causes, diphtheria, pertussis, tetanus, poliomyelitis, measles, mumps, and rubella. Top panels show the total number of deaths per 10000 individuals per year, and bottom panels show age-specific mortality rates. Dashed line in B-H shows the start of mass vaccination. \*In 1920 these age-groups changed from 5–13 to 5–14 and from 14–19 changed to 15–19.

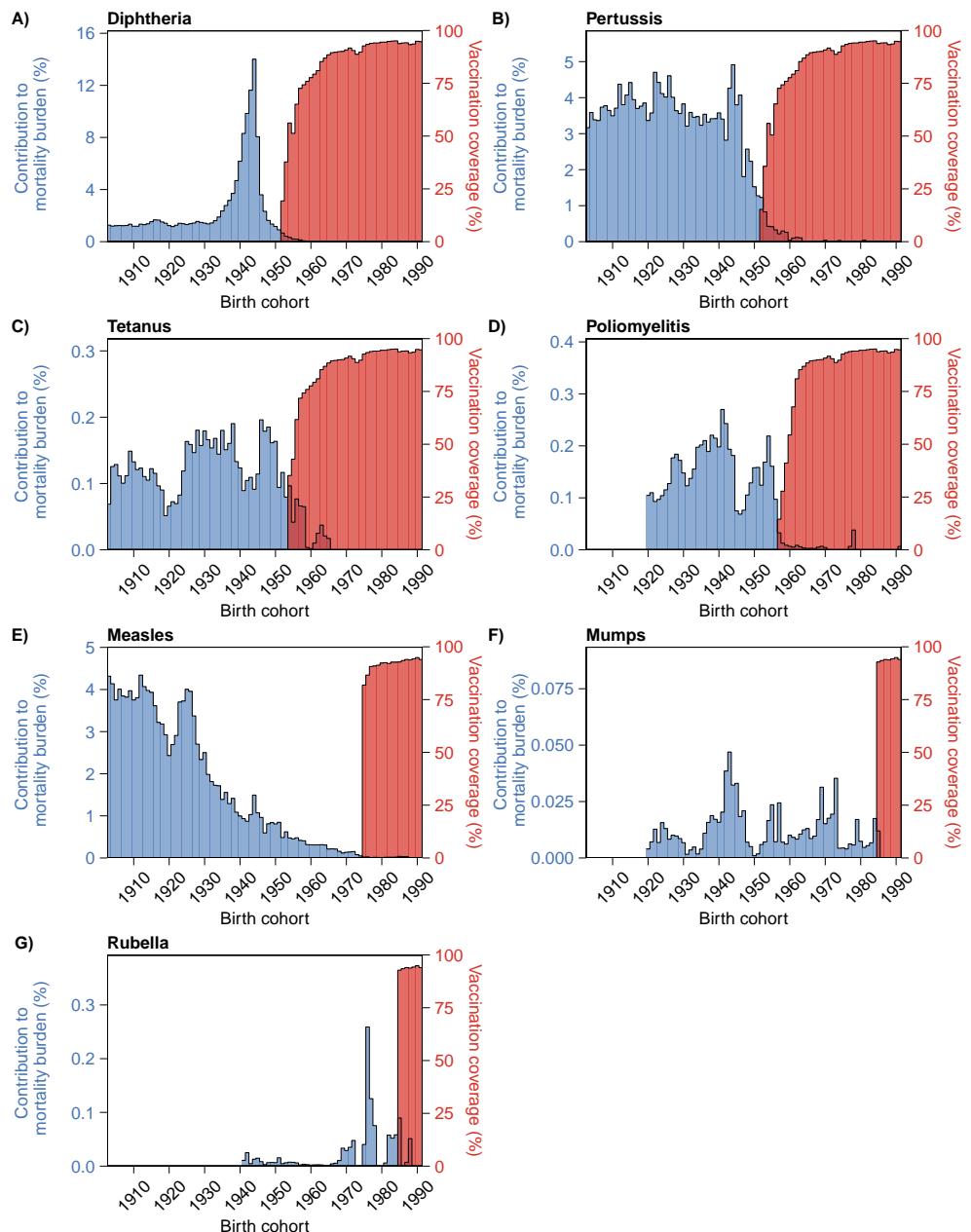
The all-cause number of life-years lost decreased with year of birth from 1903 to 1992 (Figure 2.2). The decrease is well approximated by an exponential decay, with a halving time of 19 years (Figure 2.2 inset,  $R^2 > 0.99$ ). Children born in 1903 lost, on average, 3.80 years of life before age 20, those born in 1952 lost, on average, 0.59 years of life, and those born in 1992 lost, on average, 0.16 years of life. Breaking down the life-years lost by vaccine-preventable disease, we estimated that a newborn baby in 1903 would lose, on average, 0.34 years of life (8.8% of 3.80 all-cause life-years lost) because of diphtheria, pertussis, tetanus, or measles before age 20 years. A newborn baby in 1952, just before mass vaccination was introduced, would lose, on average, 0.01 years (2.5% of 0.59 all-cause life-years lost) because of diphtheria, pertussis, tetanus, or measles before the age of 20, and another 0.001 years (0.1% of all-cause life-years lost) because of poliomyelitis, mumps, or rubella. A newborn baby in 1992 would lose, on average, 0.0001 years, or roughly 1 hour (0.1% of 0.16 all-cause life-years lost) from vaccine-preventable childhood diseases, with only pertussis and poliomyelitis contributing.

For most vaccine-preventable diseases, the contribution to the overall mortality burden before age 20 years (after correction for long-term trends in life-years lost) was constant in the pre-vaccination period (Figure 2.3 and Table 2.1). For diphtheria, this constant contribution was around 1.4%; for pertussis around 3.8%, and for tetanus around 0.1%. For poliomyelitis, the contribution to life-years lost varied between 0.07% and 0.27%. The irregularity was due to recurrent epidemics and the small number of deaths of individuals younger than 20 years. For each of these vaccine-preventable diseases, the contribution to the total mortality burden fell rapidly towards zero when mass vaccinations started. For measles, the contribution to overall mortality steadily fell from 4.3% for the birth cohort born in 1903 to 0.02% for the birth cohort born in 1975, just before the start of mass vaccination against measles. For mumps, the contributions to overall mortality in the pre-vaccination period varied between 0.01% and 0.05%. For rubella, the contribution to life-years lost was about 0.01% for birth cohorts born in 1941–1971, before mass vaccination of girls aged 11 years was introduced. The number of deaths due to measles around 1975 in the Netherlands was too small to detect an accelerated rate of decrease after the introduction of mass vaccination. For birth cohorts born after 1987—the start of mass vaccination with the combined measles–mumps–rubella vaccine—the contributions of mumps and rubella to the mortality burden fell to zero.



**Figure 2.2: All-cause childhood mortality burden in years of life lost up to age 20 years per live birth, the Netherlands 1903–1992.** Data are years of life lost up to age 20 years (YLL20) per live birth in Netherlands for birth cohorts from 1903 to 1992 (solid line) with best-fit exponential reduction (dotted line). Inset shows the log-transformed YLL20 (solid line) and the corresponding best linear fit (dotted line).

Each vaccination programme achieved a high coverage within a few years after its introduction into the national immunisation programme (Figure 2.3). The coverage of vaccination against diphtheria, pertussis, and tetanus exceeded 80% within ten years after introduction in 1953. The coverage of vaccination against poliomyelitis exceeded 80% within six years of introduction; for measles coverage exceeded 80% at the start of the programme; and for mumps and rubella coverage exceeded 80% since the start of the combined measles–mumps–rubella vaccination programme. We noted that for all the diseases considered, except measles, the rapid increase in vaccination coverage against a particular infection coincided—within a time-frame of a few years—with a rapid decrease of this disease’s contribution to life-years lost before age 20. For varicella, for which no vaccination programme exists in the Netherlands, the contribution to mortality burden was around 0.06%. For diarrhoea (combined with dysentery and enteritis), the contribution decreased rapidly in



**Figure 2.3: Vaccination coverage and disease-specific contribution to childhood mortality burden, the Netherlands 1903–1992.** Data are for birth cohorts from 1903 to 1992 (red) and the contribution (as percentage) to childhood mortality burden before the age of 20 (blue) for diphtheria, pertussis, tetanus, poliomyelitis, measles, mumps, and rubella.

## Effect of vaccination programmes on mortality burden

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the first half of the 20<sup>th</sup> century, and remained around 1.2% in the second half. Since 1950, there have been no rapid decreases of the contribution to life-years lost before age 20 for either of these negative controls (Supplementary Figure 2.6). We estimated that mass vaccination programmes averted 148 000 [95% prediction interval: 110 000, 201 000] years of life lost before age 20 among children born before 1992. This finding corresponds to 9 thousand deaths [95% prediction interval: 6, 12] averted. During the vaccination period, the population of the Netherlands grew from about 10 million in 1950 to 16 million in 1992 (Supplementary Figure 2.1). Most of the averted mortality burden was attributable to vaccination against pertussis; vaccination against diphtheria was the second biggest contributor (Table 2.1).

**Table 2.1: Effect of mass vaccination programmes against childhood infectious diseases by birth cohort, the Netherlands, 1903–1992.** The contributions over the vaccination period were taken as an average over the period, starting five cohorts after the start of mass vaccination up to cohort 1992. The contributions to the all-cause mortality burden over the pre-vaccination period were taken as an average over the period 1903–1930 for diphtheria, 1903–1946 for pertussis, 1903–1953 for tetanus, 1920–1956 for poliomyelitis, 1920–1984 for mumps, and 1941–84 for rubella. Reductions in mortality burden were estimated as the difference between the actual burden after introduction of vaccination, and the burden that would have resulted had the contribution to mortality due to that disease remained constant. YLL20 = years of life lost up to age 20 years.

Disease	Year mass vaccination started	Average contribution to all-cause mortality burden		Reduction in mortality burden due to mass vaccinations [95% prediction interval]	
		Before vaccination	After vaccination	YLL20 in thousands	Deaths in thousands
Diphtheria	1953	1.36%	0.004%	38 [28, 52]	3 [2, 4]
Pertussis	1954	3.75%	0.024%	103 [79, 134]	6 [4, 7]
Tetanus	1954	0.13%	0.003%	3 [1, 6]	0.2 [0.1, 0.4]
Poliomyelitis	1957	0.15%	0.005%	3 [1, 8]	0.3 [0.1, 0.6]
Measles <sup>1</sup>	1976			0.3 [0.2, 0.5]	0.02 [0.01, 0.03]
Mumps <sup>2</sup>	1987	0.01%			
Rubella <sup>2</sup>	1987	0.02%			

<sup>1</sup> The contribution of measles to all-cause mortality burden decreased in the pre-vaccination period, and no value is provided.

<sup>2</sup> For mumps and rubella, too few results were available after introduction of vaccinations to calculate an average.

## Discussion

We have shown that the rapid increase in vaccination coverage against a vaccine-preventable disease was accompanied by a rapid decrease in the contribution of that disease to the childhood mortality burden. Against a background of exponentially decreasing childhood mortality, vaccinations programmes had a clear effect when introduced in 1953 for diphtheria, 1954 for pertussis and tetanus, 1957 for poliomyelitis, and 1987 for mumps and rubella. These findings strongly suggest that these programmes have been highly effective in further reducing mortality burden among children and young adults. This suggestion, in turn, emphasises the importance of keeping the burden as low as possible by adhering to the programmes.

The overall exponential reduction in all-cause mortality burden during the 20<sup>th</sup> century is striking and in line with reports for other countries (Taylor et al., 1998b; Armstrong et al., 1999; Tulapurkar et al., 2000). A range of factors contributed to this decrease for a wide range of causes of death, such as better nutritional status and increased standard of living, improved hygiene, increased access to clean water, improved sewage collection and disposal, better housing, improvements in medical treatment (such as availability of antibiotics), and lower birth rates (Taylor et al., 1998b,a; Wolleswinkel-van den Bosch et al., 1998; Mackenbach and Loosman, 2013; Merler and Ajelli, 2014; Martinez-Bakker et al., 2014). However, none of these factors changed suddenly and drastically during the period after World War 2, such that they could provide a plausible explanation for the rapid decrease in contribution to mortality burden for any specific vaccine-preventable disease that we noted in our analysis. This idea is lent support by the absence of sudden decreases in the contribution to mortality burden in the negative controls, although a gradually decreasing trend was noted for diarrhoea.

For some infections, we recorded a fall in the contribution to the childhood mortality burden in birth cohorts born a few years before mass vaccination started (Figure 2.3). Because we assessed mortality burden by birth cohort, such a decrease is to be expected: older birth cohorts might have been partly protected from infection by vaccinated individuals in adjacent birth cohorts (De Melker et al., 2003). Additionally, some children in these birth cohorts might have been protected because of individual, often unregistered, administration of vaccines (in particular, this might have played a role for diphtheria and pertussis).

For measles, the contribution to the all-cause mortality burden reduced steadily over the pre-vaccination period, so once vaccination was introduced in 1976, the mortality burden was already too low to note a clear effect of vaccination. Our analysis suggests that the burden of averted mortality by mass vaccination against measles, compared with other vaccine-preventable diseases, was minimal. A possible explanation for the consistent decrease is that mortality related to measles, unlike the other infectious diseases considered in this study, is often due to secondary infections and might therefore be affected by general improvements in public health more than other infections; the reduction is reminiscent of that for diarrhoea, dysentery, and enteritis before 1950.

Changes in the registration of causes of death did not affect cause-specific contributions to the childhood mortality burden. Mortality records rely on the validity and reliability of the cause of death registered on death certificates and the subsequent coding according to the current ICD coding lists. The validity might change over time depending on the advancement of medical knowledge, the sensitivity and specificity of clinical diagnoses, new regulations, ICD revisions, coding practices, and the skills of certifiers (Janssen and Kunst, 2004). The codes used in our analysis changed little over time. Where they changed, we visually inspected the mortality trends for any discontinuities due to changes in registration. We did not record any substantial anomalies for the diseases presented in this report. Therefore, we believe it unlikely that changes in death registration caused the sudden and striking reductions in childhood mortality burden.

To the best of our knowledge, our study is the first to compare accurate vaccination coverage data with mortality rates for many birth cohorts born before and after introduction of mass vaccination, while correcting for long-term trends in mortality. Our findings are in line with those of earlier studies (Peltola et al., 1986; Armstrong et al., 1999; Roush and Murphy, 2007; Van Panhuis et al., 2013) in the Netherlands and other countries, suggesting that findings might be similar in other populations as well. Further investigation of data for other populations with similar methods would provide an opportunity to validate our results. Another possibility for further investigation involves analysing older time series to capture the epidemiological transition that started in Netherlands during the 19th century (Wolleswinkel-van den Bosch et al., 1997).

For a complete picture of the benefit of vaccination programmes, it is essential to account for the incidence of disease in addition to mortality (Van Panhuis et al., 2013). In many countries around the world, including the Netherlands, vaccine-preventable diseases continue to cause outbreaks, mainly in communities with low vaccination coverage, and are a major cause of considerable disease burden (Oostvogel et al., 1994; Van den Hof et al., 2001; Crowcroft and Pebody, 2006; Dayan et al., 2008; McCarthy, 2015).

In the continuing debate about the effectiveness of vaccinations, people who are sceptical about vaccines often use the decrease in the number of deaths due to vaccine-preventable infections before mass vaccination to cast doubt on the effectiveness of vaccination programmes. We show that, indeed, mortality burden did decrease before mass vaccination, but that after correcting for this long-term trend, the effectiveness of most vaccination programmes on mortality can be clearly detected. Our findings, when taken together, suggest that if a vaccine-preventable disease were to resurge, it would be unlikely to lead to pre-vaccination levels of mortality because of the overall decrease in childhood mortality burden. Additionally, our results suggest that the rapid reductions in the contribution of vaccine-preventable diseases to the childhood mortality burden were caused by the introduction of mass vaccination, and that vaccination programmes have been effective in further reducing the mortality burden. We believe these results will be useful to emphasise the effectiveness of vaccination programmes to both public health experts and the general population, and to help parents to make an informed decision about vaccinating their children.

### **Contributors**

MvW obtained, extracted, and analysed the data, searched the scientific literature, and wrote the first draft of the manuscript. MvW, SAM, HEdM, MJP, and JW designed the study and revised the manuscript. MJP and JW conceived the project.

### **Declaration of interests**

MJP received grants and honoraria from various pharmaceutical companies, including GlaxoSmithKline, Pfizer, and Sanofi Pasteur MSD, who are potentially interested in the subject matter of this Article.

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## Research in context

### *Evidence before this study*

We searched Medline on September 2, 2015, for historical or comparative studies on the contribution of vaccines to the decline in vaccine-preventable disease mortality or morbidity. We used the search terms for the infections of interest (“diphtheria”, “pertussis”, “tetanus”, “measles”, “rubella”, “polio”, or “mumps”), for the intervention of interest (“vaccination programme”), for the outcome of interest (“mortality” or “deaths averted”), and for the kind of study (“comparative study” or “historical article”). We allowed for common variations on each term (such as “immunization programme”) and for names for vaccines against the infections of interest (such as “MMR” and “DTP”). We identified 148 articles this way. We screened articles by title and abstract to identify papers that analysed mortality or morbidity during both the pre-vaccination period and the vaccination period. We extended the search by screening the references listed in articles that met our criteria. Our search resulted in 16 relevant articles. Most of these articles focused on the inter-epidemic period or the frequency of fade-outs, and most of these articles used case-notification or the number of cases averted as outcome measure. Five articles discussed mortality data. Of these, three articles reported on mortality and showed a declining trend before introduction of vaccination. None of these articles corrected for this long-term trend.

### *Added value of this study*

We characterise the impact of vaccination programmes using a measure that remains unaffected by any trend in mortality rates: the cause-specific contribution to the childhood mortality burden. We quantify this measure for Dutch birth cohorts born from 1903 to 1992 for seven vaccine-preventable diseases. For most of those diseases, there is no discernible temporal trend in the contribution to mortality burden before mass vaccination was introduced. We show that high vaccination coverage for a birth cohort coincides with a low cause-specific contribution to childhood mortality for that birth cohort and estimate that nine thousand deaths have been averted by

mass vaccinations. This demonstrates the impact that vaccination programmes had on mortality burden due to vaccine-preventable diseases, irrespective of any trend in mortality burden.

### *Implications of all the available evidence*

For each of the vaccine-preventable diseases, the introduction of mass vaccination coincided with a drastic decline in the cause-specific contribution to the childhood mortality burden. This finding allows policy makers to assess the effectiveness of vaccination programmes. It will also help parents to make an informed decision on vaccinating their children.

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## **Supplementary information to Chapter 2**

## Mortality data

We transcribed and digitised the number of deaths by cause of death and age-group for the period 1903–1940 from annual reports by the national census bureau (Statistics Netherlands). For the period 1941–2012 we obtained a database from Statistics Netherlands containing all deaths in this period (one record per person) with information on age-group, month and year of death, and the primary cause of death coded according to the international classification of disease (ICD). This period covered six revisions of the ICD implemented in 1941 (ICD-5), 1950 (ICD-6), 1958 (ICD-7), 1969 (ICD-8), 1979 (ICD-9), and 1996 (ICD-10). Supplementary Table 2.2 presents the codes used to create the data for each cause of death.

## Population size

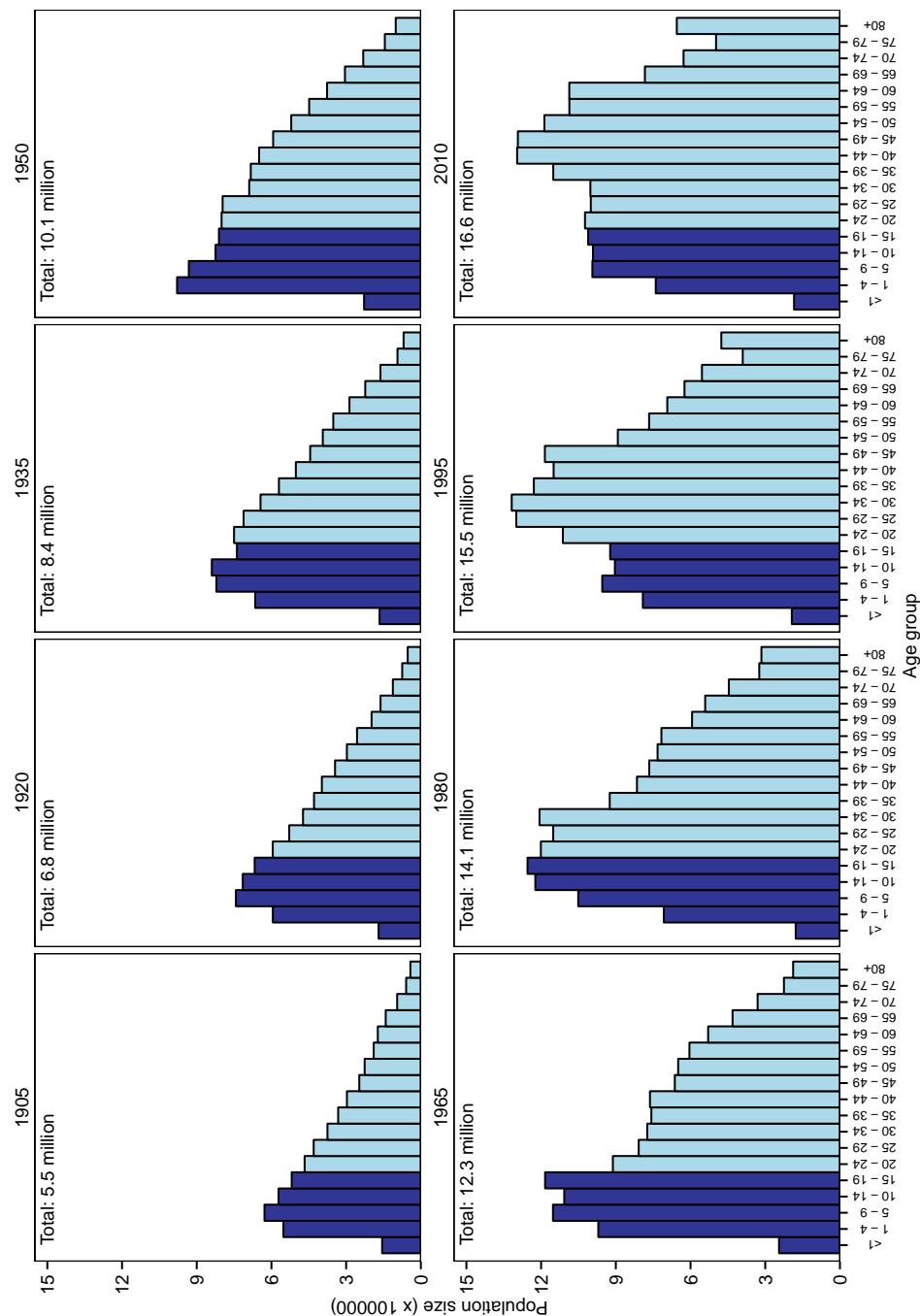
For the period 1903–1949 we transcribed and digitised the estimated population size of the Netherlands stratified by 5-year age-groups from a compilation of periodic reports by Statistics Netherlands. These population estimates were derived from periodic national census performed by Statistics Netherlands from 1899–1971 approximately every ten years. The inter-census population sizes were estimated by interpolation using age-specific mortality rates and were corrected for migration. For the period 1950–2012, a database was provided containing age-specific population estimates. During the 20<sup>th</sup> century the population of the Netherlands nearly tripled in size (Supplementary Figure 2.1).

## Vaccination coverage

National vaccination coverage was reported since the start of government funded mass vaccination in the Netherlands in 1953. We transcribed previously unavailable national vaccination coverage data for birth cohorts 1952–1969 from annual reports by the Dutch Health Care Inspectorate. Data for birth cohorts 1970–2012 were obtained from the Dutch National Institute for Public Health and the Environment (RIVM). Some vaccines were already in use prior to mass vaccination. Data on this early uptake were only available for a few small regions and is of questionable quality. Chapter 6 Table 6.1 gives an overview of the major developments in the Dutch mass vaccination programme since its implementation in 1953.

Supplementary Table 2.2: ICD codes used for the causes of death.

Cause of death	ICD code list (period)								
	ICD-1 (1903-1910)	ICD-2 (1911-1920)	ICD-3 (1921-1930)	ICD-4 (1931-1940)	ICD-5 (1941-1949)	ICD-6/7 (1950-1968)	ICD-8 (1969-1978)	ICD-9 (1979-1994)	ICD-10 (1995-2012)
Diphtheria (incl. croup)	9	9	10	20	10	055	032	032	A36
Pertussis	8	8	9	9	9	056	033	033, 4843	A37
Tetanus	72	24	29	22	12	061	037	037, 7713	A33-A35
Poliomyelitis (ind. sequelae)			22	16	36	080, 081	040-044	045, 138, 7307	A80, B91, G14, 896
Measles	6	6	7	7	35	0850, 0851	055	055	B05
Mumps			13	44b	44c	089	072	072	B26
Rubella incl. congenital rubella (excl. stillbirths)				38d	086	056, 7613	056, 7710	B06, P350	
Varicella excl. zoster				44a	38e	087	52	52	B01
Diarrhoea, dysentery, and enteritis (excl. cholera)	14, 105, 106	14, 104, 105	16, 111b, 113, 114	119, 120	13, 117b, 120, 123a	27, 117b 119, 5410, 541, 571, 572, 764, 7851	045-048, 004, 532, 561-563	004- 006-009, 532, 555-558, 562	A03, A04, A06-A09, K26, K50-K52, K55, K57



**Supplementary Figure 2.1: Population by age, the Netherlands 1905–2010.** Age-specific estimates of the population in the Netherlands for the years 1905, 1920, 1935, 1950, 1965, 1980, 1995, and 2010. Dark blue bars indicate the ages used in the analysis.

We used the vaccination coverage at 11 months (primary series plus the first booster shot) for diphtheria, pertussis, tetanus, and poliomyelitis (DPTP), and we used the coverage at 14 months (the first shot) for measles, mumps, and rubella (MMR). For birth cohorts 1953 and 1958–1961 coverage data at these two ages were missing, and we linearly interpolated the coverage data from adjacent birth cohorts. For cohorts born in the period 1952–1957, we used the number of vaccines distributed and the number of eligible children to estimate the vaccination coverage.

### *Determining and interpreting national vaccination coverage*

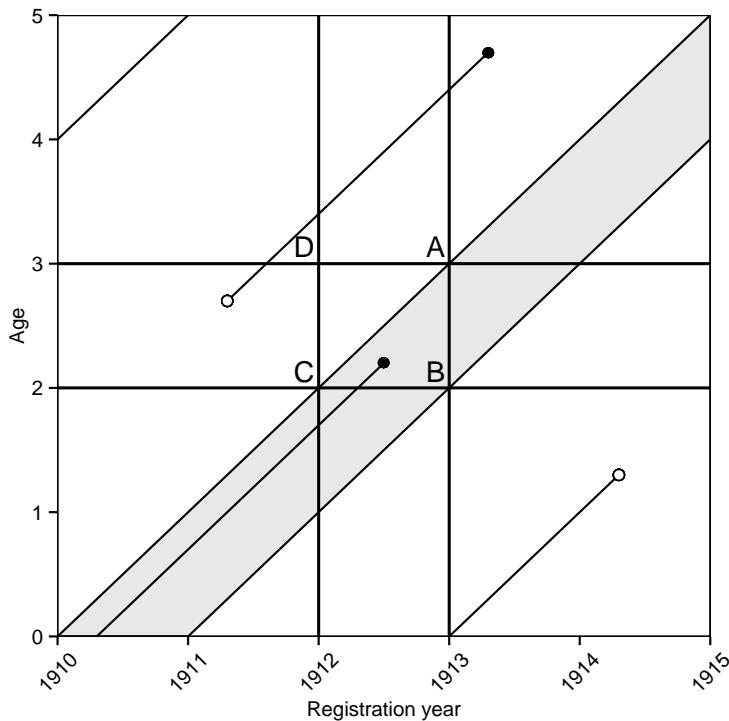
The method to calculate the national vaccination coverage changed several times over the years. These changes in the calculation have little impact on the resulting estimates. Until 1962, the number of vaccines distributed was divided by the number of registered children of a certain age. From 1962 to 1986 the national vaccination coverage was determined by taking a cross-section of the Dutch population on the first of September, counting all children at a certain age who had received a certain amount of shots (Van Lier et al., 2012). In 1987 the date the cross-section was taken changed to the first of January. Since 2005 coverages are determined based on DPTP-3 at 1 year of age, DPTP-4 and MMR-1 at 2 years of age, DPTP-5 at 5 years of age and DPT-6 and MMR-2 at 10 years of age. A national coverage as reported in this study refers to the proportion of children in a birth cohort that had the prescribed number of shots according to the programme. For diphtheria, pertussis, tetanus and poliomyelitis this means that the coverage as used here is lower than the actual proportion of children who received at least one shot of vaccination.

### **Reconstruction of cohort-specific mortality**

Mortality counts were available by calendar year and age of death. We estimated mortality counts by birth cohort and age using Lexis-diagrams. As, an example Supplementary Figure 2.2 shows a Lexis-diagram for the period 1910–1915 covering the age-range from 0 to 5 years of age. In this diagram the life-course of each individual can be represented by a diagonal line, starting at age zero at the time of birth and continuing up to the moment of death. The grey area between the diagonal lines that start at the January 1st and December 31th 1910 thus contains the life courses of the entire birth cohort of 1910. The diagonal lines that end in the square ABCD (a Lexis-square) represent the information available through mortality

registries: all individuals that died at age  $a = 2$  in the year  $i = 1912$ . Lexis-squares contain two Lexis-triangles, in this case the upper triangle ACD and lower triangle ABC. The lines that end within triangle ABC represent children that were born in 1910 and died in 1912 at 2 years of age. The lines that end within triangle ACD represent children that were born in 1909 and died in 1912 at 2 years of age. In general, the deaths at age  $a$  reported in year  $i$  that are represented by lines that end in an upper Lexis-triangle correspond to individuals born in the year  $i \sim a \sim 1$ , and those represented by lines that end in the lower triangle correspond to individuals born in the year  $i \sim a$ . If deaths occur uniform over a Lexis-triangle, the average age at death in the upper Lexis-triangle is  $a + \frac{2}{3}$  while the average age in the lower triangle is  $a + \frac{1}{3}$  (this follows from the mathematical property of a triangle that the centroid is always one third from the base to the top).

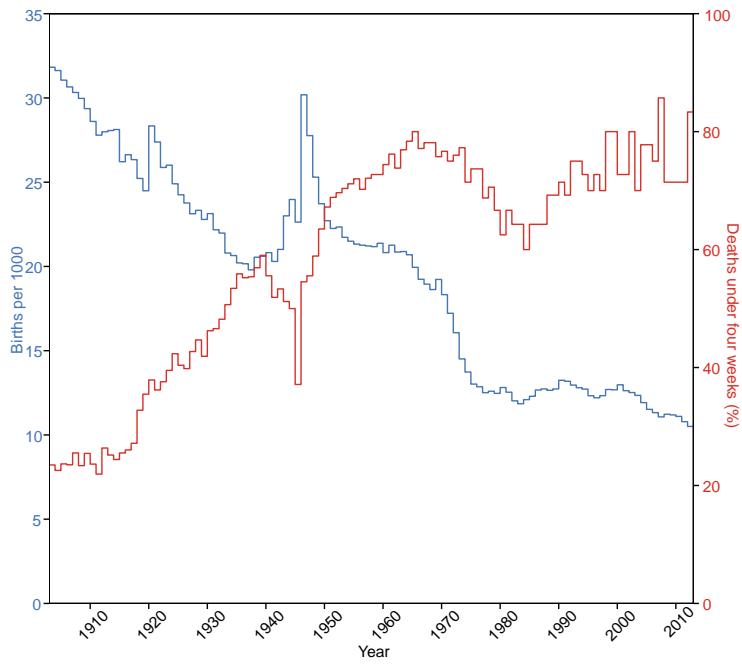
We have information on the number of deaths by registration year and by age-group (Lexis-squares), and we need to obtain the corresponding number of deaths by birth cohort (Lexis-triangles). To achieve this, we first assigned each reported death a specific age. For the age-groups 5–13, 14–19, 20–29, 30–39, 40–49, 50–79, and 80+ we assumed that deaths occur uniformly over an age-group, for age-group 1–4 we assumed that more deaths occur in the first and second year of life than in the third and fourth. Second, we assign each reported death at a specific age in a specific year at random to one of the two possible birth cohorts, with a probability proportional to the size of the birth cohorts (that is, within a Lexis-square we assign each death to either the upper or lower Lexis-triangle). We assumed that all deaths occur at age  $a + \frac{2}{3}$  for the upper Lexis-triangle and at age  $a + \frac{1}{3}$  for the lower Lexis-triangle. For the youngest age-group we estimated the number of deaths in the first four weeks of life using the overall proportion of neonatal deaths (Supplementary Figure 2.3). We assumed that for neonatal deaths the year of death was also the year of birth, except for those born in the first four weeks of the year. We assign a cohort to all neonatal deaths that occurred in the first four weeks of the year and all non-neonatal deaths under 1 year of age. We assumed that those that died in the first four weeks of life lived on average two weeks. To rule out chance effects in the process of assigning deaths to birth cohorts, we repeated this assigning process a hundred times and averaged the results.



**Supplementary Figure 2.2: Example of a Lexis-diagram (1).** Diagonal lines represent an individual's life course. Closed circles represent deaths and open circles represent migration events. The shaded area represents the entire follow-up time of birth cohort 1910.

## Birth rates and neonatal mortality

Birth rates and neonatal mortality data since 1903 were collected from Statistics Netherlands (Statline). During the 20<sup>th</sup> century the birth rate declined from more than 30 births per 1000 in 1903 to little over 10 births per 1000 in 2012 (Supplementary Figure 2.3). The proportion of neonatal deaths increased from 23% in 1903 to 83% in 2012 (Supplementary Figure 2.3), indicating that by the end of the 20<sup>th</sup> century most deaths under 1 year of age occur in the first weeks of life. We use the proportion neonatal deaths to inform the assignment of birth cohorts.



**Supplementary Figure 2.3: Live births and neonatal death rate, the Netherlands 1903–2010.** Number of live births per 1000 population (blue), and the percentage of deaths under 1 year of age that died within four weeks of life (red) in the Netherlands for the period 1903–2010.

## Years of Life Lost (YLL) estimation

To estimate the cause-specific burden of mortality for each birth cohort we estimated the expected number of life-years lost for each cause of death using the restricted mean lifetime method within a competing risks framework (Andersen, 2013; Andersen et al., 2013). We consider  $k$  mutually exclusive causes of death with event times  $0 < t_1 < \dots < t_m < \tau$ . The overall survival probability  $S$  is estimated by the standard Kaplan-Meier estimator for survival up to time  $t_i$ :

$$\hat{S}(t_i) = \prod_{t_i \leq t} \frac{n_{i-1} - \sum_{j=1}^k d_{i,j}}{n_{i-1}} \quad (2.1)$$

Where  $d_{i,j}$  is the number of deaths due to cause  $j = 1, \dots, k$ , at time  $t_i$ , and  $n_i$  is the

total number of individuals at risk at time  $t_i$ . The corresponding expected lifetime, restricted to a cut-off age  $\tau$ , is:

$$E_\tau = \int_0^\tau \hat{S}(t) dt \quad (2.2)$$

The cause-specific cumulative incidence,  $F_j$ , is estimated by:

$$\hat{F}_j(t) = \sum_{i:t_i \leq t} \hat{S}(t_{i-1}) \frac{d_{i,j}}{n_i} \quad (2.3)$$

This cause-specific cumulative incidence  $\hat{F}_j(t)$  gives the probability at birth of dying from cause  $j$  before age  $\tau$ . The corresponding expected number of years of life lost before age  $\tau$  due to cause  $j$ ,  $L_j$ , is:

$$L_j(0, \tau) = \int_0^\tau \hat{F}_j(t) dt \quad (2.4)$$

For each birth cohort at any age  $t$ , the number of survivors and the number deaths to all possible causes should satisfy the balance equation:

$$\hat{S}(t) + \sum_{j=1}^k \hat{F}_j(t) = 1 \quad (2.5)$$

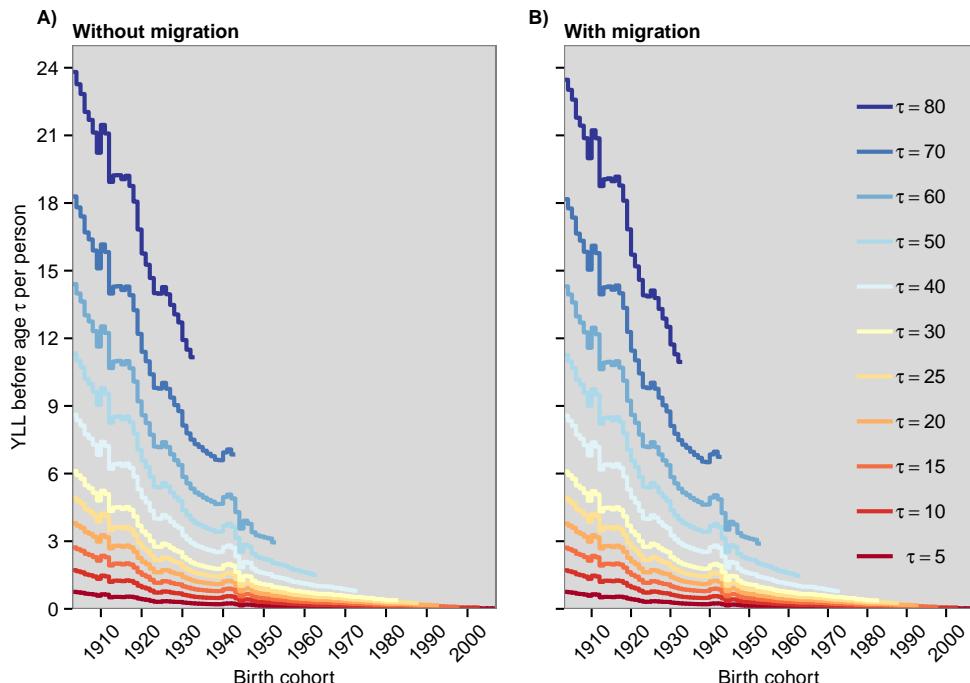
When we integrate the balance equation from age 0 to age  $\tau$  we obtain:

$$\int_0^\tau \hat{S}(t) dt + \sum_{j=1}^k \int_0^\tau \hat{F}_j(t) dt = \tau \quad (2.6)$$

Recognising the first part of the left-hand side as the expected restricted lifetime, and the second part of the left-hand side as a sum over expected number of years of life lost, we can simplify this integrated balance equation to:

$$E_\tau + \sum_{j=1}^k L_j(0, \tau) = \tau \quad (2.7)$$

which states that the sum of the life expectancy up to age  $\tau$ , measured in years, and the number of years of life lost before age  $\tau$  due to all causes  $j$ , should equal the cut-off age  $\tau$ . For each birth cohort we estimated the number of years of life lost before age  $\tau$  due to all causes  $j$ . The results are shown in Figure 2.2 using a cut-off age  $\tau = 20$  years. For our data, the rate of decline of the number of life-years lost was not specific to the particular choice for the cut-off age; see Supplementary Figure 2.4 where we varied the cut-off age from 5 to 80 years.



**Supplementary Figure 2.4: Years of life lost with and without migration for various cut-off ages, the Netherlands 1902–2012.** Average all-cause years of life lost before age  $\tau$  per live birth in the Netherlands from 1903–2012 for a range of cut-off ages  $\tau$  from 5 to 80 years. (A) Estimates without taking migration into account; (B) estimates taking migration into account.

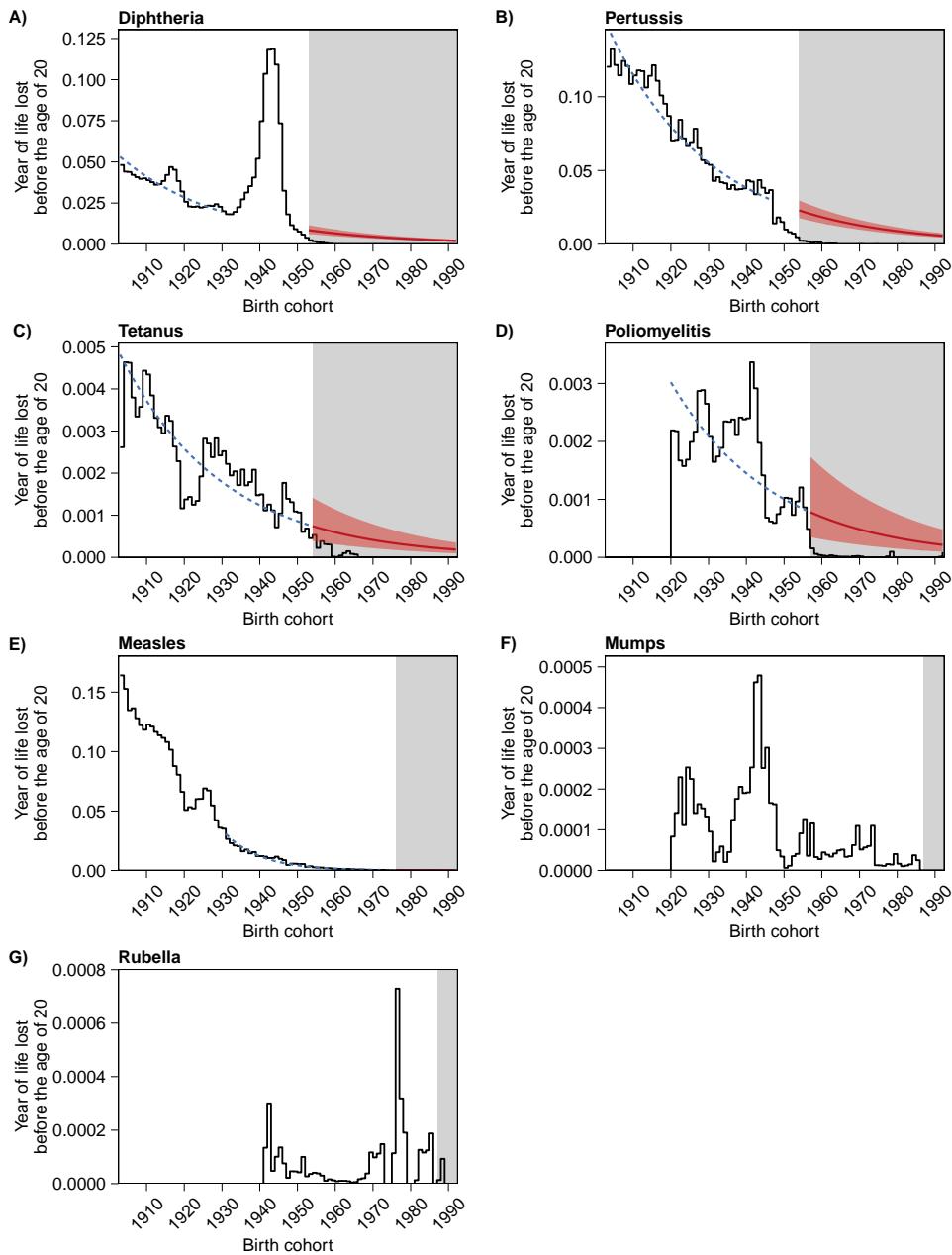
Since the cause-specific life-years lost add up to the total life-years before age  $\tau$ , we can define the contribution of each cause of death to the total years of life lost before age  $\tau$ :

$$C_j(0, \tau) = \frac{L_j(0, \tau)}{\sum_{j=1}^k L_j(0, \tau)} \quad (2.8)$$

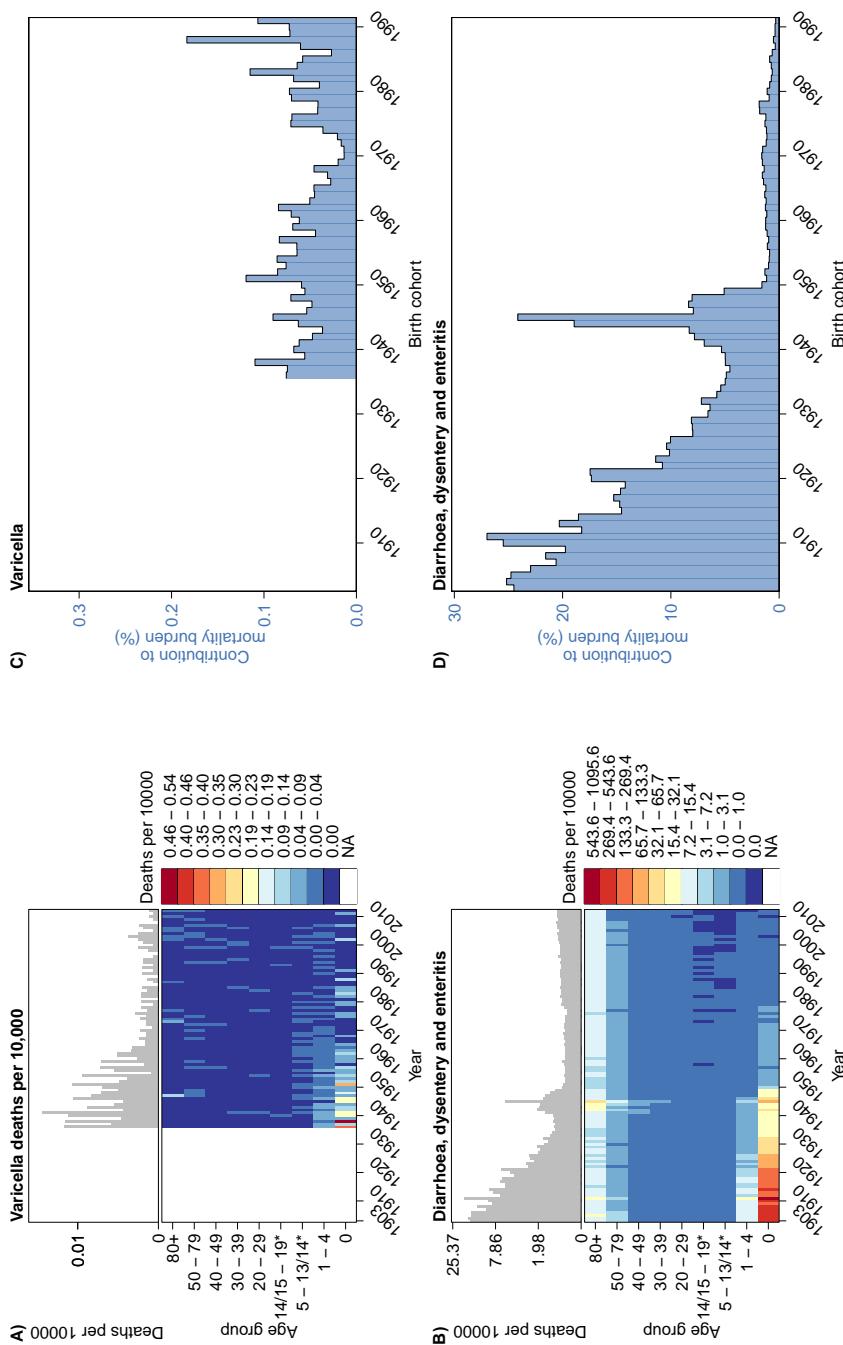
For each birth cohort we estimated the number of life-years lost before age  $\tau$  due to cause  $j$ ,  $L_j(0, \tau)$ , using a cut-off age  $\tau = 20$ . The results are shown in Supplementary Figure 2.5. For each birth cohort we also estimated the cause-specific contribution to this mortality burden,  $C_j(0, \tau)$ . These results are shown in Figure 2.3.

## Reduction in mortality burden due to mass vaccination programmes

In order to assess the order of magnitude of the years of life lost that were averted due to mass vaccinations, we extrapolated the pre-vaccination trends to the vaccination period. We assumed that the observed trends would continue as if vaccination programmes had not been introduced. We excluded mumps and rubella from this analysis as there were very few reported deaths in the pre-vaccination period. The all-cause years of life lost declined exponentially by birth cohort (Figure 2.2), and diphtheria, pertussis, tetanus and poliomyelitis showed a relatively constant contribution to the all-cause years of life lost. To capture this similar rate of decline, we fitted a linear regression model, with a single coefficient “birth cohort”, to the log-transformed cause-specific years of life lost in the pre-vaccination era using the regression coefficient for birth cohort in the all-cause model as coefficient in the cause-specific models (as an offset-term). As the contribution of measles to the all-cause years of life lost declined well before the start of mass vaccination programmes, we estimated the regression coefficient for birth cohort in the measles model separately. We fit each model to the parts of the time series where the contribution to mortality burden was relatively constant: for diphtheria from 1903 to 1930 (excluding the impact of the World War 2), for pertussis from 1903 to 1946, for tetanus from 1903 to 1953, for poliomyelitis from 1920 to 1956, and for measles between 1931 and 1972. We then extrapolated the resulting regression lines from



**Supplementary Figure 2.5: Average years of life lost before the age of 20 per live birth, the Netherlands 1903–1992.** Blue dotted line indicates best fit exponential decline for (A) diphtheria from 1903 to 1930; (B) pertussis from 1903 to 1946; (C) tetanus from 1903 to 1953; (D) poliomyelitis from 1920 to 1956; (E) measles between 1931 and 1972; (F) mumps (no fit); and (G) rubella (no fit). Red line indicates the extrapolation of the best fit into the vaccination period; red band indicates the prediction interval; and the grey area indicates the vaccination period.



**Supplementary Figure 2.6: Mortality rates and the contribution to childhood mortality burden for varicella and diarrhoea, dysentery and enteritis, the Netherlands 1903–2012.** Mortality rates for (A) varicella; and diarrhoea, dysentery and enteritis. Top panel shows the total number of deaths per 10 000 per year, bottom panels show age-specific mortality rates. The contribution (as percentage) to the all-cause childhood mortality burden before the age of 20 for varicella (C), and diarrhoea, dysentery and enteritis (D). \*in 1920 these age-groups changed from 5–13 to 5–14 and from 14–19 changed to 15–19.

the start of their respective mass vaccination programmes up to the cohort born in 1992, and calculated the 95% prediction intervals pertaining to these regression lines (Supplementary Figure 2.5).

The total years of life lost were obtained by multiplying the cohort-specific years of life lost by the birth cohort size and summing over each year of the vaccination period. The number of deaths averted were calculated by dividing the total years of life lost averted by the average years of life lost per death (calculated as the total years of life lost over the entire pre-vaccination period divided by the total number of deaths in that period). The average years of life lost before the age of 20 per death for diphtheria was 13.9 years (2.5%–97.5% percentile range: 9.7, 16.1), for pertussis 18.7 years (2.5%–97.5% percentile range: 18.4, 19.2), for tetanus 15.4 years (2.5%–97.5% percentile range: 11.6, 18.5), for poliomyelitis 11.8 years (2.5%–97.5% percentile range: 2.3, 17.7), and for measles 17.6 years (2.5%–95% percentile range: 16.4, 18.4). Fitting the regression coefficient for birth cohort for each cause of death separately gave similar results (data not shown).

## Migration

To see if migration had any influence on our estimates, we also estimated the years of life lost by cohort corrected for migration. Migration data over the period 1903–2012 were collected from Statistics Netherlands (Statline). For the period 1903–1976 no age-stratified data were available. We used multiple imputation to reconstructed migration by age for this period, using the age-distributions from 1977 to 2012. Migrants were assigned a birth cohort and specific age using the method described above. To obtain estimates corrected for migration we corrected the population at risk for the net-migration in the previous time step at every age for each birth cohort. There was little difference in the estimates of years of life lost with and without migration (Supplementary Figure 2.4).

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## Supplementary information

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# Chapter 3

## **Estimating the population-level effectiveness of vaccination programmes in the Netherlands**

The contents of this chapter have been published in Epidemiology:

**Estimating the population-level effectiveness of vaccination programmes in the Netherlands**  
Maarten van Wijhe, Scott A. McDonald, Hester E. de Melker, Maarten J. Postma, Jacco Wallinga  
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## Abstract

### *Background*

There are few estimates of the effectiveness of long-standing vaccination programmes in high income countries. To fill this gap, we investigate the direct and indirect effectiveness of childhood vaccination programmes on mortality at the population level in the Netherlands.

### *Methods*

We focused on three communicable infectious diseases, diphtheria, pertussis, and poliomyelitis, for which we expect both direct and indirect effects. As a negative control, we used tetanus, a non-communicable infectious disease for which only direct effects are anticipated. Mortality data from 1903–2012 were obtained from Statistics Netherlands. Vaccination coverage data were obtained from various official reports. For the birth cohorts 1903 through 1975, all-cause and cause-specific childhood mortality burden was estimated using restricted mean lifetime survival methods, and a model was used to describe the pre-vaccination decline in burden. By projecting model results into the vaccination era, we obtained the expected burden without vaccination. Programme effectiveness was estimated as the difference between observed and expected mortality burden.

### *Findings*

Each vaccination programme showed a high overall effectiveness, increasing to nearly 100% within ten birth cohorts. For diphtheria, 14.9% [95% uncertainty interval (UI): 12.3%, 17.6%] of mortality burden averted by vaccination was due to indirect protection. For pertussis, this was 32.1% [95% UI: 31.3%, 32.8%]. No indirect effects were observed for poliomyelitis or tetanus with -2.4% [UI: -16.7%, 7.1%] and 0.6% [UI: -17.9%, 10.7%] respectively.

### *Interpretation*

Vaccination programmes for diphtheria and pertussis showed substantial indirect effects, providing evidence for herd protection.

## Introduction

Estimates of the effectiveness of long-standing vaccination programmes provide insight into the value of these programmes to public health (Metcalf et al., 2015). These insights are especially important for policy makers to motivate the continuation of these interventions in this time of increasing vaccine hesitancy (Schuchat and Bell, 2008). Halloran et al. described the overall effectiveness of a vaccination programme as the ratio of the observed disease burden in a population with a vaccination programme, to that in a population without such a programme (Halloran and Struchiner, 1991). Such a measure takes both direct and indirect protection into account. Including indirect protection is important as it is the distinguishing feature of most vaccination programmes (Fine, 1993; Haber, 1997, 1999; Shim and Galvani, 2012; Metcalf et al., 2015). One approach for estimating vaccine programme effectiveness would be to compare the burden in the pre-vaccination era to the burden shortly after the introduction of the programme (Taranger et al., 2001). However, such comparisons for long-standing vaccination programmes typically ignore secular trends in disease burden. Another approach is to construct a so-called counterfactual: the expected situation had the vaccination programme not been introduced. One can then directly compare the observed disease burden (in the actual situation with an implemented vaccination programme) to the expected burden in the same population without a vaccination programme.

Constructing a counterfactual is not straightforward as diverse pre-vaccination dynamics need to be taken into account. This is especially the case for the earlier vaccines, such as diphtheria, pertussis, tetanus, and polio, which were introduced in many high income countries in the mid-20<sup>th</sup> century. Indeed, few studies have focused on the effectiveness of early mass vaccination programmes due to lack of data and proper analysis methods.

Here we examine the population-level overall effectiveness of vaccination programmes on mortality burden, and show that this overall effectiveness can be partitioned into a direct and indirect component. To do so, we make use of data from the Netherlands, where detailed mortality statistics are available from 1903 onwards (Wolleswinkel-van den Bosch et al., 1997; Van Wijhe et al., 2016). In a previous analysis of these data, we showed that the all-cause childhood mortality burden declined

exponentially over the 20<sup>th</sup> century, and that the mortality burden of many vaccine-preventable diseases declined at a similar exponential rate in the pre-vaccination period (Van Wijhe et al., 2016). Besides mortality data, information on vaccination coverage is available since the implementation of mass vaccination programmes in 1953. This makes the Dutch data uniquely equipped for investigating vaccination programme effectiveness.

We pose the following research questions: is there evidence for indirect effects of vaccination programmes on mortality burden, and what is the magnitude of these indirect effects? To address these questions, we constructed counterfactual scenarios (i.e. scenarios in which vaccination programmes were not implemented) using a model to describe trends in the pre-vaccination era, and estimated programme effectiveness with respect to childhood mortality burden in the first two decades following the start of mass vaccination in the 1950s. We quantified the magnitude of direct and indirect effects for three communicable vaccine-preventable diseases (diphtheria, pertussis, and polio), and one non-communicable vaccine-preventable disease (tetanus), which serves as a negative control (Lipsitch et al., 2016).

## Materials and methods

### *Childhood mortality burden*

We used data on vaccination coverage and cause-specific mortality as previously reported in Van Wijhe et al. (2016). Briefly, these data, spanning the period 1903–2012, were obtained from the national census bureau (Statistics Netherlands) and consist of the cause-specific number of deaths from various infectious diseases, including vaccine-preventable diseases. Deaths were stratified by year and age-group (for 1903–1920: <1 year, 1–4, 5–13, 14–19, 20–29, 30–39, 40–49, 50–79 and ≥80 years; for 1930–1940 the same age-groups were available, except that 5–14 and 15–19 replaced 5–13 and 14–19; for 1941–2012, data were available by 5-year age-group, with separate groups for <1 year and ≥80 years). Here we focus on the mortality due to diphtheria, pertussis, tetanus, and polio during the period 1903–1996. Data were available for the entire period, except for poliomyelitis which was included as a cause of death since 1920.

We quantified the childhood mortality burden as years of life lost before the age of 20. Each reported death was randomly assigned a specific age within each

age-group and a birth cohort using multiple imputation methods. Cause-specific mortality burden was then calculated using restricted mean lifetimes survival analysis (Andersen et al., 2013; Andersen, 2013). This method estimates the years of life lost due to a specific cause up to a cut-off age within a competing risks framework. For our analysis we choose a cut-off age of 20 years, as most mortality due to our diseases of interest occurred before that age. Each one-year birth cohort between 1903 and 1975 was followed up to 20 years of age. Cumulative incidence curves for each cause of death were constructed using the Aalen-Johansen estimator, and the corresponding age-specific childhood mortality burden attributable to each cause was calculated from the area under the cumulative incidence curves. For more details on the data preparation and survival analysis, see Supplementary information to Chapters 2 and 3.

### *Vaccination coverage*

Vaccination coverage by birth cohort was obtained from various official reports by the Dutch Health Care Inspectorate (period 1949–1969) and the Dutch National Institute for Public Health and the Environment (period 1970–1975) Van Wijhe et al. (2016). Missing cohorts (1953 for diphtheria, pertussis, and tetanus and 1960–1961 for poliomyelitis) were linearly interpolated from adjacent birth cohorts. As far as data allowed, we used age-specific national vaccination coverage. In the early years of mass vaccination (prior to 1962), registration of vaccination coverage was less stringent and it is unknown how many vaccines each child had received at which age. For this period, vaccination coverage was determined from the number of children that had already been vaccinated at one-year of age, and when entering kindergarten or elementary school. We assumed this calculated coverage represents the coverage at the ages of three months, four years, and six years of age respectively. As coverage metric we used the proportion of children who had received at least one vaccine during their lifetime, and we assumed a 95% vaccine effectiveness against mortality regardless of the number of vaccine doses (Bisgard et al., 2000; Centers for Disease Control and Prevention (CDC), 2015; Plotkin et al., 2013). In Supplementary Figures 3.7 to 3.11 we present sensitivity analyses exploring the impact of this choice on our results.

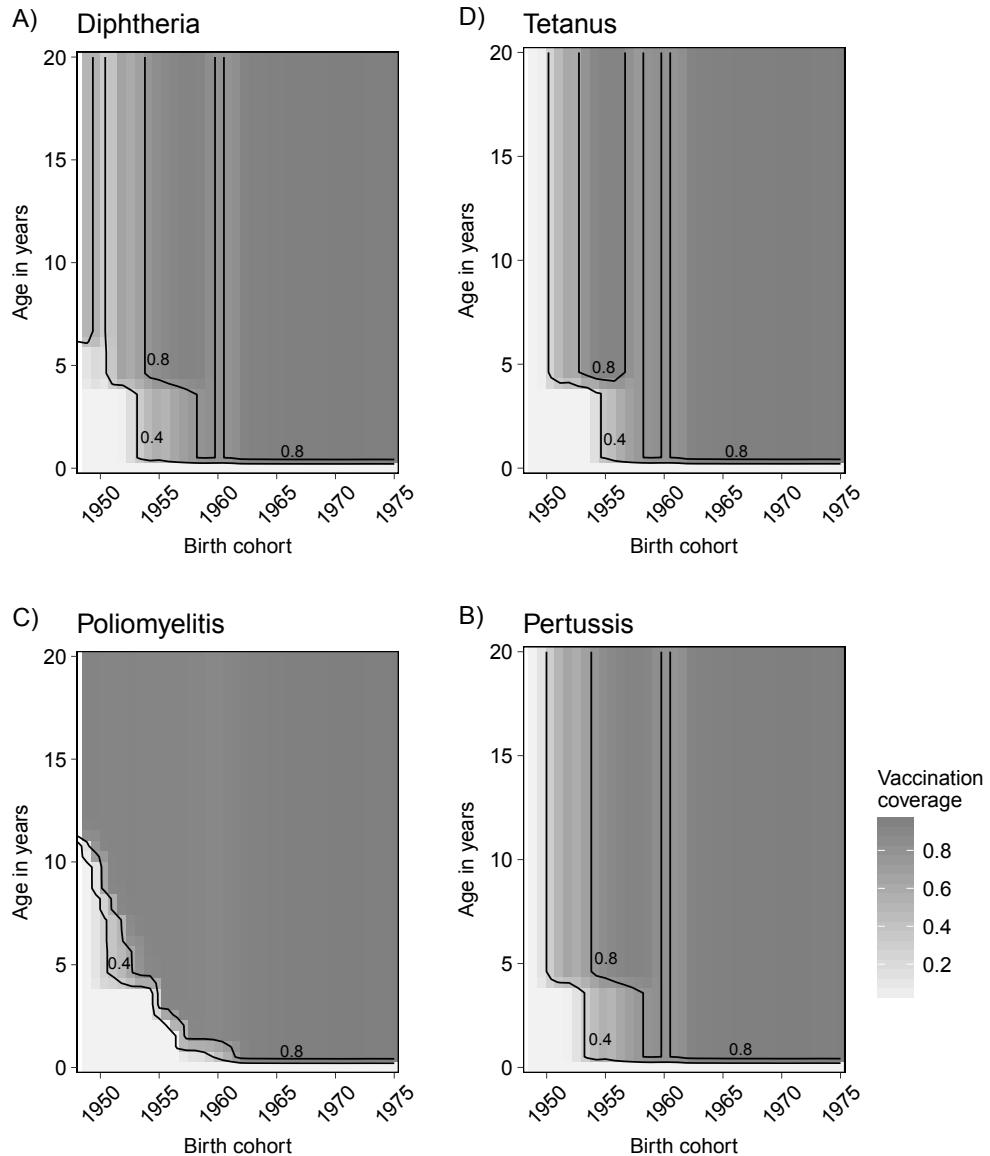
Mass vaccination with the diphtheria toxoid vaccine started in 1953 in the Netherlands. Prior to the start of the mass vaccination programme against diphtheria in

1953, vaccination was already ongoing and mainly administered at 4–14 years of age (Hoogendoorn, 1954). In 1954 the diphtheria vaccine was combined with vaccines against pertussis and tetanus (DTP). Polio vaccination followed in 1957 with a staggered catch-up campaign of all children born since 1945. The polio vaccine was combined with DTP in 1962 (DTP-IPV) and was offered at 3, 4, 5, and 11 months. Starting in 1965, DT-IPV re-vaccination was offered at 4 and 9 years of age. Figure 3.1 shows the vaccination by age (percentage of children vaccinated at least once) for each birth cohort since 1945. National vaccination coverage increased rapidly for each of these mass vaccination programmes and reached 90% or higher within a decade after each vaccine introduction.

### *Modeling overview*

We estimated the overall effectiveness of a vaccination programme on mortality, by comparing the observed childhood mortality burden with the expected mortality burden had the vaccination programme not been introduced, i.e. the counterfactual. To capture overall pre-vaccination trend in childhood mortality burden, the counterfactual model was based on two components: the exponential decline in all-cause childhood mortality burden and contribution of a specific disease to this all-cause childhood mortality burden. The exponential decline was modelled by fitting a linear regression model to log-transformed pre-vaccination all-cause childhood mortality burden over birth cohorts 1903–1940. The cause-specific contributions to the all-cause childhood mortality burden were calculated for each age separately as the ratio of the age- and cause-specific mortality burden to the total all-cause childhood mortality burden. We assumed the age-specific contributions were constant in the pre-vaccination period (see Supplementary Figures 3.3 to 3.6 where we show there were no relevant age trends in the pre-vaccination period). To reflect uncertainty, the age-specific contributions of each vaccine-preventable disease were re-sampled from the pre-vaccination period with a higher sampling weight for more recent birth cohorts. The distribution of the rate of exponential decline was obtained using the semi-parametric bootstrap by resampling residuals (see Supplementary Figure 3.1 for the distributions of parameters used in constructing the counterfactual).

We extrapolated the counterfactual model from birth cohort 1948 up to and including the 1975 birth cohort. The overall vaccination programme effectiveness in terms of mortality burden averted was defined as the ratio of observed and counterfactual



**Figure 3.1: Vaccination coverage by age and birth cohort, the Netherlands, 1948–1975.** Vaccination coverage in the Netherlands for (A) diphtheria; (B) pertussis; (C) poliomyelitis; and (D) tetanus. Vaccination coverage is defined as the proportion of children having received at least one dose during their lifetime.

childhood mortality burden. By incorporating vaccination coverage and vaccine effectiveness in the estimation, direct and indirect effects of vaccination programmes can be distinguished. The direct effects of vaccination were defined as the product of the vaccination coverage and vaccine effectiveness (i.e. the expected proportion of children at a specific age who are immunised). Indirect effects were defined as the remaining childhood mortality burden averted after subtracting direct effects. The model is described in more detail in the following sections.

### *Counterfactual model*

We constructed the counterfactual by projecting the exponential decline forward from the start of mass vaccination programmes, assuming the rate of decline in childhood mortality burden,  $r$ , and the relative contribution of cause  $i$  to the all-cause childhood mortality burden at age  $a$ ,  $p_{i,a}$ , remained constant at their pre-vaccination values (see Supplementary information to Chapter 3). In the following we indicate the counterfactual by superscript  $c = 0$ , and the observed situation by  $c = 1$ . Let  $y_0$  be the all-cause childhood mortality burden in birth cohort  $t_0$ , then for each birth cohort with birth year  $t$ , the age-specific counterfactual childhood mortality burden was calculated as:

$$Y_{i,a}^{c=0}(t) = p_{i,a} Y_0 e^{-r(t-t_0)} \quad (3.1)$$

Both  $y_0$  and  $r$  were estimated by fitting a linear regression model to the log-transformed all-cause childhood mortality burden in the pre-vaccination period 1903–1940 (i.e. the intercept and the regression coefficient for birth cohort). The distributions of  $r$  and  $y_0$  were obtained using semi-parametric bootstrap by re-sampling residuals. We assumed  $p_{i,a}$  remained constant in the counterfactual situation, assuming the hypothesis that the relative contribution did not change had vaccination programmes not been introduced. We estimated  $p_{i,a}$  for each birth cohort in the pre-vaccination period by dividing the age-specific years of life lost due to cause  $i$  by the all-cause years of life lost. To reflect uncertainty,  $p_{i,a}$  was re-sampled from the distributions in the pre-vaccination periods with a higher weight for more recent birth cohorts, 1903–1930 for diphtheria; 1903–1940 for pertussis; 1920–1940 for poliomyelitis; and 1903–1940 for tetanus (we excluded World War 2).

### *Overall, direct, and indirect programme effectiveness*

The overall effectiveness of a vaccination programme for cause  $i$  in birth cohort  $t$  up to age  $\tau$  can be defined as the ratio of the observed mortality burden,  $Y_{i,a}^{c=1}(t)$  and the expected mortality burden in the counterfactual,  $Y_{i,a}^{c=0}(t)$ , (Halloran et al., 1997):

$$E_i(t) = \frac{\sum_{a=1}^{\tau} [Y_{i,a}^{c=0}(t) - Y_{i,a}^{c=1}(t)]}{\sum_{a=1}^{\tau} Y_{i,a}^{c=0}(t)} \quad (3.2)$$

The overall programme effectiveness can also be partitioned into the direct and indirect programme effectiveness:  $E_{i,a}(t) = E_{i,a}^{\text{direct}}(t) + E_{i,a}^{\text{indirect}}(t)$ . The expected direct programme effectiveness is the product of the vaccine effectiveness,  $v$ , and the vaccination coverage at age  $a$ ,  $C_a(t)$ , such that  $E_{i,a}^{\text{direct}(t)} = vC_a(t)$ . The indirect programme effectiveness, defined here as any reduction in mortality burden not explained by direct protection (in other words, the difference between the observed and expected mortality burden if only direct protection would play a role), can then be calculated as:

$$E_i^{\text{indirect}}(t) = \frac{\sum_{a=1}^{\tau} [(1 - vC_a(t))Y_{i,a}^{c=0}(t) - Y_{i,a}^{c=1}(t)]}{\sum_{a=1}^{\tau} Y_{i,a}^{c=0}(t)} \quad (3.3)$$

We calculated the indirect effects of vaccination programmes using a vaccine effectiveness against mortality of 95% for all vaccines. Varying the vaccine effectiveness had little qualitative and quantitative impact on our results other than increasing or decreasing the estimated indirect effects slightly (Supplementary Figures 3.7 to 3.11). Uncertainty intervals reflect the uncertainty inherent in the imputation of single-year ages from age-group specific data (Figure 3.2, shaded areas), combined with the resampling of pre-vaccination period  $p_{i,a}$ , and bootstraps of  $r$  and  $y_0$ , yielding 95% uncertainty intervals. All analyses were performed in R statistical programming environment, version 3.2.0 (R Foundation for Statistical Computing, Vienna, Austria).

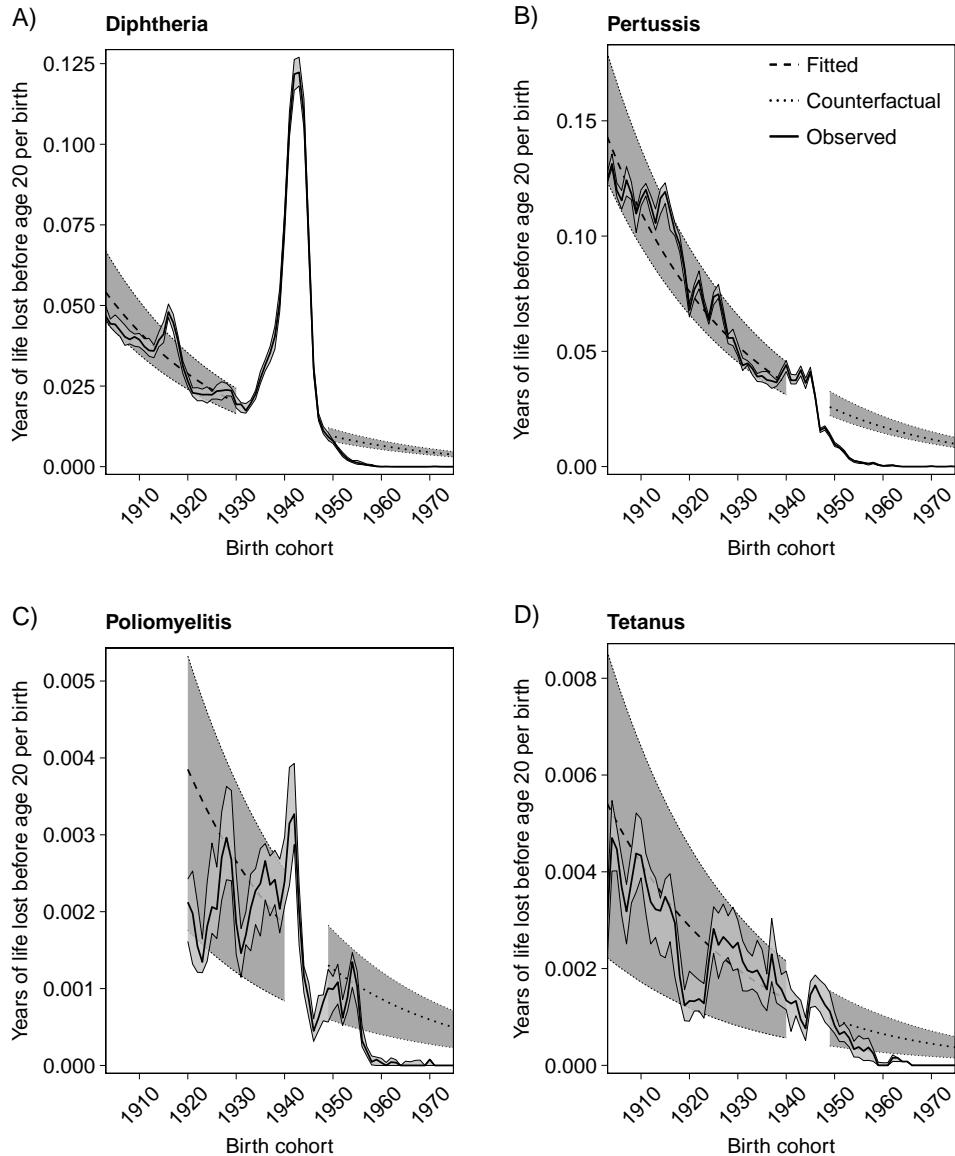
## Results

Figure 3.2 shows the observed childhood mortality burden along with model fit to the pre-vaccination period and the estimated counterfactual (the situation had

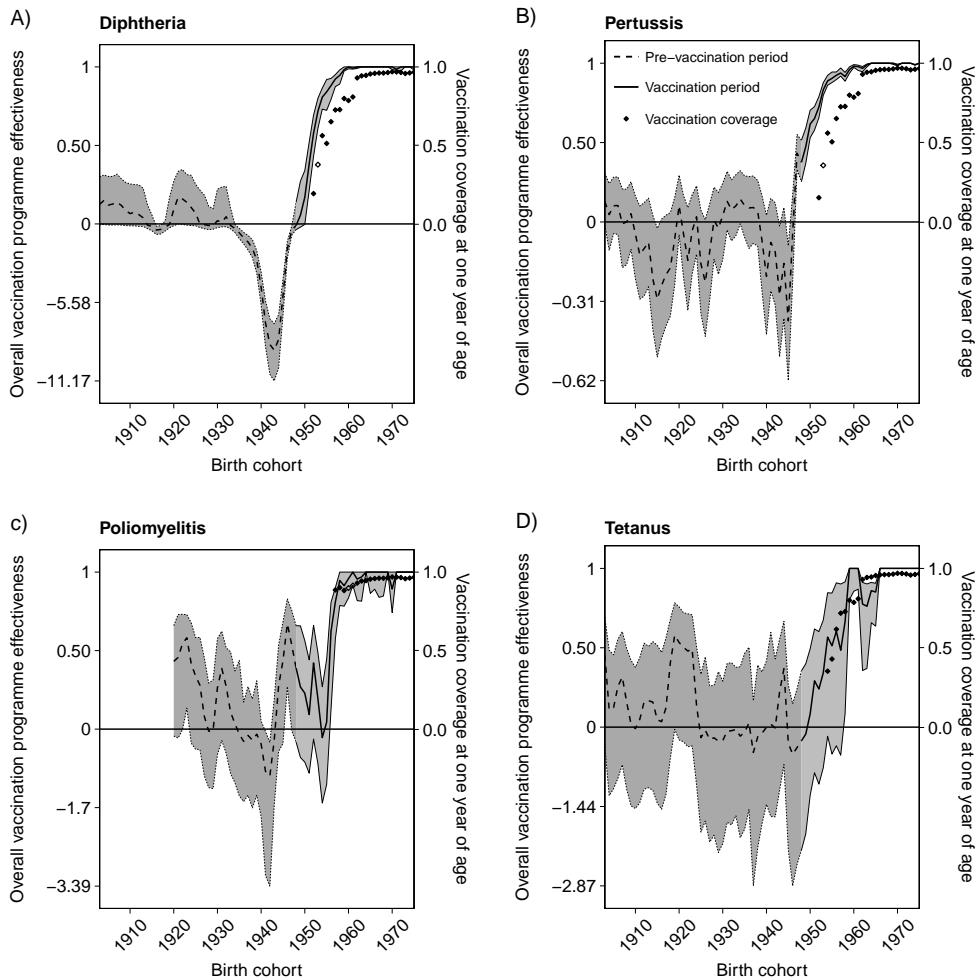
vaccination programmes not been introduced). Our model adequately captures the observed pre-vaccination childhood mortality burden. Upon the start of mass vaccination, the counterfactual and observed childhood mortality burdens rapidly diverge. For pertussis (and to a lesser extent poliomyelitis) this divergence starts several cohorts prior to the start of mass vaccination. Because we look at birth cohorts, this early divergence may be due to indirect effects from vaccination of later birth cohorts or due to unregistered vaccination. This would result in a decline in mortality burden before the start of mass vaccination.

The overall effectiveness of vaccination programmes against diphtheria, pertussis, poliomyelitis, and tetanus increased rapidly after the start of mass vaccinations and reached near 100% within ten birth cohorts for each vaccine-preventable disease (Figure 3.3).

Figure 3.4 shows the estimated direct and indirect vaccination programme effectiveness in the Netherlands up to and including the 1975 cohort for diphtheria, pertussis, poliomyelitis, and tetanus. Mainly diphtheria and pertussis showed signs of indirect protection, with a maximum estimated indirect effect of 0.25 [95% uncertainty interval (UI): 0.24, 0.25] in birth cohort 1960 for diphtheria, and 0.62 [UI: 0.54, 0.69] in birth cohort 1951 for pertussis. Over time, as the proportion of children that got vaccinated increased and the direct programme effectiveness increased, the indirect programme effectiveness for diphtheria and pertussis diminished. We expected to see indirect effects for poliomyelitis, but there was no clear evidence of indirect effects as in most birth cohorts the uncertainty intervals are broad and overlap with zero. No indirect effects were observed for tetanus, which is to be expected as it is not a communicable disease. By birth cohort 1965 almost no mortality burden was observed due to pertussis, diphtheria, poliomyelitis, or tetanus and the indirect programme effectiveness is reduced to the complement of the direct programme effectiveness (Equation (3.3)); hence the small, positive value seen in all plots between the 1965 and 1975 birth cohorts.



**Figure 3.2: Observed and estimated childhood mortality burden per live birth, the Netherlands, 1903–1975.** The observed (solid), fitted (dashed), and estimated counterfactual (dotted) (Equation (3.1)) years of life lost before the age of 20 per live birth by birth cohort in the Netherlands for (A) diphtheria; (B) pertussis; (C) poliomyelitis; and (D) tetanus. Lines indicate medians and area's indicate 95% uncertainty intervals.



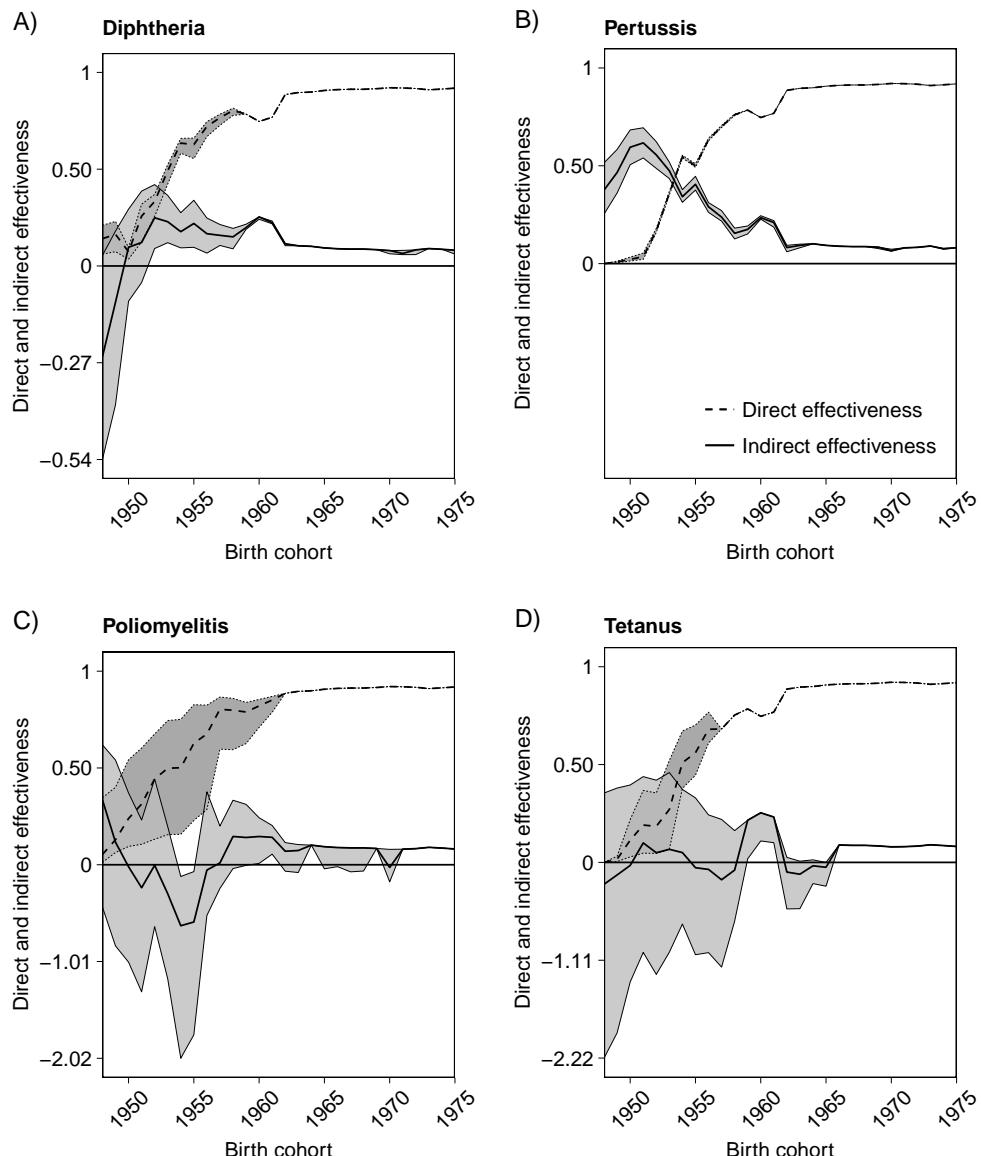
**Figure 3.3: Overall vaccination programme effectiveness and vaccination coverage, the Netherlands, 1903–1975.** Overall vaccination programme effectiveness and vaccination coverage in the Netherlands for (A) diphtheria; (B) pertussis; (C) poliomyelitis; and (D) tetanus. Lines indicate medians and areas indicate 95% uncertainty intervals for the pre-vaccination period (dashed) and the vaccination period (solid). Overall programme effectiveness is defined as the ratio of averted childhood mortality burden to the expected childhood mortality burden had vaccination programmes not been introduced (Equation (3.2)). The dashed line represents the same calculation carried over to the pre-vaccination as a control. Vaccination coverage at one year of age is indicated by the diamond symbols, where open symbols represent interpolated data points. Here we assume a vaccine effectiveness against mortality of 95%.

Overall, since birth cohort 1948 and up to the 1975 birth cohort, 14.9% [95% UI: 12.3%, 17.6%] of all childhood mortality burden averted due to diphtheria vaccination was due to indirect protection (Figure 3.4 and Supplementary Figure 3.2, which shows the averted mortality burden due to indirect effects). For pertussis 32.1% [95% UI: 31.3%, 32.8%] was due to indirect protection. For poliomyelitis and tetanus this was -2.4% [95% UI: -16.7%, 7.1%] and 0.6% [95% UI: -17.9%, 10.7%] respectively.

## Discussion

According to our analysis, there are substantial indirect effects of mass vaccination against diphtheria and pertussis on childhood mortality burden, and programme effectiveness was considerably higher than would be expected based on direct effects of vaccination alone. These indirect effects were especially high at the start of mass vaccination when vaccine coverage was still low; up to 25% of the averted diphtheria mortality burden was due to indirect effects and up to 62% for pertussis. These results provide evidence for herd protection, of which the impact seems to be highest in the early years of vaccination programmes when vaccination coverages (and direct effects) were still relatively low.

We did not observe indirect effects due to vaccination against poliomyelitis. This was unexpected and may be due to the low number of deaths observed or due to the regular epidemics in the pre-vaccination period, which increased the uncertainty in our analysis. The staggered catch-up campaign of all children born since 1945 initiated in 1957, together with the broad age-distribution of deaths due to poliomyelitis, further increased the width of the uncertainty intervals for both direct and indirect programme effectiveness. Although we did estimate a high overall effectiveness of vaccination programmes (Figure 3.3) our method may not be sensitive enough to detect indirect effects for poliomyelitis. It is likely that any indirect effects are more apparent in morbidity data than mortality. Here we restricted our analysis to mortality data, as these detailed data have been systematically collected for long time periods. Similarly, indirect effects for pertussis and diphtheria, although present in mortality statistics, may be more pronounced in morbidity data.



**Figure 3.4: Direct and indirect vaccination programme effectiveness, the Netherlands, 1948–1975.** Direct (dashed) and indirect (solid) effectiveness of vaccination programmes in the Netherlands, for (A) diphtheria; (B) pertussis; (C) poliomyelitis; and (D) tetanus. Lines indicate medians and area's 95% uncertainty intervals. Direct and indirect programme effectiveness sum to the overall programme effectiveness. Here we assume a vaccine effectiveness against mortality of 95%.

We included tetanus, a non-communicable vaccine-preventable disease, as a negative control for which we expect no indirect protection; indeed, we observed no indirect effects. To further check our calculation, we verified that the overall programme effectiveness (Equation (3.2)) over the pre-vaccination period was zero (Figure 3.3). If our model performs well, the ‘overall programme effectiveness’ in the pre-vaccination period should fluctuate around the null and rapidly increase from the start of mass vaccination. This was the case for each vaccine-preventable disease in our study period (a decline can be seen for diphtheria during the World War 2 when large epidemics swept across Europe (Stuart, 1945)). This finding, together with the near-zero estimate of indirect protection for the tetanus vaccination programme, gives credence to our methodology.

There are several limitations and possible biases to our approach. First of all, our estimated counterfactual may be overestimated due to other, unaccounted for, factors unrelated to vaccination that also impact upon childhood mortality burden, most notably the increasing use of antibiotics around the time mass vaccination programmes started. The impact of antibiotics is partially taken into account by the exponential decline in the all-cause childhood mortality burden, but may still show residual impact. This would lead to an overestimation of our indirect effects. To investigate the potential impact of antibiotics on our results, we performed additional analyses (see Supplementary information to Chapter 3 for details on the sensitivity analysis) in which we assume that antibiotics reduce the mortality burden in the counterfactual either by a constant, or by increasing the rate of exponential decline. These analyses indicated that our results are sensitive to the influence of antibiotics, specifically if they influence mortality burden by increasing the exponential decline. However, even at a moderately high impact of antibiotics, indirect effects are still present for pertussis and diphtheria. These effects decrease rapidly as the effect of antibiotics increases. Although our results are influenced by the potential reduction in mortality burden due to antibiotics (and other prevention measures than vaccination), if their impact is limited, indirect effects remain apparent, especially at lower levels of vaccination coverage.

Second, we assumed that the contributions of vaccine-preventable diseases to the total mortality burden remained constant in the counterfactual. This is a reasonable assumption for most vaccine-preventable diseases, given their small and relatively constant contributions to the total mortality burden in the pre-vaccination period

(Van Wijhe et al., 2016). The constancy assumption is also attractive as one would expect the cause-specific mortality burden to decline at a similar rate to the total mortality burden. In additional analyses we tested whether there were any age-specific trends in the pre-vaccination period (Supplementary Figures 3.3 to 3.6). We did not find relevant trends in the pre-vaccination period; however, any effects of existing trends would be overwhelmed by the existing uncertainty in the analysis. Our assumption of a constant contribution from all vaccine-preventable diseases to the counterfactual seems justified, and allows us to restrict the model to the decline in all-cause mortality, obviating the need to construct multiple disease-specific models.

Third, we assumed the exponential decline in the pre-vaccination period would hold subsequent to the start of mass vaccination. Exponential declines in (childhood) mortality rates throughout the 20<sup>th</sup> century have been observed in many high income countries besides the Netherlands (Tulapurkar et al., 2000). For our time-frame of interest—the period directly following the introduction of mass vaccinations—it is unlikely that the trends in the counterfactual would look radically different than those in the pre-vaccination period, as these have been stable for the entire pre-vaccination period.

Another factor that may have biased our results is the uncertainty in registered vaccination coverage. Registration of vaccination coverage improved over time, and starting 1962, detailed records are available. In the early years of mass vaccination, registration of vaccination status was often incomplete, and before the implementation of nationwide mass vaccination programmes there may have been substantial unregistered vaccination taking place (Hoogendoorn, 1954). Our vaccination coverage data may thus underestimate actual coverage. In addition, it is unclear how many children and at what age children were vaccinated; a substantial number of vaccines may have been given to children who were already immune due to natural infection. Our assumed vaccine effectiveness of 95% may therefore be unrealistic in the early part of the vaccination period. Decreasing vaccine effectiveness slightly increased the indirect effects and increasing vaccine effectiveness slightly decreased the indirect effects (Supplementary Figures 3.8 to 3.11). The interplay of these factors makes it difficult to determine if the vaccination coverage—and in extension the proportion immunised and our estimated indirect effects—is biased and in which direction.

This research focused on the population-wide direct and indirect effectiveness of vaccination programmes on mortality in the Netherlands. Indirect protection is a well-established phenomenon in infectious disease epidemiology (Fine, 1993). However, a quantitative estimate of the magnitude of indirect protection compared with direct protection has been lacking for the older vaccination programmes, and specifically the literature on the population effectiveness of vaccination programmes using population-wide surveillance data is deficient (Breiman et al., 2004). Other studies looking into the population effectiveness of vaccination programmes have mainly focused on contemporary vaccines such as meningococcal serogroup C conjugate vaccines (Ramsay et al., 2003; Trotter et al., 2004; Bijlsma et al., 2014), multivalent pneumococcal conjugate vaccines (Grijalva and Griffin, 2008; Jokinen et al., 2015), rotavirus vaccines (Panozzo et al., 2014; Pollard et al., 2015), *Haemophilus influenzae* serotype b conjugate vaccines (Morris et al., 2008; O'Loughlin et al., 2010), and influenza vaccines (Baguelin et al., 2013). Our research provides a quantitative insight into the population direct and indirect effectiveness of older vaccination programmes using already existing data sources.

Future research should focus on the effectiveness of vaccination programmes on morbidity by including hospitalisation or notification data. This is especially important for diseases such as poliomyelitis for which programme effectiveness may not be well estimated using mortality data, and for which a major share of disease burden is attributed to long-term sequelae. Alternatively, our methods could be verified using mortality data from other countries. In addition, spatial heterogeneity should be accounted for, as vaccination coverage shows substantial geographical differences (Van Lier et al., 2016). This heterogeneity may provide more insight into the indirect effects of vaccination when comparing high- and low-coverage regions.

Our analysis shows that the indirect effects of the early vaccination programmes for diphtheria and pertussis are pronounced even in mortality statistics, indicating that for a proper appreciation of the impact of vaccination programmes and the monitoring of their effectiveness, both direct and indirect effects should be taken into account.

## Contributors

MvW obtained, extracted, and analysed the data, searched the scientific literature, and wrote the first draft of the manuscript. MvW, SAM, HEdM, MJP, and JW designed the study and revised the manuscript. MJP and JW conceived the project.

## Declaration of interests

MJP received grants and honoraria from various pharmaceutical companies, including GlaxoSmithKline, Pfizer, and Sanofi Pasteur MSD, who are potentially interested in the subject matter of this Article.

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## **Supplementary information to Chapter 3**

## Survival analysis

### *Data preparation*

Annual mortality data were available from 1903 through 1975 except for poliomyelitis, which was included as a cause of death since 1920. Deaths were stratified by year and age-group (for 1903–1920: <1 year, 1–4, 5–13, 14–19, 20–29, 30–39, 40–49, 50–79 and  $\geq 80$  years; for 1930–1940 the same age-groups were available, except that 5–14 and 15–19 replaced 5–13 and 14–19; for 1941–2012, data were available by 5-year age-group, with separate groups for <1 year and  $\geq 80$  years). See also Chapter 2.

In order to estimate the years of life lost in each birth cohort, we needed to reconstruct the age-specific mortality by birth cohort. First, each death within an age-group was assigned a one-year age-group assuming deaths occurred uniform within an age-group. For age-group 1–4 years we assumed more deaths occurred at age one and two than at ages three and four. This ratio was estimated based on age-specific population estimates. Second, we assigned each death within a one-year age-group to a birth cohort by using Lexis-diagrams. See the overview by Carstensen 2007 for an explanation of Lexis-diagrams and how one could use them. In short, each one-year age-group is composed of two cohorts: those born in year  $i \backslash a - 1$  and those born in the year  $i - a$ , where  $i$  is the registration year and  $a$  is the age at death. These cohorts are divided along the diagonal, thus creating an upper and lower Lexis-triangle (see also Chapter 2, Supplementary Figure 2.2). If deaths occur uniform over a Lexis-triangle, the average age at death in the upper Lexis-triangle is  $a + \frac{2}{3}$  while the average age in the lower triangle is  $a + \frac{1}{3}$ . Deaths are assigned to one of the two possible birth cohort at random, with a probability proportional to the size of the birth cohorts. We assumed that all deaths occur at age  $a + \frac{2}{3}$  for the upper Lexis-triangle and at age  $a + \frac{1}{3}$  for the lower Lexis-triangle. To rule out chance effects in the process of assigning deaths to birth cohorts, we repeated this imputation step ten times.

### *Calculating the years of life lost*

To estimate the cause-specific years of life lost for each birth cohort (see above) we estimated the number of life-years lost for each cause of death using the restricted mean lifetime method (Andersen, 2013; Andersen et al., 2013). Consider  $k$  mutually exclusive causes of death with event times  $0 < t_a < \dots < t_m < \tau$ . We estimated

the overall survival probability  $S$  using the Kaplan-Meier estimator for survival up to age  $t_a$ :

$$\hat{S}(t_a) = \prod_{t_a \leq t} \frac{n_{a-1} - \sum_{j=1}^k d_{a,j}}{n_{a-1}} \quad (3.4)$$

Here  $d_{a,j}$  is the number of deaths due to cause  $j = 1, \dots, k$ , at age  $t_a$ , and  $n_a$  is the total number of individuals at risk at age  $t_a$ . The expected lifetime up to age  $\tau$ , is:

$$E_\tau = \int_0^\tau \hat{S}(t) dt \quad (3.5)$$

The cause-specific cumulative incidence as estimated by the Aalen-Johansen estimator,  $\hat{F}_j$ , is:

$$\hat{F}_j(t) = \sum_{t_a \leq t} \hat{S}(t_{a-1}) \frac{d_{a,j}}{n_a} \quad (3.6)$$

$\hat{F}_j(t)$  is the probability at birth of dying from cause  $j$  before age  $\tau$ . The expected number of years of life lost before age  $\tau$  due to cause  $j$ ,  $L_j$ , is:

$$L_j(0, \tau) = \int_0^\tau \hat{F}_j(t) dt \quad (3.7)$$

We estimated the number of years of life lost before age  $\tau$  due diphtheria, pertussis, poliomyelitis, tetanus, and all other causes of death. These results are shown in Figure 3.2 and Supplementary Figure 3.1.

### *Age-specific contribution*

The cause- and age-specific years of life lost add up to the total years of life lost. We can therefore calculate the contribution of mortality burden at each particular age to the total mortality burden up to age  $\tau$ :

$$C_j(a) = \frac{\hat{F}_j(a)}{\sum_{j=1}^k L_j(0, \tau)} \quad (3.8)$$

For each birth cohort we estimate the number of life-years lost up to the age  $\tau$  for each age,  $a$ , using a cut-off age  $\tau = 20$  (Supplementary Figure 3.1).

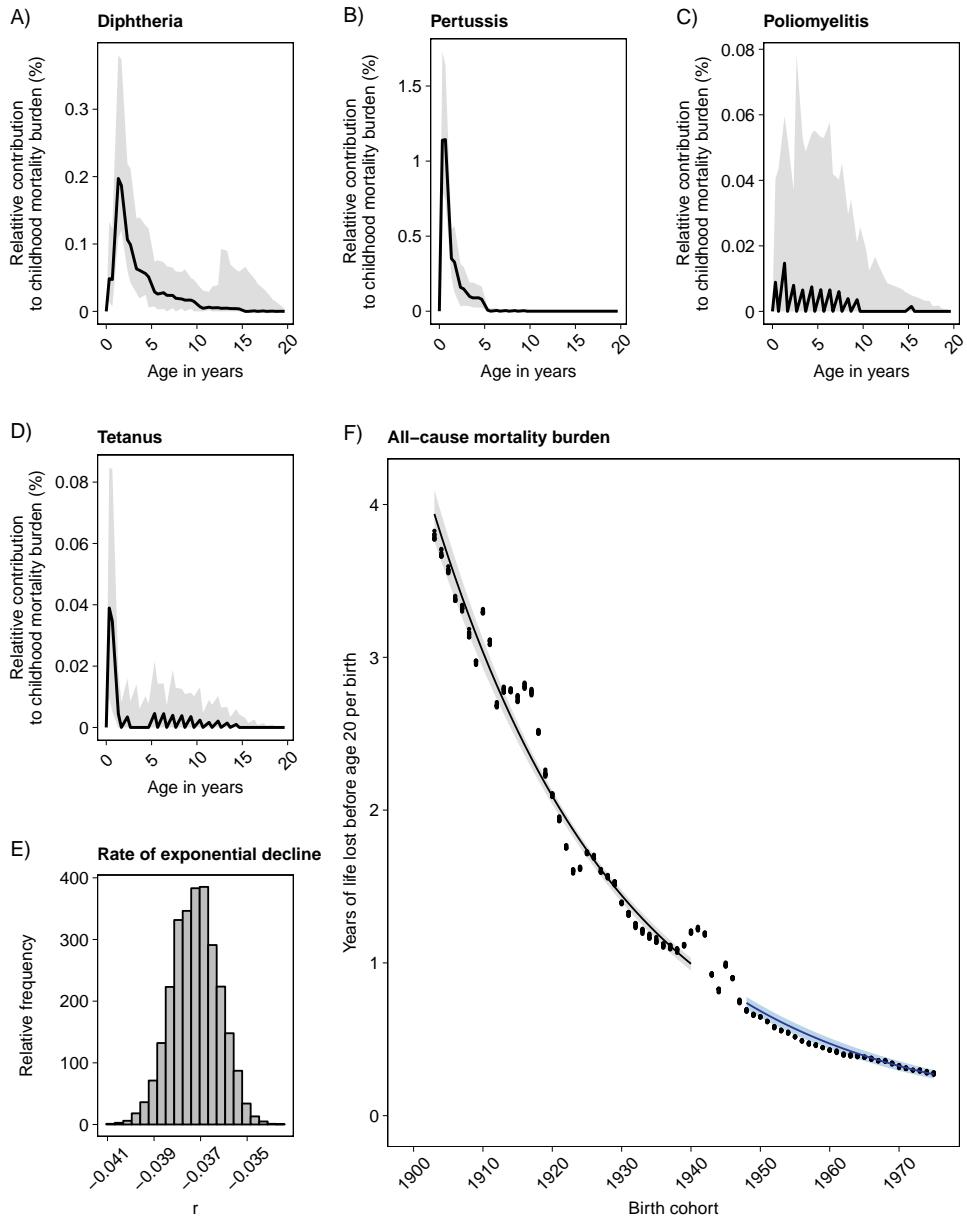
### *Pre-vaccination contribution*

In our analysis we assumed that the pre-vaccination contributions to the all-cause childhood mortality burden were constant. To ascertain whether this is the case, we tested for any linear trends using OLS linear regression analysis of the form  $C_j(a) = b_0 + b_1x$  with  $x$  the year of birth for the cohort, and tested whether the regression coefficient  $b_1$  differed from zero ( $\alpha = 0.05$ ). As our results are realisations of ten imputations, we used corrected degrees of freedom with  $df = (n - 1)l$  where  $l$  is the length of the time series and  $n$  is the number of imputations. The results are presented in Supplementary Figures 3.3 to 3.6. This analysis was performed only for those ages where the contribution was non-zero in at least half of the time series.

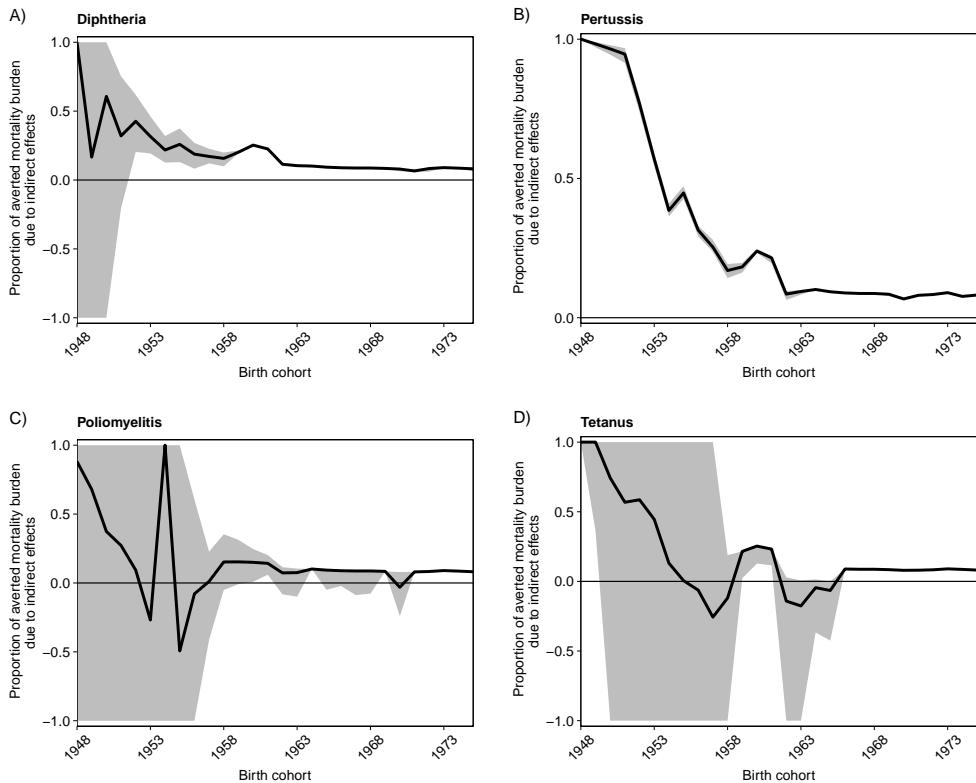
For each cause of death, there were several statistically significant linear trends in the pre-vaccination period. The largest value for the regression coefficient was found for pertussis for the youngest age-group (<1 year): 0.00003 per cohort. This would result in an increase in contribution less than 0.1% over a period of 30 birth cohorts. We concluded that existing trends in the contribution to childhood mortality are negligibly small relative to the uncertainty of the contribution. We re-sampled age-distributions from the pre-vaccination period with higher weights for more recent cohorts (Supplementary Figure 3.1). We also checked whether the total contribution (aggregated over all ages) in the pre-vaccination period showed any linear trends. This analysis did not reveal linear trends that were sufficiently large to impact our findings.

### *Impact of antibiotics*

The use of antibiotics increased around the same period that vaccination efforts intensified in the Netherlands. Use of sulphanilamide started in 1936, penicillin in 1944 (with limited supplies until 1947), streptomycin in 1947, and chloramphenicol



**Supplementary Figure 3.1: Distributions of parameters used in constructing the counterfactual.** Age distribution of the relative contribution,  $p_{I,a}$ , to the total childhood mortality burden in the pre-vaccination period for (A) diphtheria for cohorts 1903–1930; (B) pertussis 1903–1940; (C) poliomyelitis 1920–1940; and (D) tetanus 1903–1940. Solid black lines indicate the median and grey areas indicate the upper and lower 95% quantiles. (E) Density distribution of the semi-parametric bootstrap samples of the exponential decline,  $r$ , in the all-cause childhood mortality burden estimated by re-sampling the residuals from the linear regression over birth cohort 1903–1940 (mean  $R^2 > 0.97$ ;  $sd = 0.006$ ). (F) All-cause childhood mortality burden over birth cohorts 1903–1975 (dots) with exponential fit (solid black line) over birth cohort 1903–1940. The counterfactual over birth cohorts 1948–1975 is represented by the solid line with 95% uncertainty interval (blue area).



**Supplementary Figure 3.2: Childhood mortality burden averted due to indirect effects of vaccination, the Netherlands, 1948–1975.** Childhood mortality burden averted due to indirect effects of vaccination programmes in the Netherlands for (A) diphtheria; (B) pertussis; (C) poliomyelitis; and (D) tetanus. Solid lines indicate the median and the coloured area's indicated 95% uncertainty intervals. Here we assume a vaccine effectiveness against mortality of 95%.

in 1949. There was no central registration of drugs sales in the Netherlands, so no information is available on the actual use of antibiotics. In a study on the impact of antibiotic use on cause-specific mortality, a higher rate of decline was observed for various causes of death after 1947. For certain causes of death like pneumonia, the rate increased from 4% to 5%, for upper respiratory infections from 0% to 8%, and for acute bronchitis from 7% to 9% (Mackenbach and Looman, 1988). As antibiotics may thus have a substantial impact on mortality due to infectious diseases, mainly by preventing mortality due to co-infections, we performed a sensitivity analysis

investigating the potential impact of the increased use of antibiotics. For simplicity, we assumed that antibiotics were introduced in 1947.

### Sensitivity analysis

Antibiotics may have an immediate impact on childhood mortality burden, or they may modulate the rate of exponential decline in childhood mortality burden. To reflect the way antibiotics could influence childhood mortality burden, we modify Equation (3.1) in the main text, as follows:

$$Y_{i,a}^{c=0}(t) = sp_{i,a}Y_0e^{-zr(t-t_0)} \quad (3.9)$$

Where  $s$  is the immediate reduction in childhood mortality burden and  $z$  is the increase in exponential decline following the increased availability of antibiotics in 1947. We performed a sensitivity analysis and calculated the total childhood mortality burden due to indirect effects from 1948 through 1975 for varying high and low values of  $s$  and  $z$ . Here,  $s$  takes the values 0.95 and 0.75, equivalent to a reduction of our estimated counterfactual mortality burden by 5% and 25% respectively, and  $z$  take the values 1.05, 1.2, and 2, equivalent to an increase in the rate of decline by 5%, 20%, and 100%. In the base case  $s$  and  $z$  are set to 1. In addition to the impact of antibiotics, we also investigate the impact of a reduced or increased vaccine effectiveness,  $v$  (Equation (3.3)). In the base case  $v$  is set to 95%; here we also set  $v$  to 75% and 99%.

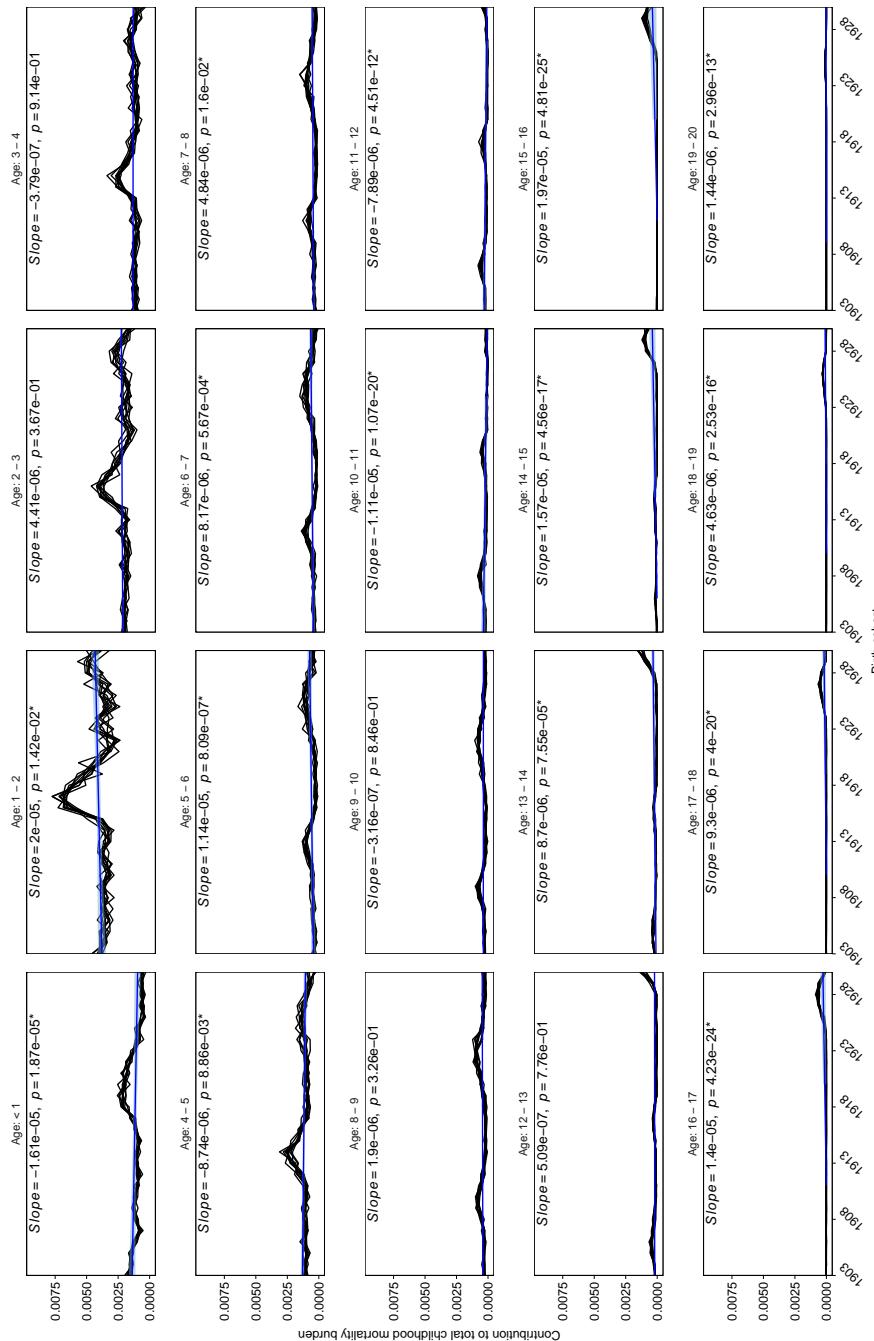
### Results

The results of this sensitivity analysis are presented in Supplementary Figures 3.7 to 3.9. As expected, if we assume that a constant proportion of the expected mortality burden is averted due to the use of antibiotics, the expected indirect effects are significantly decreased. Similarly, if we assume that after 1947 the rate of exponential decline in mortality burden increases, the indirect effects decline, although to a lesser extent. However, indirect effects can still be observed for pertussis and diphtheria. The indirect effects for diphtheria only disappear with a high impact of antibiotics ( $s = 0.75$  and  $z = 2$ ). Assuming lower vaccine effectiveness increases the indirect effects, and higher vaccine effectiveness decreases indirect effects. Supplementary

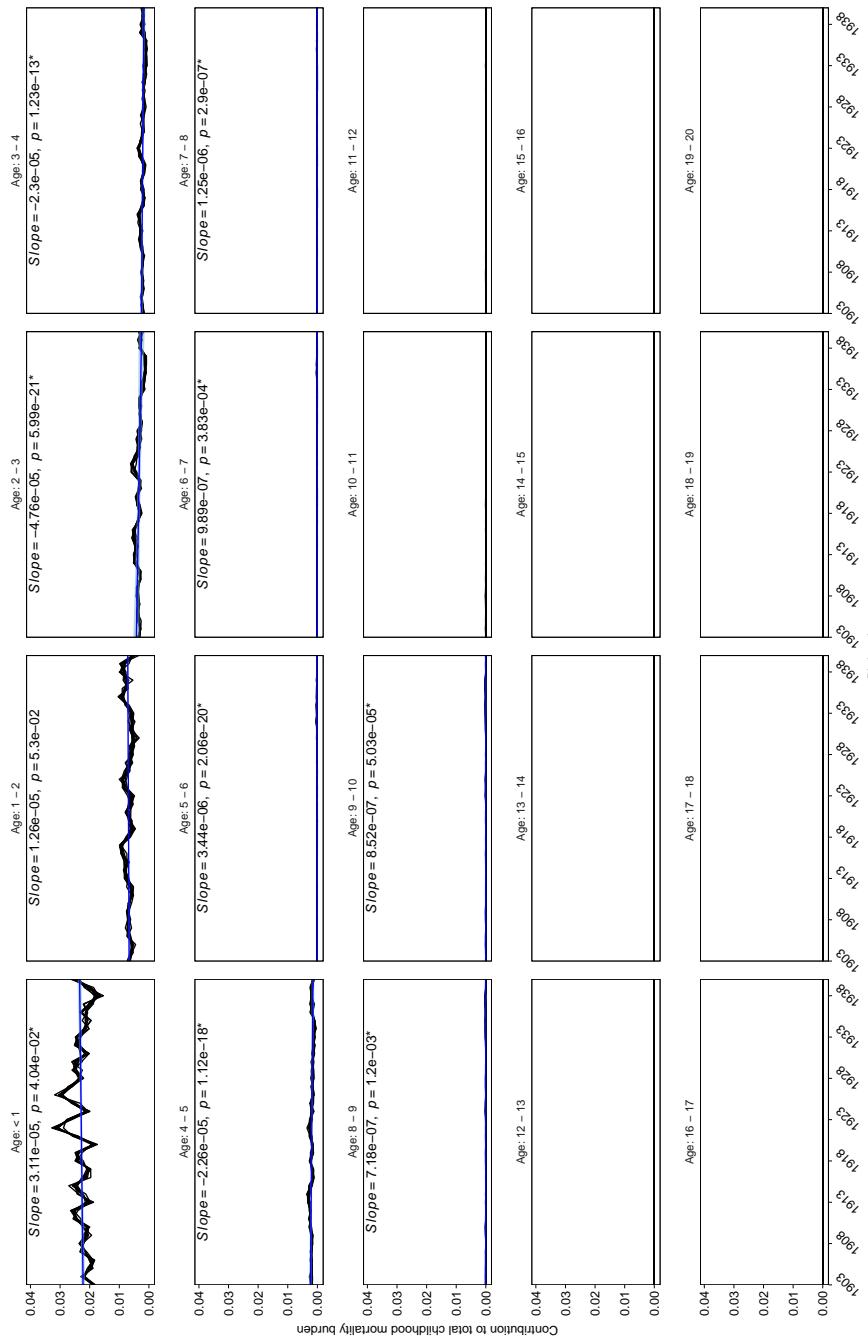
Figures 3.10 and 3.11 presents the indirect and direct effects when assuming a vaccine effectiveness of 75% and 99% respectively (similar to Figure 3.4). With an effectiveness of 75% the indirect effects for each vaccine-preventable disease are more apparent, including poliomyelitis. With an effectiveness of 99% the indirect effects are lower but still present for both pertussis and diphtheria. From these analyses we conclude that indirect effects can still be observed even if there is a substantial impact of antibiotics on the expected mortality burden and when vaccine effectiveness is near 100%. Indirect effects for diphtheria disappear only at the extremes. In other cases the general conclusions remain the same.

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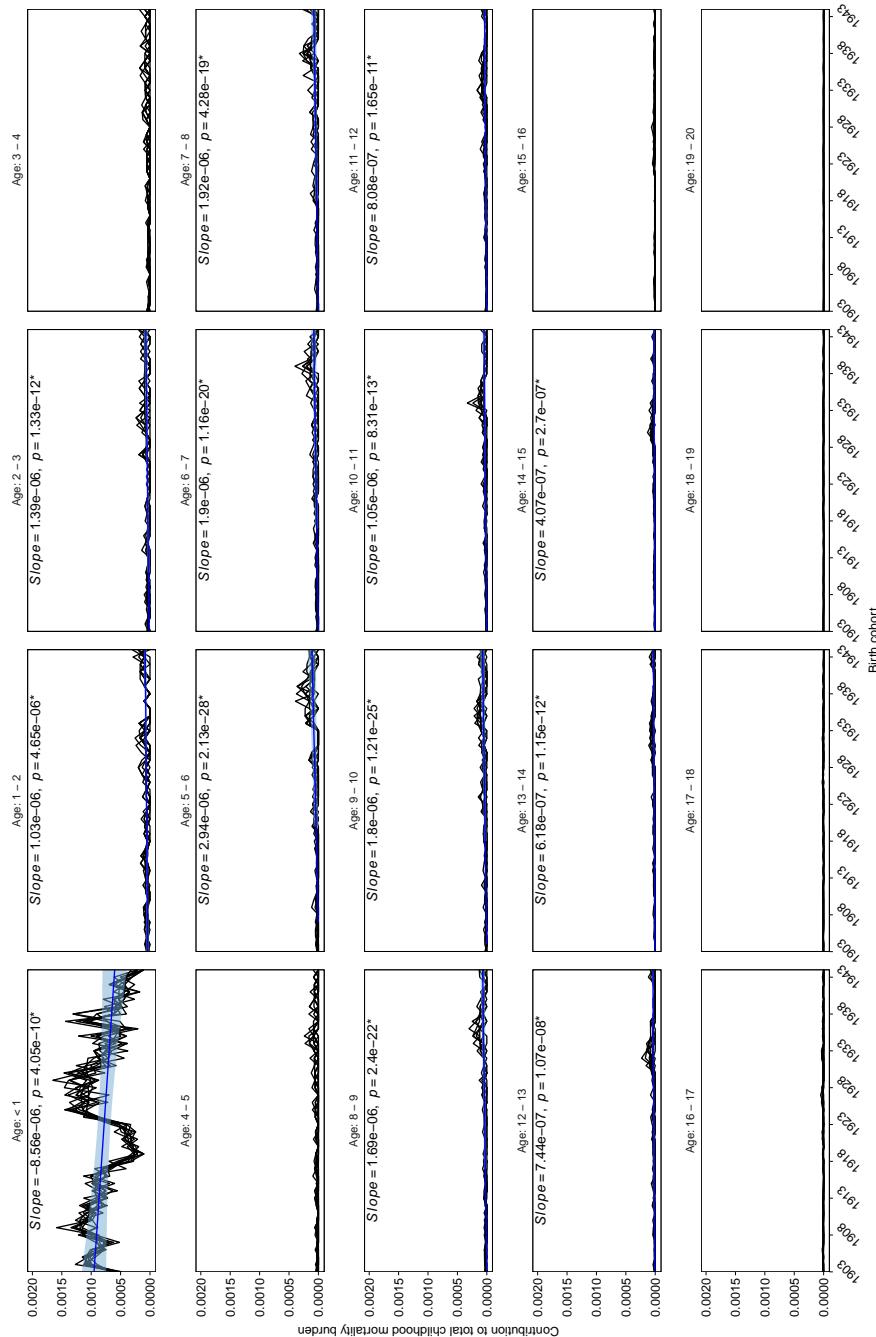
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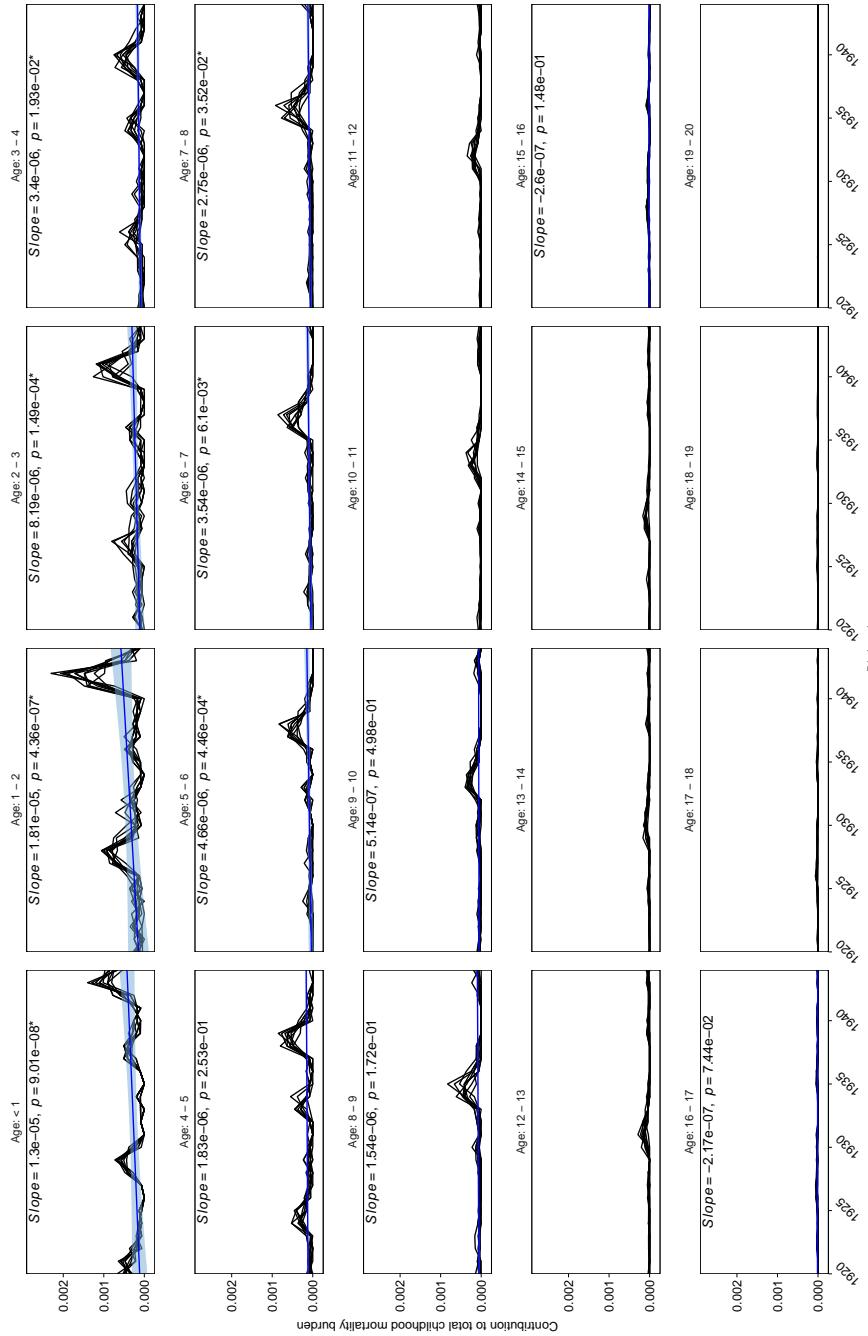
**Supplementary Figure 3.3: Proportion all-cause childhood mortality burden due to diphtheria by birth cohort and by age, the Netherlands, 1903–1930.** Solid black lines represent the realisation of ten imputations. Solid blue line represents the fitted values of the OLS linear regression. Blue area's represent the 95% confidence interval of the mean. coefficients for slope, and its corresponding corrected SE and p-value are depicted at the top of each panel.



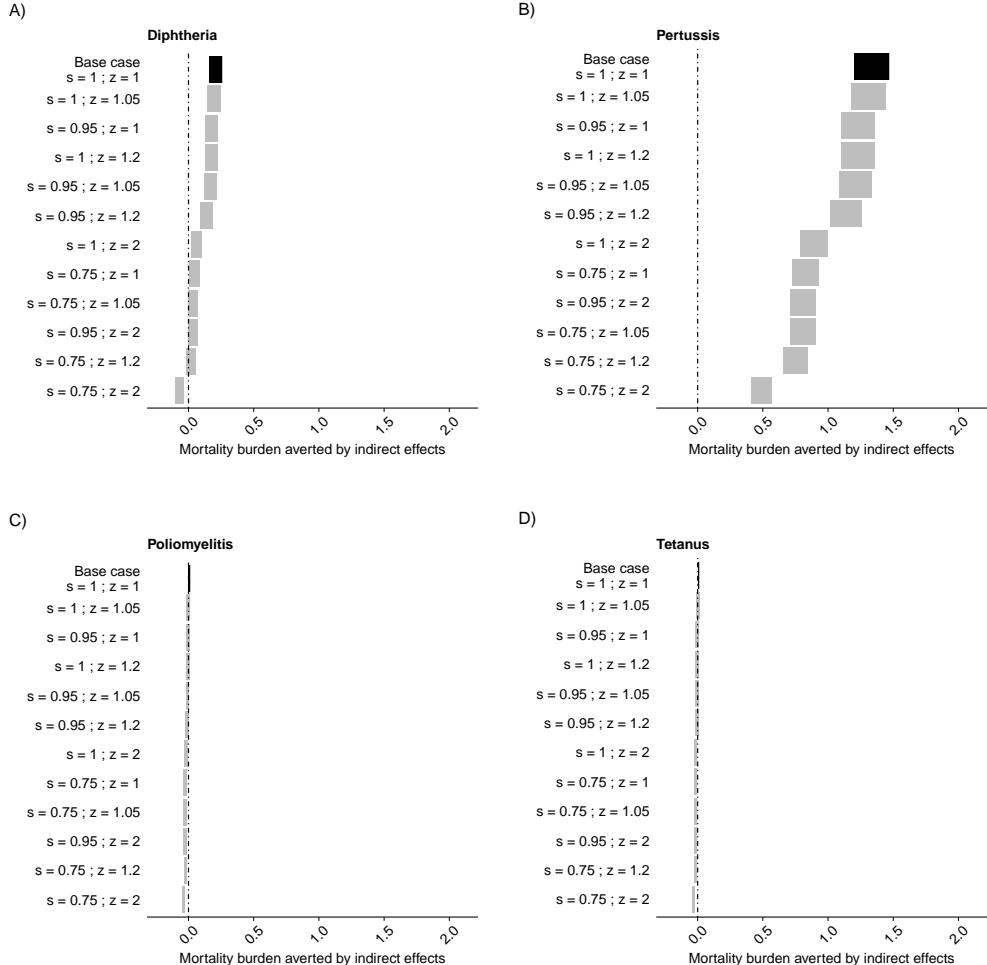
**Supplementary Figure 3.4: Proportion all-cause childhood mortality burden due to pertussis by birth cohort and by age, the Netherlands, 1903–940.** Solid black lines represent the realisation of ten imputations. Solid blue line represents the fitted values of the OLS linear regression. Blue area's represent the 95% confidence interval of the mean. Coefficient for slope, and its corresponding corrected SE and p-value are depicted at the top of each panel.



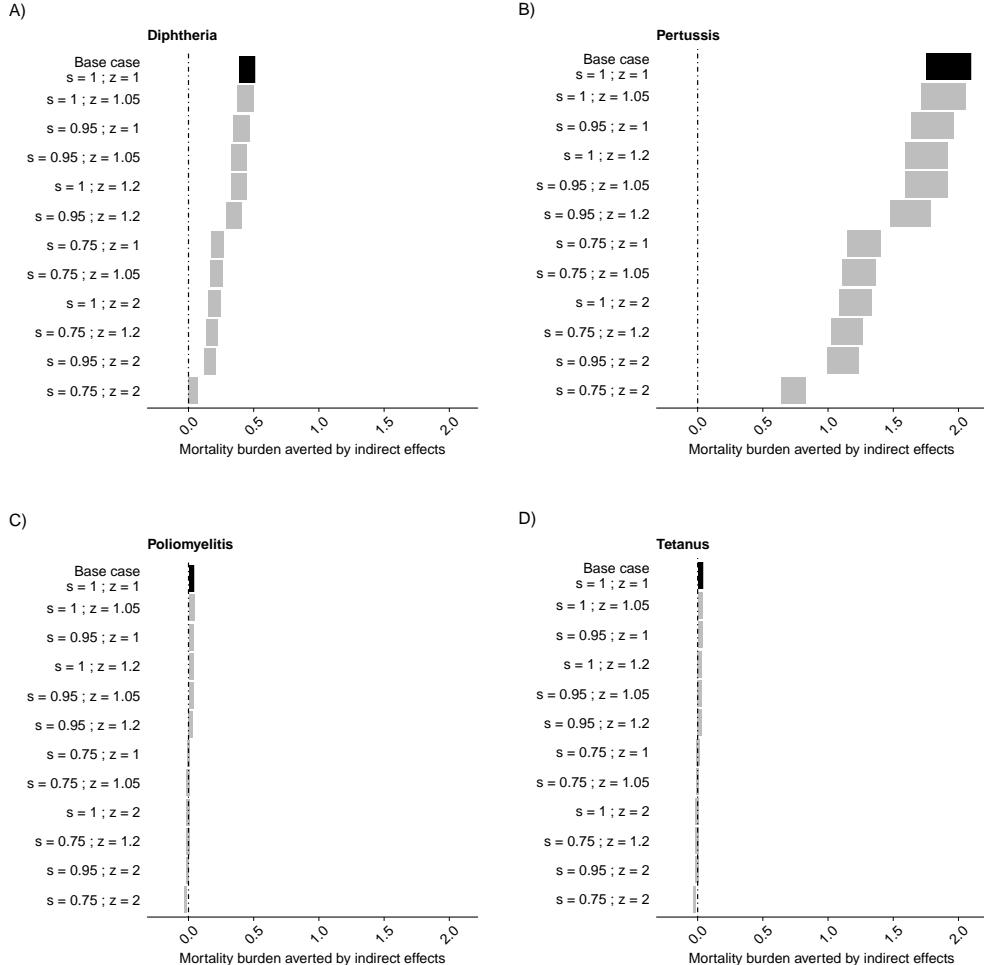
**Supplementary Figure 3.5: Proportion all-cause childhood mortality burden due to poliomyelitis stratified by birth cohort and by age, the Netherlands, 1920–1944.** Solid black lines represent the realisation of ten imputations. Solid blue line represents the fitted values of the OLS linear regression. Blue area's represent the 95% confidence interval of the mean. Coefficient for slope, and its corresponding corrected SE and p-value are depicted at the top of each panel.



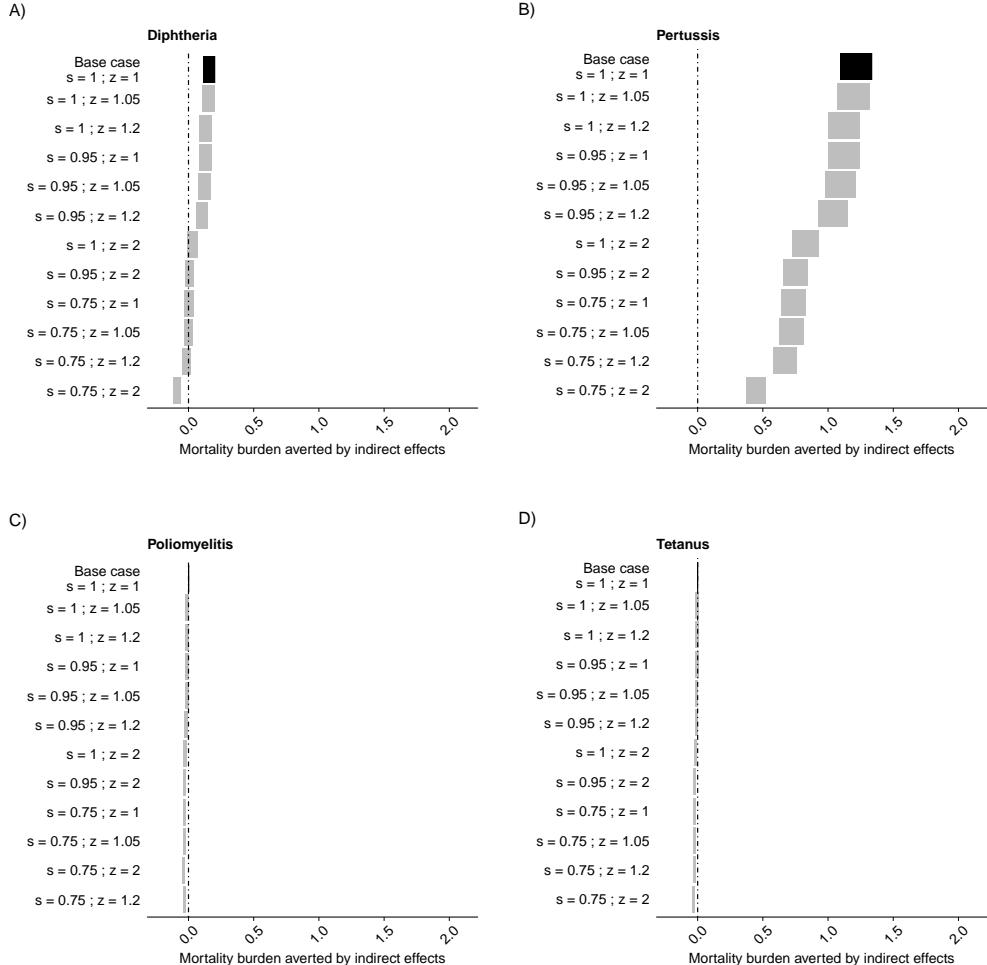
**Supplementary Figure 3.6: Proportion all-cause childhood mortality burden due to tetanus stratified by birth cohort and by age, the Netherlands, 1903–1944.** Solid black lines represent the realisation of ten imputations. Solid blue line represents the fitted values of the OLS linear regression. Blue area's represent the 95% confidence interval of the mean. Coefficient for slope, and its corresponding corrected SE and p-value are depicted at the top of each panel.



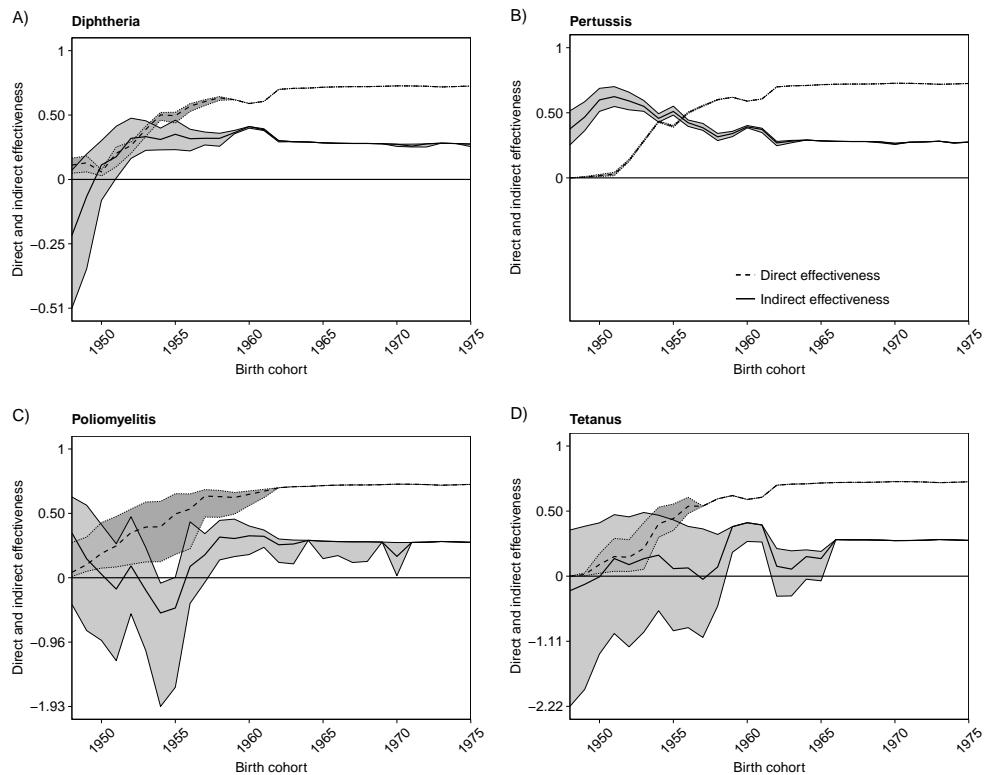
**Supplementary Figure 3.7: Sensitivity analysis for total indirect effects with vaccine effectiveness at 95%.** Sensitivity analysis over birth cohorts 1948–1975 when taking antibiotics into account for (A) diphtheria; (B) pertussis; (C) poliomyelitis; and (D) tetanus. We assume antibiotics lower the estimated counterfactual burden by a constant proportion  $s$  and increase the rate of exponential decline by a factor  $z$ . Bars represent the 95% uncertainty interval. The base case ( $s = 1, z = 1$ ) is represented by black bar. Here we assumed a vaccine effectiveness against mortality of 95%.



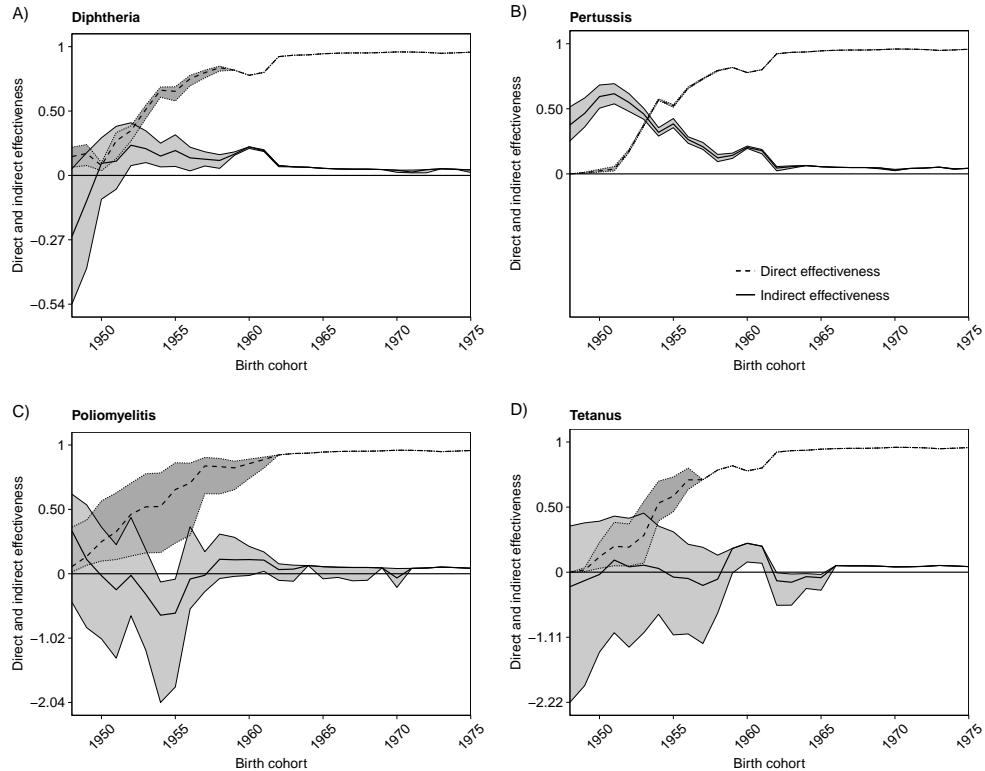
**Supplementary Figure 3.8: Sensitivity analysis for total indirect effects with vaccine effectiveness at 75%.** Sensitivity analysis over birth cohorts 1948–1975 when taking antibiotics into account for (A) diphtheria; (B) pertussis; (C) poliomyelitis; and (D) tetanus. We assume antibiotics lower the estimated counterfactual burden by a constant proportion  $s$  and increase the rate of exponential decline by a factor  $z$ . Bars represent the 95% uncertainty interval. The base case ( $s = 1, z = 1$ ) is represented by black bar. Here we assumed a vaccine effectiveness against mortality of 75%.



**Supplementary Figure 3.9: Sensitivity analysis for total indirect effects with vaccine effectiveness at 99%.** Sensitivity analysis over birth cohorts 1948–1975 when taking antibiotics into account for (A) diphtheria; (B) pertussis; (C) poliomyelitis; and (D) tetanus. We assume antibiotics lower the estimated counterfactual burden by a constant proportion  $s$  and increase the rate of exponential decline by a factor  $z$ . Bars represent the 95% uncertainty interval. The base case ( $s = 1, z = 1$ ) is represented by black bar. Here we assumed a vaccine effectiveness against mortality of 99%.



**Supplementary Figure 3.10: Direct and indirect vaccination programme effectiveness, the Netherlands, 1948–1975.** Direct (dashed) and indirect (solid) effectiveness of vaccination programmes in the Netherlands, for (A) diphtheria; (B) pertussis; (C) poliomyelitis; and (D) tetanus. Lines indicate medians and area's 95% uncertainty intervals. Note that direct and indirect programme effectiveness sum to the overall programme effectiveness. Here we assume a vaccine effectiveness against mortality of 75%.



**Supplementary Figure 3.11: Direct and indirect vaccination programme effectiveness, the Netherlands, 1948–1975.** Direct (dashed) and indirect (solid) effectiveness of vaccination programmes in the Netherlands, for (A) diphtheria; (B) pertussis; (C) poliomyelitis; and (D) tetanus. Lines indicate medians and area's 95% uncertainty intervals. Note that direct and indirect programme effectiveness sum to the overall programme effectiveness. Here we assume a vaccine effectiveness against mortality of 99%.



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## **Chapter 4**

### **Years of life lost due to influenza-attributable mortality in older adults in the Netherlands: a competing risks approach**

The contents of this chapter have been published in the American Journal of Epidemiology:

**Years of life lost due to influenza-attributable mortality in older adults in the Netherlands:  
a competing risks approach**

Scott A. McDonald, Maarten van Wijhe, Liselotte van Asten, Wim van der Hoek, Jacco Wallinga  
American Journal of Epidemiology, Feb 6 2018

## Abstract

We estimated the influenza mortality burden in adults 60 years of age and older in the Netherlands in terms of years of life lost, taking into account competing mortality risks. Weekly laboratory surveillance data for influenza and other respiratory pathogens and weekly extreme temperature served as covariates in Poisson regression models fitted to weekly age-group specific mortality data for the period 1999/2000 through 2012/2013. Burden for age-groups 60–64 through 85–89 years was computed as years of life lost before age 90 (YLL90) using restricted mean lifetimes survival analysis and accounting for competing risks. Influenza-attributable mortality burden was greatest for persons aged 80–84 years, at 914 YLL90 per 100 000 persons [95% uncertainty interval (UI): 867, 963], followed by 85–89 years (787 YLL90 per 100 000; 95% UI: 741, 834). Ignoring competing mortality risks in the computation of influenza-attributable YLL90 would lead to substantial over-estimation of burden, from 3.5% for 60–64 years to 82% for persons aged 80–89 years at death. Failure to account for competing mortality risks has implications for accuracy of disease burden estimates, especially among persons aged 80 years and older. As the mortality burden borne by the elderly is notably high, prevention initiatives may benefit from being redesigned to more effectively prevent infection in the oldest age-groups.

## Introduction

Worldwide, infection with the influenza virus is responsible for considerable illness, hospitalisation, and mortality, especially among older adults and elderly persons (Simonsen et al., 2005, 2007), whose immune response is diminished compared with younger adults (Bernstein et al., 1999; Parodi et al., 2011). The mortality burden attributed to influenza virus infection is difficult to quantify from vital statistics data, because (i) death certificates often do not list influenza as an underlying or contributing cause when death is due to subsequent bacterial infection; (ii) influenza infection may serve to worsen existing chronic respiratory or circulatory disease so the chronic condition is entered as the underlying cause on the death certificate (Glezen et al., 2000); and (iii) laboratory confirmation of influenza infection is seldom done prior to death.

Given the public health significance of the large number of deaths presumed to be caused by influenza (e.g., influenza was estimated to have caused 11% of all deaths occurring in persons aged 65 years or older during the 2000–2009 influenza seasons in France (Bonmarin et al., 2015)) but are not registered as such (Sprenger et al., 1993), statistical modelling methods have been used to infer the true number of influenza-associated deaths from all-cause or cause-specific mortality data. Numerous studies have adopted an ecological approach to the estimation problem, by fitting generalised linear models that specify time series of positive tests for influenza and other co-circulating respiratory pathogens from virological surveillance systems as covariates, possibly adjusting for systematic seasonal variation and other factors, to estimate the time series of influenza-attributable mortality (Pitman et al., 2007; Goldstein et al., 2012; Van Asten et al., 2012; Charu et al., 2013; Green et al., 2013; Hardelid et al., 2013; Kessaram et al., 2015; Matias et al., 2016; Schanzer et al., 2013). Such methods exploit the seasonal patterns in pathogen activity, and are successful in that—given the modelling assumptions—the under-estimation in influenza mortality burden, if relying only on cause-of-death coding, can be overcome.

Although mortality is an important epidemiological indicator of the impact of an infectious disease in a population, the years of life lost (YLL) measure provides a more precise quantitative measurement of the burden of influenza (and other diseases) among the elderly than mortality incidence; with YLL, age at death (and

so the expected remaining healthy life-years) is incorporated. The more prematurely that death occurs, the higher the burden. Particularly for the elderly population, for whom the prevalence of chronic multi-morbidity is high (Marengoni et al., 2008; Van den Akker et al., 1998), it is vital to compute YLL for influenza treating death from other causes as competing risks. The implicit assumption when calculating YLL associated with a single cause of death such as influenza is that removing this cause of death from the population would have no effect on the probability of dying from other causes. However, this independence assumption is in general not viable (Allignol et al., 2011; Andersen et al., 2012). To avoid over-estimation of population-level total mortality burden, the YLL associated with each possible cause of death should sum exactly to the YLL calculated on the basis of all-cause mortality, and appropriate estimation methods are therefore required to ensure that cause-specific YLL correctly acknowledges competing mortality risks (Lai and Hardy, 1999; Andersen, 2013; Van Wijhe et al., 2016). The relevance of this issue grows with the probability of death from other causes; i.e., with increasing age.

Thus, the principal objective of the current study is to estimate the weekly and annual mortality burden from influenza in adults 60 years of age and older in terms of YLL, taking into account competing mortality risks. Our secondary objective was to compare this measure to 'standard' YLL, which ignores competing mortality risks.

## Methods

### *Study design and period*

To model influenza-attributable deaths we considered mortality from any cause as the primary dependent variable. We also considered two other, more specific, cause-of-death categories: circulatory/respiratory causes and respiratory-only causes (Charu et al., 2013; Van den Wijngaard et al., 2010). The latter was defined as cause of death codes J00–J99 (ICD-10) or 460–519 (ICD-9), and the former was supplemented with the circulatory disease codes I00–I99 (ICD-10) and 390–459 (ICD-9).

The study period was defined as the 1999/2000 through 2012/2013 influenza seasons. Because death certificate coding practice changed from the beginning of 2013, leading to notable changes in distribution over certain cause-of-death code categories, for the two more specific mortality outcomes the study period was defined to end one season earlier, at 2011/2012.

### *Data sources*

All deaths in the Netherlands are registered with Statistics Netherlands. Weekly mortality data with primary cause of death information, stratified by 5-year age-group (60–64 through 80–84 years, and additionally 85+ years), were obtained for the period 1999–2013. Causes of death were coded using ICD-10. Because influenza circulates mainly during the winter months, seasons were defined as week 40 of a given year through week 39 of the following year.

Routine weekly surveillance data on positive laboratory results for a range of respiratory pathogens have been reported since 1989. Between 17 and 21 laboratories in the Netherlands submit weekly reports to a centralised database (the Weekly Surveillance System of the Dutch Working Group on Clinical Virology (Dutch Working Group on Clinical Virology, 2016)). From these data, we counted PCR-confirmed positive samples for the following viral and bacterial agents: influenza A/B, respiratory syncytial virus, rhinovirus, parainfluenza, and *Mycoplasma pneumoniae*. We extracted data from 1999/2000 through 2012/2013, with seasons defined similarly as for mortality.

### *Poisson regression modelling of influenza-attributable mortality*

In common with the general ecological modelling approach used in previous research (Pitman et al., 2007; Goldstein et al., 2012; Van Asten et al., 2012; Charu et al., 2013; Green et al., 2013; Hardelid et al., 2013; Schanzer et al., 2013; Kessaram et al., 2015; Matias et al., 2016), we assumed that seasonal variability in mortality can be explained, in part, by temporal variation in the reporting incidence of various respiratory pathogens. The proportion of mortality attributable to influenza can then be determined after adjusting for the co-circulation of other pathogens and other factors via linear regression techniques. We assumed additivity in this relationship for simplicity (i.e., a given death cannot be caused by more than one respiratory pathogen).

Separate Poisson regression models, with identity link function to enable an additive interpretation of model coefficients, were fitted to the weekly mortality data for each age-group. Laboratory virological surveillance data were not available stratified by age; therefore each age-group specific regression model adjusted for the total positive samples reported for the pathogen.

*Covariates.* Besides influenza A (coded using separate variables for each season, to capture seasonal variation in severity), the candidate pathogen covariates considered were influenza B, respiratory syncytial virus, rhinovirus, *Mycoplasma pneumoniae*, and parainfluenza. Temperature is known to be an important correlate of mortality (Kunst et al., 1993; Donaldson and Keatinge, 2002), although the relationship is not straightforward, as it may be that only periods of extreme cold and heat influence the risk of death. We defined two covariates for temperature extremes, by first calculating the average weekly temperatures ( $T$ , in degrees Celsius) from daily temperatures recorded at the de Bilt (centrally located in the Netherlands) weather station and made available online by the Royal Netherlands Meteorological Institute (Royal Netherlands Meteorological Institute (KNMI), 2016), and then coding low extreme temperature using the function  $\max(0, 5 - T)$  and high extreme as  $\max(0, T - 17)$  (Van Asten et al., 2012). This coding effectively treats temperatures as extreme if below 5C or above 17C.

*Model selection.* A defined model selection procedure was carried out for each age-group separately. First, linear and quadratic terms were entered to model temporal trends in mortality (and so avoid over-estimation of attribution to influenza or the other pathogens). We term this the *base* model. We next considered the impact of 0- to 4-week lags between weekly surveillance reports of influenza A and B and other co-circulating pathogens and mortality (Van Asten et al., 2012). Respiratory pathogens were explored one at a time using a forward selection procedure: each lagged covariate was added independently to the base model, with the lag associated with the largest AIC reduction selected. Next, to the base model now augmented with the selected lags for influenza A and B and the other respiratory pathogens, low and high extreme temperature terms were specified, and trigonometric terms were added to account for the assumed sinusoidal-shaped background mortality (modelling seasonal variation due to other causes). Next, pathogen covariates with negative coefficients were removed on grounds of biological implausibility (it is not plausible that pathogen infection would decrease the risk of death). Finally, the single influenza A term was replaced with 14 separate season-specific influenza coefficients; if any of these coefficients were negative, the model was refitted after removing these terms. Models were therefore fitted of the form:

$$\begin{aligned}
E(Y_i) = & \beta_0 + \gamma_1 w_i + \gamma_2 w_i^2 + \sum_{s=1}^N (\alpha_s Z_{s,i}) + \sum_{j=1}^n (\beta_j X_{(i-t_j)j}) + \\
& \gamma_3 T_{\text{high},i} + \gamma_4 T_{\text{low},i} + \gamma_5 \sin\left(\frac{2\pi i}{52.143}\right) + \gamma_6 \cos\left(\frac{2\pi i}{52.143}\right)
\end{aligned} \tag{4.1}$$

We use the index  $i$  to refer to the week of the study period, the index  $j$  to refer to the pathogen, and the index  $s$  to refer to the season.  $Y$  is assumed to follow a Poisson distribution.  $Y_i$  is the observed number of deaths in week  $i$ ,  $\beta_0$  is a constant (or intercept) term; the next terms capture linear and quadratic temporal trends with  $w_i$  defined as the  $i$ th week in the study period.  $N$  is the total number of seasons for which season-specific influenza A coefficient  $\alpha_s$  is non-negative,  $Z_{s,i}$  are the weekly laboratory reported positive influenza A samples within season  $s$ ,  $X_{i,1\dots n}$  are the weekly laboratory reported positive samples for up to  $n$  co-circulating pathogens (i.e., model fit-based selection from: influenza B, respiratory syncytial virus, rhinovirus, parainfluenza, and *Mycoplasma pneumoniae*), with potential lag of  $t_j$  weeks. Additional included terms are for extreme temperature:  $T_{\text{high},i}$  and  $T_{\text{low},i}$ , and the two harmonic terms:  $\sin\left(\frac{2\pi i}{52.143}\right)$  and  $\cos\left(\frac{2\pi i}{52.143}\right)$ . The same procedure was applied to fit regression models to circulatory/respiratory and respiratory-only underlying cause mortality data. We constructed 95% prediction intervals (PIs) around predicted weekly influenza-attributable deaths using bootstrapping methods.

### *Computation of years of life lost (YLL)*

YLL are standardly defined as the number of cause-specific deaths multiplied by the expected number of healthy life-years lost conditional on the age at death. This residual life expectancy (LE) is defined as how long a person would expect to live in an ideal world that is free of disease assuming access to health care. For instance, the WHO Global Health Estimates projected LE values for 2050, citing a LE at birth of 92 years (World Health Organization, 2013).

Andersen (2013) definition of YLL computed in a competing risk framework requires estimation of cause-specific cumulative risks of death, which in turn requires age-and/or time-specific cause-specific mortality data. Note that this approach differs

from the ‘standard’ YLL definition, in that the  $\tau$ -restricted mean lifetime method from survival analysis is used instead of adopting age-specific LE from life tables. We defined  $\tau = 90$ , so we effectively calculate YLL based on a LE of 90 years. We denote this variant of YLL as ‘YLL90’, which can be interpreted as the expected number of life years lost before reaching the age of 90. To quantify the anticipated over-estimation of mortality burden that would occur if competing mortality risks were ignored, we compare YLL90 to YLL computed based on Kaplan-Meier survival curves (see Supplementary information to Chapter 4).

The estimation of YLL90 was carried out using a simulation procedure applied to conditional survival functions defined for ‘cohorts’ consisting of all persons within each age-group at death (see Supplementary information to Chapter 4 for a detailed description). Cumulative mortality incidence curves were then constructed for (i) influenza-attributable deaths, and (ii) all other causes of death, and YLL90 for each cause category calculated accordingly (Supplementary information to Chapters 2 and 4; see also Andersen (2013); Van Wijhe et al. (2016)). This simulation procedure was repeated 1000 times, with the uncertainty inherent in the resulting age-group specific distributions of influenza-attributable YLL90 combined with the 95% PIs for predicted influenza-attributable deaths, yielding 95% uncertainty intervals (UIs) for YLL90.

Within each iteration, YLL90 was calculated for each age-group and season, simulating conditional survival functions based on the weekly predicted number of influenza-attributable deaths derived from the corresponding fitted Poisson models and the national population estimates (see Supplementary information to Chapter 4 for further details).

### *Outcomes and statistical analysis*

We present the weekly and annual YLL90 due to influenza-attributable mortality both in absolute terms, and also as the proportion of annual total YLL90 within the entire outcome category (all-cause, circulatory/respiratory, or respiratory only); thus considering deaths from causes other than influenza as competing risks. The latter measure—proportion of total YLL90—permits declining secular trends in mortality to be taken into account. In addition, to allow comparisons of mortality burden between age-groups, we report YLL90 per 100 000. This measure controls for

differences in age-group population size (and thus adjusts for demographic change; i.e., the growing and ageing Dutch population (National Kompass Volksgezondheid (NKV), 2016)) so that influenza mortality burden can be meaningfully compared across age-groups. Finally, inter-season variability was quantified as the standard deviation of the YLL90 per 100 000 measure. All modelling was conducted in the R statistical programming environment, version 3.2.0 (R Development Core Team, 2015).

## Results

The total number of influenza-attributable deaths in persons aged 60+ years ranged from 40 to 3330 over season (1.3% of all deaths) and varied by age-group, with the highest influenza mortality rate estimated for the 85+ years age-group (see Supplementary Table 4.3 and Supplementary Figure 4.3). Models fitted to more specific cause-of-death data (i.e., respiratory/circulatory underlying causes, and respiratory causes only) showed similar temporal patterns, but with smaller absolute numbers (Supplementary Figures 4.4 and 4.5).

### *Years of life lost before age 90*

Influenza-attributable mortality burden exhibited considerable seasonal variability, with YLL90 ranging from 480 to 30 680 across seasons within the study period (Table 4.1). The 85–89 years age-group, although contributing the largest estimated number of influenza-associated deaths (1.7% of the cumulative total registered deaths in this age-group over the study period), did not incur the largest absolute influenza-attributable burden; this was observed for the 80–84 years group, with across-season average YLL90 of 2992 (Table 4.2).

Between 0.04% and 2.37% of the total YLL90 per season in persons aged 60–89 years was attributed to influenza (Table 4.1 and Figure 4.1). This proportion measure, which adjusts for any secular changes in overall mortality risk, tended to decrease over the study period. The 85–89 years age-group was responsible for the largest age-group specific share of the total mortality burden (1.61%) (Table 4.2).

Estimates using more specific cause-of-death data—respiratory/circulatory underlying causes and respiratory causes only—were comparable to the all-cause results,

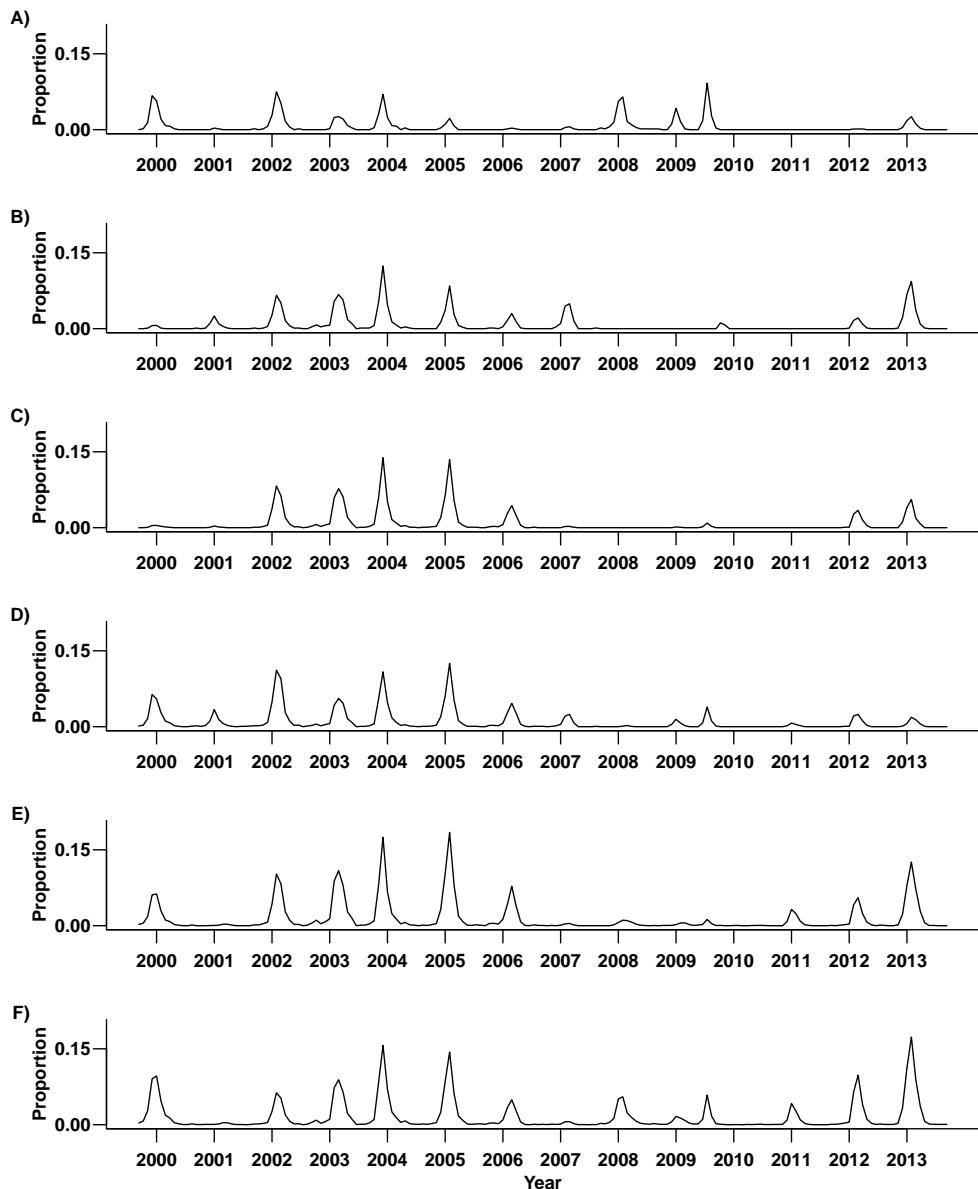
**Table 4.1: Total and influenza-attributable YLL90 for persons aged 60–89 years, the Netherlands, seasons 1999/2001 through 2012/2013.** Shown are the total and the proportion of total YLL90 attributable to influenza, and influenza-attributable YLL90 per 100 000 stratified by 5-year age-group at death. Temporal variability in YLL90 per 100 000 per age-group is indicated by the standard deviation (SD). Data is based on all-cause mortality. Only point estimates are shown.

Season	YLL90			Influenza-attributable YLL90 per 100 000					
	Total	Influenza-attributable	Proportion (%)	60–64	65–69	70–74	75–79	80–84	85–89
1999/2000	1 343 300	14 580	1.09%	430	50	60	997	1176	1333
2000/2001	1 334 700	3340	0.24%	18	170	25	374	45	57
2001/2002	1 347 400	25 860	1.92%	437	540	914	1617	1598	746
2002/2003	1 331 800	24 120	1.81%	168	681	995	862	1894	1235
2003/2004	1 295 400	30 680	2.37%	330	782	1172	1248	2057	1610
2004/2005	1 306 100	28 370	2.17%	99	486	1143	1363	2349	1464
2005/2006	1 263 900	10 500	0.83%	12	166	395	517	945	539
2006/2007	1 230 100	4180	0.34%	24	320	24	252	55	63
2007/2008	1 258 000	5890	0.47%	345	4	0	13	171	647
2008/2009	1 258 800	8020	0.64%	427	10	8	362	91	469
2009/2010	1 289 900	480	0.04%	3	42	0	0	13	19
2010/2011	1 261 100	2370	0.19%	3	0	2	58	314	291
2011/2012	1 297 900	8530	0.66%	10	108	245	229	580	812
2012/2013	1 320 800	21 170	1.60%	120	543	401	158	1503	1730
Inter-season variability (SD)				175	281	464	543	831	578

YLL: Years of life lost.

in showing similar decreasing temporal trends in the proportion of total YLL90 attributed to influenza (Supplementary Figures 4.6 and 4.7), and similar rankings of this proportion over age-group. However, lower absolute YLL90 and YLL90 per 100 000 rates (Supplementary Tables 4.4 and 4.5) were obtained, due to smaller numbers of influenza-attributed deaths.

Influenza-attributable YLL90 per 100 000 persons for all-cause mortality is depicted in Supplementary Figure 4.8. The YLL90 rates for the younger age-groups (i.e., 60–64, 65–69 years) varied widely across seasons of the study period, but variation in the burden was even more pronounced for persons aged 80–89 years (Figure 4.2 and Table 4.1). A similar age pattern was observed if YLL90 is calculated using more specific cause-of-death data (Supplementary Figures 4.9 and 4.10). When standardising for age-group population size and aggregating over season, the highest burden (YLL90 of 914 per 100 000; 95% UI: 867, 963) was observed for the 80–84 years age-group, with the second highest burden (787 per 100 000; 95% UI:



**Figure 4.1: Contribution of influenza to total YLL90 by age-group, the Netherlands, seasons 1999/2000 through 2012/2013.** Proportion of total YLL90 attributable to influenza based on all-cause mortality data, aggregated to 4-week intervals for the period 1999/2000 through 2012/2013. Each age-group is shown as a separate panel: (A) 60–64 years; (B) 65–69 years; (C) 70–74 years; (D) 75–79 years; (E) 80–84 years; and (F) 85–89 years.

**Table 4.2: Comparison of age-group specific influenza-attributable YLL90 in the Netherlands, seasons 1999/2000 through 2012/2013.** Shown are averages over seasons 1999/2000 through 2012/2013. Data is based on all-cause mortality.

Age-group (years)	Influenza-attributable YLL90			Influenza-attributable YLL (Kaplan-Meier survival) <sup>2</sup>		
	Absolute	Proportion (%)	Per 100 000 (mean [95% UI])	Absolute	Proportion (%)	Per 100 000 (mean [95% UI])
60–64	1493	0.67%	173 [152, 199]	1544	0.69%	179 [157, 205]
65–69	1980	0.82%	279 [255, 303]	2116	0.87%	297 [272, 323]
70–74	2243	0.84%	385 [357, 415]	2492	0.93%	427 [396, 460]
75–79	2658	1.00%	575 [540, 613]	3106	1.17%	671 [629, 716]
80–84	2992	1.50%	914 [867, 963]	4095	2.03%	1236 [1173, 1303]
85–89	2053	1.61%	787 [741, 834]	5055	3.70%	1878 [1782, 1981]
All [60–89] <sup>1</sup>	13 433	1.03%	423 [412, 435]	18 468	1.40%	573 [559, 589]

YLL: Years of life lost; UI: uncertainty interval.

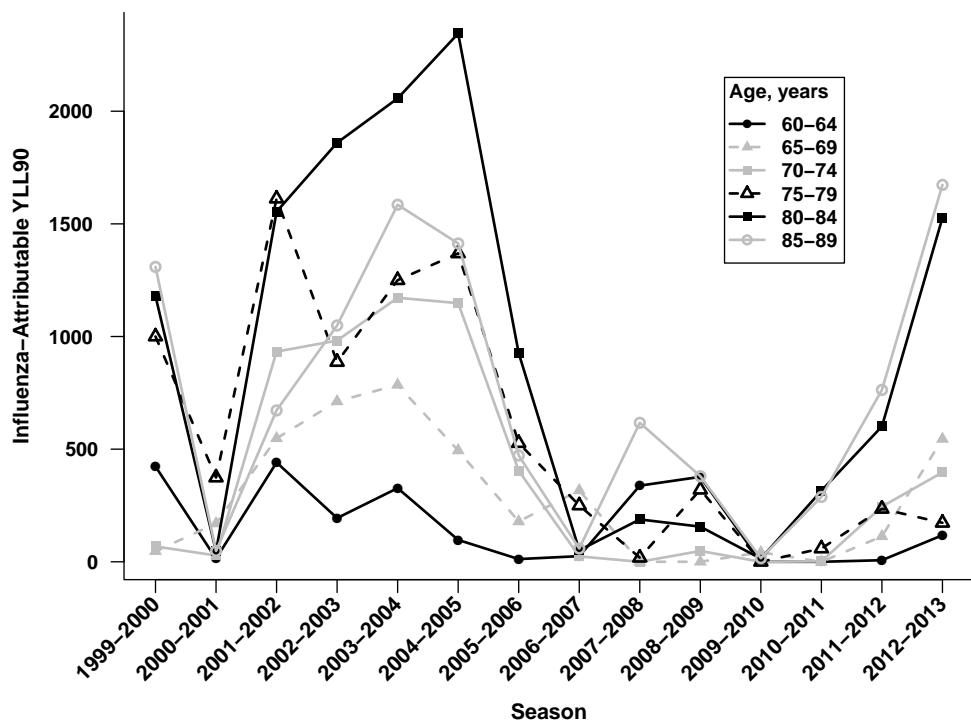
<sup>1</sup> Influenza-attributable YLL90 or YLL for individual age-groups do not sum to the value for All [60–89], as the latter was computed using the aggregated age-group 60–89 years.

<sup>2</sup> YLL based on Kaplan-Meier Survival, and so does not account for competing mortality risks.

741, 834) for persons aged 85–89 years (Table 4.2). YLL90 for these two age-groups is notably high, as YLL90 for the age-group with next highest burden, 75–79 years, was 37% lower, at 575 per 100 000 [95% UI: 540, 613]. Ignoring competing mortality risks tended to over-estimate the overall mortality burden. For persons aged 60–64 years at death, YLL computed based on Kaplan-Meier survival curves yielded an overall 3.5% higher total mortality burden attributed to influenza compared with YLL90 (Table 4.2). However, the extent of over-estimation increased with age; for persons aged 80–89 years, over-estimation was 82%.

## Discussion

In terms of the estimated number of influenza-attributable deaths the highest burden was observed for persons aged 85 years and older. However, the YLL90 measure provides an alternative view of mortality burden by taking into account age at death and competing risks of death from other causes. Of the total YLL90 calculated from all-cause mortality, the greatest proportion attributable to influenza—1.61%—was also among persons aged 85–89 years. The next youngest age-groups (80–84 years and 75–79 years) had the second and third largest influenza-attributable shares of the mortality burden. However, the age-standardised mortality burden measure



**Figure 4.2: Median influenza-attributable YLL90 per 100 000 by season and age-group, the Netherlands, seasons 1999/2000 through 2012/2013.** Data is based on all-cause mortality, aggregated by season, and plotted separately by 5-year age-group.

YLL90 per 100 000 localised the highest mortality burden to the 80–84 years age-group, followed by the 85–89 years age-group.

Our estimates of the proportion of total YLL90 per season in 60- to 89-year-olds that is due to influenza, although small on average (ranging from 0.04% to 2.37% across seasons; Table 4.1), are also lower than if YLL is computed ignoring competing mortality risks. Age-group specific burden varied between the two measures; for persons aged 80–89 years, the latter YLL measure yielded a notably higher (82%) estimated mortality burden. This suggests that competing risks for mortality in the elderly should be considered when estimating influenza mortality burden using statistical modelling approaches.

The age group-specific influenza-attributable proportion ranged from an across-season average of 0.67% for 60- to 64-year-olds to an average of 1.61% for 85- to 89-year-olds (Table 4.2). However, averaging influenza-attributable mortality burden obscures variation over time. There was also substantial variation in age-group specific YLL90 per 100 000, particularly for persons 80 years and older (Figure 4.2), which suggests that variation in season severity may disproportionately affect the most aged segment of the population (Lofgren et al., 2007). This variation reflects a complex interplay between the circulating virus strain distribution, vaccine mismatch, and degree of natural immunity (Viboud and Epstein, 2016).

The temporal patterns and magnitude of influenza-attributable mortality we obtained were comparable to previous statistical modelling exercises conducted using Netherlands data for wider age-groups. Van Asten et al. (2012) estimated that 1.5% of total deaths in 65-year-olds and over in the period 1999–2007 was due to influenza A; we observed 1.4% of total deaths due to influenza A/B for the same age group in the longer period 1999 through 2013. Van den Wijngaard et al. (2010) calculated annual age-specific YLL for the period 1999 through 2010 (however, not taking competing mortality risks into account and using lower LE norms), and reported total YLL per season that varied from 0 to approximately 18 000 for person aged 75+ years. Our estimated YLL90 range for the same age-group over our study period was 102 to 17 630, which is necessarily lower due to the incorporation of competing mortality risks in the YLL90 calculation.

Consistent with previous research (Van den Wijngaard et al., 2010; Wielders et al., 2012), we observed a relatively low influenza mortality burden among older adults—0.04% of total YLL90 based on all-cause deaths—for the 2009/2010 pandemic year. Other than for 2009/2010, for which 100% of influenza A samples were subtype H1N1 and for 2003/2004, for which 100% were H3N2 (Darvishian et al., 2017), there was no clear correspondence between seasonal total YLL90 and dominant circulating virus type.

We used all-cause mortality in the main analysis. Because influenza infection plays a larger role for certain causes of death, one can also estimate burden based on more specific cause-of-death categories. Supplementary analyses using circulatory/respiratory and respiratory-only mortality data were largely consistent

with the results based on all-cause mortality. Although the estimated influenza-attributable YLL90 and YLL90 per 100 000 were lower, the greater mortality burden for persons 80–89 years was replicated.

Attribution of influenza-caused mortality via Poisson regression is technically challenging and is consequently subject to several limitations (Simonsen and Viboud, 2012). First, through inclusion of harmonic terms to capture seasonal patterns in mortality unaccounted for by the included covariates, we effectively made the assumption that the impact of these unmeasured influences is static across seasons. This could lead to over- or under-estimation of the associations between the activity of other pathogens and mortality in a given season; alternative regression modelling techniques may improve model fit (Muscattello et al., 2014). Related to this issue, by fitting a single, time-invariant regression coefficient for each circulating pathogen other than influenza A, the number of weekly deaths attributable to these pathogens was constrained to be a constant proportion of the reported positive tests. Finally, we assumed that there were no historical changes in testing/reporting that would affect the laboratory surveillance data.

As age at death was available only at a granularity of five years, our method randomly allocated an age at death for the calculation of cumulative mortality incidence and YLL90. This led to lower precision in age-specific YLL90 than if the exact age at death were known. The restricted mean lifetime approach requires definition of a maximum attainable age. Using a higher limit, e.g., 95 years, would inflate the estimated absolute YLL90 and YLL90 per 100 000 values, but age group-specific proportions would not change appreciably.

Our quantitative estimation of the mortality burden due to influenza in the Netherlands over a 14-season analysis period indicates that the greatest burden, adjusting for population size, is borne by persons aged 80 years and over, and is highest for the 80–84 age-group. The more aged segment of persons targeted by the Dutch national influenza prevention programme has a historically higher vaccination uptake (75+ years: 85% in 2008) than younger eligible persons (65–74 years: 73% in 2008) (Statistics Netherlands (CBS), 2011), but uptake does not translate directly into protection. Although the single large randomized trial conducted to date yielded a vaccine efficacy (VE) of 59% [95% CI: 20%, 79%] for the youngest (60–69 years) decade of our study population (Govaert et al., 1994), evidence regarding VE of the (inactivated)

flu vaccine for persons aged 70 years and over is lacking. As the Dutch residual life expectancy upon reaching one's 80<sup>th</sup> birthday is about nine years, substantial mortality burden could be averted by preventing influenza in the elderly. Given the large observed degree of inter-season variability in mortality burden borne by the oldest age-groups—related to the strain distribution, vaccine mismatch (De Jong et al., 2000), virus pathogenicity, vaccination coverage, and drivers of transmission—the most vulnerable elderly may benefit from being targeted for further prevention measures as supplement to routine flu vaccination.

### **Declaration of interests**

The authors have no conflicts of interest to declare.

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## Chapter 4

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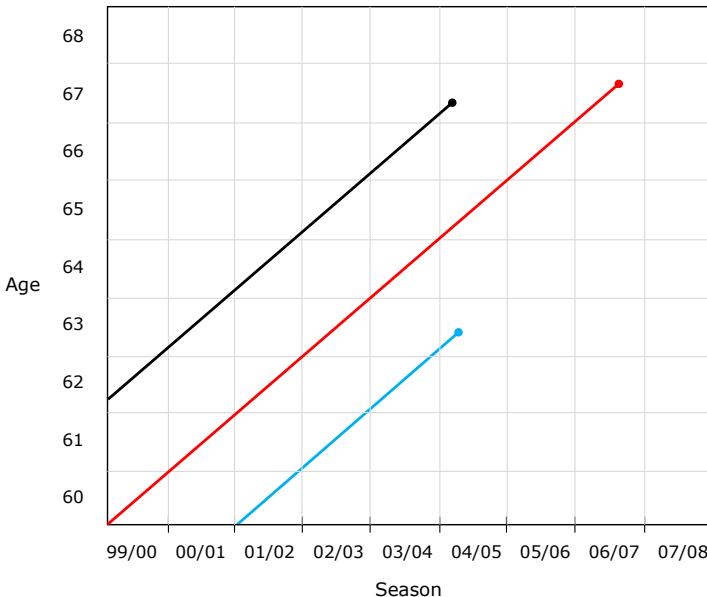
## **Supplementary information to Chapter 4**

## Simulation of cumulative mortality curves conditional on being alive at age $y$

Conditional survival functions (i.e., conditional on being alive at age  $y$ ) were defined for 'cohorts' constructed from all members of all age-groups at death. Entry to follow-up for each cohort was defined as turning age 60 (i.e.,  $y$  was set to 60 years). Given the coarse age-granularity of the mortality data, age of death was simulated within each five-year age interval by randomly sampling discrete ages at death from a uniform distribution. For the oldest age-group we assumed a uniform distribution between 85 and 89 years. The simplification of treating deaths occurring after  $\tau = 90$  years as occurring within the interval 85 to <90 has little impact, as relatively few deaths were recorded in persons  $\geq 90$  years: 16% of all deaths in those aged 60+ years in the period 1999/2000 to 2012/2013 occurred at  $\geq 90$  years ((Statistics Netherlands (CBS), 2016)).

After age of death was assigned, the season-cohort to which each individual belonged (i.e., the season in which he/she turned 60 years old) could be determined. For instance, persons dying at age 68 years entered follow-up on first day of the season in which their 60<sub>th</sub> birthday fell (see Supplementary Figure 4.1 for simplified example life trajectories plotted as a Lexis diagram), but follow-up was constrained to begin no earlier than the beginning of the 1999/2000 season. Thus, for deaths in the older age-groups in the earlier seasons, follow-up necessarily started at their age in 1999/2000 (e.g., black trajectory, Supplementary Figure 4.1). Deaths were actually simulated to fall within either the upper or lower 'Lexis triangle' within a given square of the season-by-age grid; this depended on the week of the season in which the death was recorded. Thus, individuals who died at age  $a$  in season  $s$  and who had a simulated life trajectory with end point in the lower Lexis triangle were assigned to age cohort  $(a - 60)$  in season 0, where  $s = 0$  for 1999/2000,  $s = 1$  for 2000/2001, etc. Those whose simulated trajectory ended in the upper Lexis triangle were assigned to age cohort  $(a - 60 + 1)$  in season 0. For individuals with start of follow-up after season 0, assignment was to age cohort 60 in season  $(s - (a - 60))$  (upper Lexis triangle or to age cohort 60 in season  $(s - (a - 60 - 1))$  (lower Lexis triangle). Next, total cohort membership at entry to follow-up for each age cohort in 1999/2000 (and for each of the 13 cohorts of individuals turning 60 in seasons 2000/2001 through 2012/2013) was assigned based on the national age-specific population size for the season. The latter was determined as the population on 1st

January falling within the season ((Statistics Netherlands (CBS), 2016)). There is now sufficient information to construct conditional survival curves for each age/season cohort.



**Supplementary Figure 4.1: Example of a Lexis diagram (2).** Lexis diagram with example trajectories for three individuals. The black and red individuals both died at age 67; for the death in the 2006/2007 season, follow-up started at age 60, at the beginning of season 1999/2000; for the person who died in 2004/2005, follow-up began at age 62 in 1999/2000. The blue individual, who died at age 63 in season 2004/2005 could only be followed-up starting in 2000/2001, from age 60.

## Computation of cause-specific YLL90

After constructing cause-specific cumulative mortality incidence curves (using the Aalen-Johansen estimator) for each age/season cohort, for influenza and other causes of death, YLL90 for each cumulative incidence curve corresponding to the interval of interest, e.g. the incidence in a particular season multiplied by the period between age at death and age 90 and the starting population size of the cohort (see Andersen (2013) and Supplementary information to Chapter 2).

Specifically, if  $\tau_0$  is the age at entry to follow-up and  $\tau$  is the maximum possible lifespan in years, the expected years of life lost between age  $\tau_0$  and age  $\tau$  due to cause  $j$ ,  $L_j$ , is:

$$L_j(\tau_0, \tau) = \int_{\tau_0}^{\tau} \hat{F}_j(t) dt \quad (4.2)$$

where  $\hat{F}_j(t)$  is the Aalen-Johansen estimator for the cause  $j$  cumulative mortality incidence, and is the closed-form expression (where  $\hat{S}$  is the Kaplan-Meier estimator,  $d_{j,i}$  is the number of deaths from cause  $j$  at time  $t_i$ ;  $n_i$  is the number of persons at risk at time  $t_i$ ):

$$\hat{F}_j(t) = \sum_{i:t_i \leq t} \hat{S}(t_{i-1}) \frac{d_{j,i}}{n_i} \quad (4.3)$$

The sum over each cause-specific YLL,  $L_j$ , and the Kaplan-Meier estimator,  $\hat{S}$ , for survival between  $\tau_0$  and  $\tau$  necessarily satisfies the balance equation:

$$\int_{\tau_0}^{\tau} \hat{S}(t) dt + \sum_{j=1}^k L_j(\tau_0, \tau) = \tau - \tau_0 \quad (4.4)$$

The above equation states that the number of years of life lost between age  $\tau_0$  and age  $\tau$  due to all causes  $j$ , plus the years of life lived, should equal the difference between the starting cohort age and the maximum lifespan. This balance equation is what differentiates the competing risk method for deriving cause-specific years of life lost from a method using Kaplan-Meier (K-M) survival curves to estimate cause-specific years of life lost. For each age/season cohort separately, we can therefore estimate the number of years of life lost due to each cause  $j$ , while taking into account the competing risk of mortality from other causes.

## Comparison of YLL90 with YLL derived from Kaplan-Meier survival

We next defined years of life lost for a given cause, but ignoring competing mortality risks; this we term Kaplan-Meier based years of life lost. This is comparable to the 'standard' definition of YLL for a given cause (ie. disease, injury or condition), which is calculated as remaining life expectancy at age of death. Summed 'standard' YLL calculated separately for a number of causes can be paradoxically greater than the total YLL 'possible' (when calculated for deaths from any cause).

In the Kaplan-Meier based YLL approach, the expected years of life lost (with respect to the maximum possible lifespan  $\tau$ ) for cause  $\tau$  are defined as:

$$L_j(\tau_0, \tau) = \int_{\tau_0}^{\tau} \hat{G}_j(t) dt \quad (4.5)$$

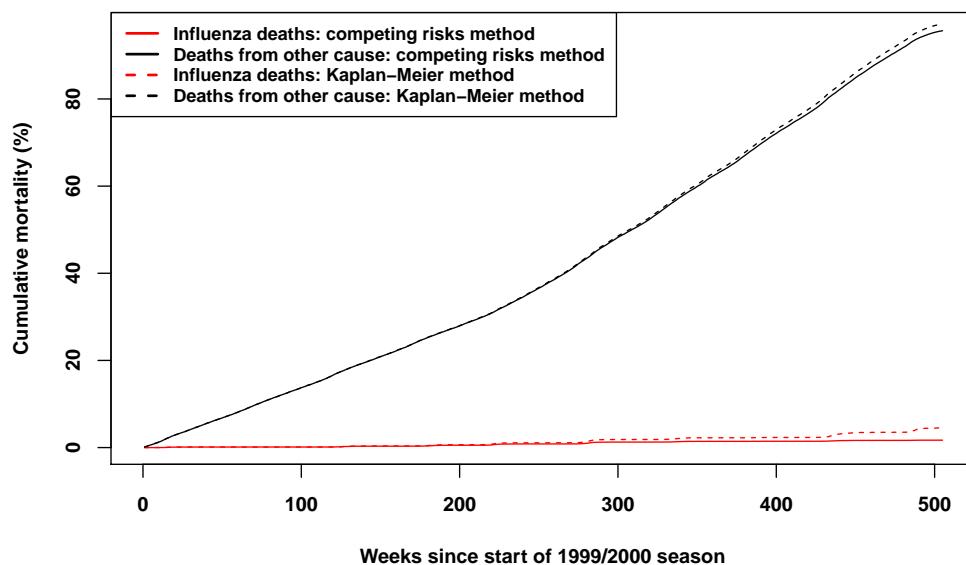
where the cumulative mortality incidence due to cause  $j$ ,  $\hat{G}_j$  is estimated as one minus the cumulative survival probability ('1 - K-M estimate'), defined as follows:

$$\hat{S}_j(t) = \prod_{t_i \leq t} \frac{n_{i-1} - d_{j,i}}{n_{i-1}} \quad (4.6)$$

$$\hat{G}_j(t) = 1 - \hat{S}_j(t) \quad (4.7)$$

where  $d_{j,i}$  is the number of deaths from cause  $j$  at time  $t_i$  and  $n_i$  is the number of persons at risk at time  $t_i$  (in which deaths from other causes are considered censoring events). Note that this definition of YLL will not satisfy the balance equation above.

To illustrate the difference between YLL90, and YLL based on Kaplan-Meier survival calculated separately for influenza and for other causes of death, we graphically compare cumulative incidence of mortality curves computed using the present competing risk approach, to cumulative mortality curves computed based on Kaplan-Meier survival (1 - K-M estimate). As an example, consider the cohort of 80-year-olds commencing follow-up at the beginning of season 1999/2000 (Supplementary



**Supplementary Figure 4.2: Example cumulative mortality incidence curves.** Influenza mortality computed using the Aalen-Johansen estimator is compared with the Kaplan-Meier method. Starting cohort is a cohort of 80-year-olds in season 1999/2000. Data is based on all-cause mortality data.

Figure 4.2). This cumulative mortality incidence plot indicates that the K-M method slightly over-estimates influenza-attributable mortality, and thus would over-estimate YLL due to influenza. The curve for cumulative mortality attributable to influenza is upwardly biased when competing mortality risks from other causes are ignored (because death from other causes is incorrectly treated as a censoring event, which assumes that persons would still be at risk of dying from influenza had they been followed-up longer), compared with when competing risks are taken into account.

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Statistics Netherlands (CBS). Mortality by sex, age and marital status [bevolking; geslacht, leeftijd en burgerlijke staat]. 2016. [Available at: <http://statline.cbs.nl/>]. [Accessed: 23 August 2016].

**Supplementary Table 4.3: Estimated age-specific influenza-attributable mortality rates, the Netherlands, seasons 1999/2000 through 2012/2013.** Mortality rate are in deaths per 10 000 persons. Values in square brackets are 95% prediction intervals.

Season	Age-group at death in years				
	60–64	65–69	70–74	75–79	80–84
1999/2000	1.6 [1.5, 1.8]	0.22 [0.20, 0.25]	0 [0, 0]	7.8 [74, 82]	14.0 [13.3, 14.7]
2000/2001	0 [0, 0]	0.81 [0.73, 0.85]	0 [0, 0]	3.1 [3.0, 3.2]	0.55 [0.49, 0.62]
2001/2002	1.6 [1.5, 1.7]	2.3 [2.2, 2.4]	4.9 [47, 5.1]	12.8 [12.3, 13.5]	20.6 [20.0, 21.4]
2002/2003	0.53 [0.49, 0.58]	3.0 [2.9, 3.1]	5.7 [5.5, 6.0]	6.2 [6.1, 6.5]	24.3 [23.8, 24.9]
2003/2004	1.1 [1.0, 1.2]	3.3 [3.2, 3.5]	6.6 [6.2, 6.9]	9.5 [9.0, 9.8]	25.9 [25.0, 27.3]
2004/2005	0.25 [0.23, 0.28]	1.9 [1.8, 2.1]	6.4 [6.2, 6.7]	10.1 [9.7, 10.5]	30.3 [29.4, 31.4]
2005/2006	0 [0, 0]	0.69 [0.66, 0.75]	2.2 [2.1, 2.3]	3.8 [3.7, 4.0]	12.1 [11.7, 12.7]
2006/2007	0 [0, 0]	1.5 [1.4, 1.6]	0 [0, 0]	2.1 [2.0, 2.2]	0.59 [0.56, 0.65]
2007/2008	1.3 [1.2, 1.4]	0 [0, 0]	0 [0, 0]	0.06 [0.04, 0.08]	1.5 [1.4, 1.6]
2008/2009	1.6 [1.5, 1.8]	0 [0, 0]	0 [0, 0]	2.9 [2.7, 3.0]	0.88 [0.82, 0.93]
2009/2010	0 [0, 0]	0.19 [0.17, 0.21]	0 [0, 0]	0 [0, 0]	0.17 [0.11, 0.20]
2010/2011	0 [0, 0]	0 [0, 0]	0 [0, 0]	0.32 [0.30, 0.35]	3.9 [3.6, 4.0]
2011/2012	0 [0, 0]	0.45 [0.42, 0.48]	1.4 [1.4, 1.5]	1.6 [1.5, 1.7]	6.7 [6.4, 6.9]
2012/2013	0.29 [0.27, 0.32]	2.5 [2.4, 2.6]	2.4 [2.3, 2.5]	0.55 [0.51, 0.59]	17.9 [17.4, 18.5]
					65.3 [63.8, 67.2]
					$\geq 85$

**Supplementary Table 4.4: Competing risks versus Kaplan-Meier using circulatory/respiratory mortality, the Netherlands, seasons 1999/2000 through 2011/2012.** Comparison of age-group specific influenza-attributable YLL90 with YLL based on Kaplan-Meier survival. Influenza-attributable YLL90 was derived using circulatory/respiratory mortality and averaged over seasons 1999/2000 through 2011/2012. Values in square brackets are 95% uncertainty intervals.

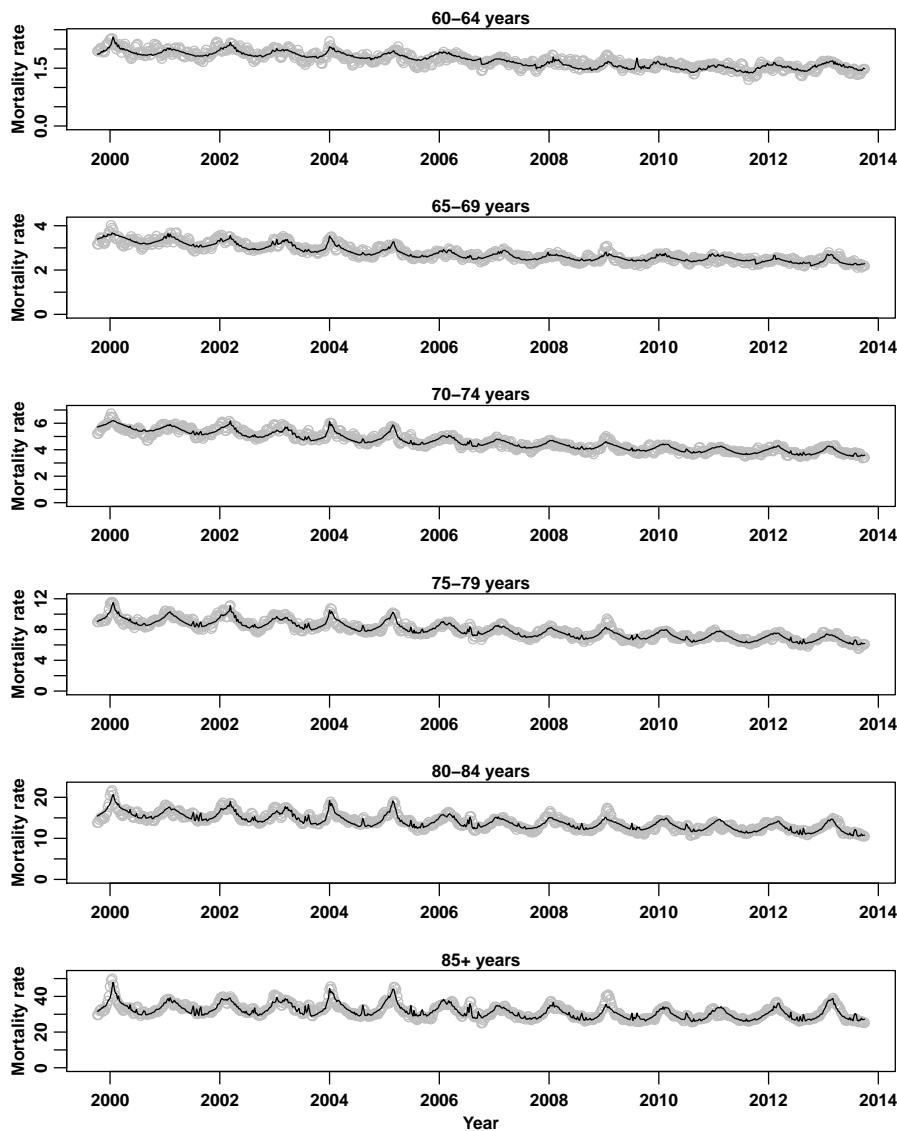
Age-group (years)	Influenza-attributable YLL90			Influenza-attributable YLL (Kaplan-Meier survival) <sup>2</sup>		
	Absolute	Proportion (%)	Per 100 000 (mean [95% UI])	Absolute	Proportion (%)	Per 100 000 (mean [95% UI])
60–64	1159	0.53%	145 [124, 167]	1196	0.55%	149 [128, 172]
65–69	1138	0.47%	170 [150, 191]	1208	0.50%	181 [159, 203]
70–74	1693	0.62%	295 [267, 324]	1864	0.69%	324 [293, 356]
75–79	2230	0.86%	483 [445, 520]	2616	1.00%	566 [522, 609]
80–84	2005	1.03%	630 [589, 672]	2652	1.35%	825 [771, 880]
85–89	1077	1.04%	442 [407, 477]	2462	2.27%	988 [913, 1062]
All (60–89)	9302	0.72%	302 [292, 313]	11998	0.93%	387 [374, 400]

YLL: Years of life lost.

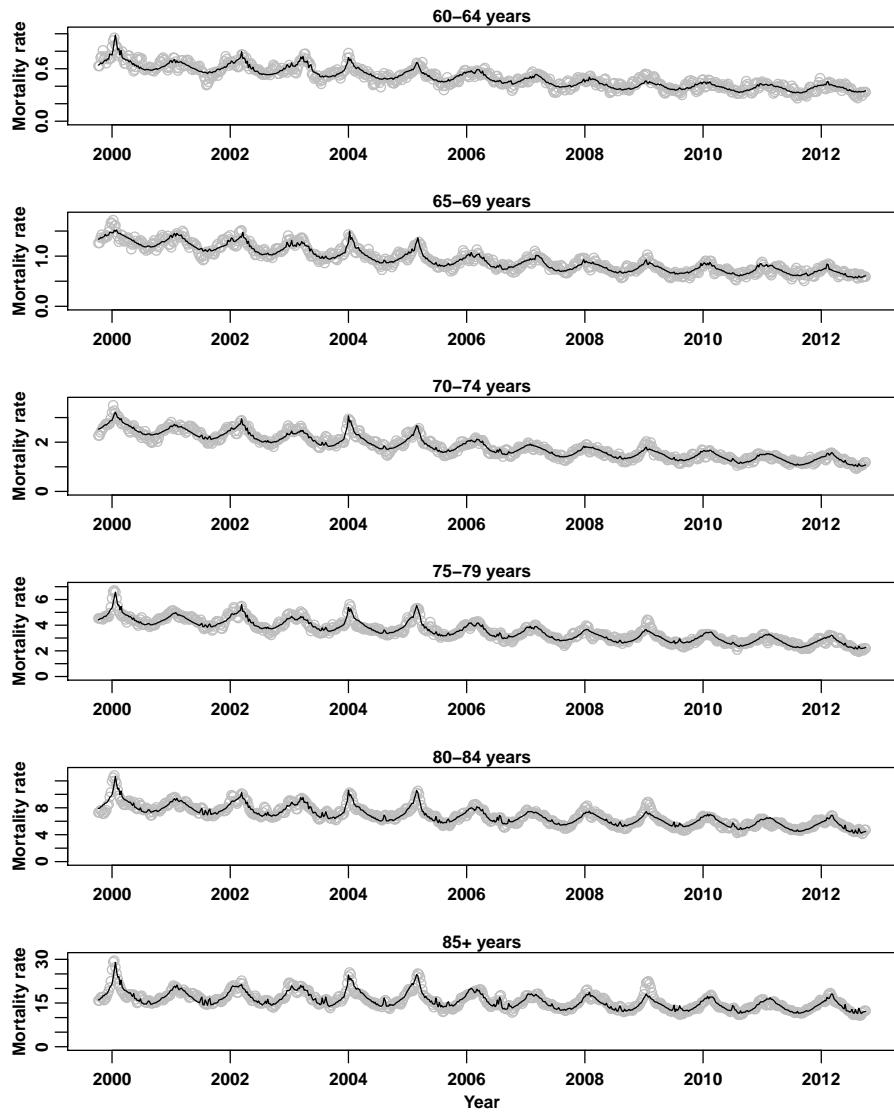
**Supplementary Table 4.5: Competing risks versus Kaplan-Meier using respiratory mortality, the Netherlands, seasons 1999/2000 through 2011/2012.** Comparison of age-group specific influenza-attributable YLL90 with YLL based on Kaplan-Meier survival. Influenza-attributable YLL90 was derived using circulatory/respiratory mortality and averaged over seasons 1999/2000 through 2011/2012. Values in square brackets are 95% uncertainty intervals.

Age-group (years)	Influenza-attributable YLL90			Influenza-attributable YLL (Kaplan-Meier survival) <sup>2</sup>		
	Absolute	Proportion (%)	Per 100 000 (mean [95% UI])	Absolute	Proportion (%)	Per 100 000 (mean [95% UI])
60–64	464	0.22%	59 [42, 77]	478	0.22%	61 [44, 79]
65–69	584	0.24%	87 [65, 111]	619	0.26%	92 [69, 117]
70–74	1088	0.40%	190 [160, 222]	1190	0.44%	207 [175, 243]
75–79	1155	0.45%	249 [214, 285]	1366	0.53%	294 [252, 337]
80–84	1346	0.70%	423 [378, 473]	1798	0.92%	558 [499, 625]
85–89	791	0.76%	325 [286, 367]	1783	1.66%	716 [634, 809]
All (60–89)	5434	0.42%	176 [165, 188]	7245	0.56%	232 [218, 248]

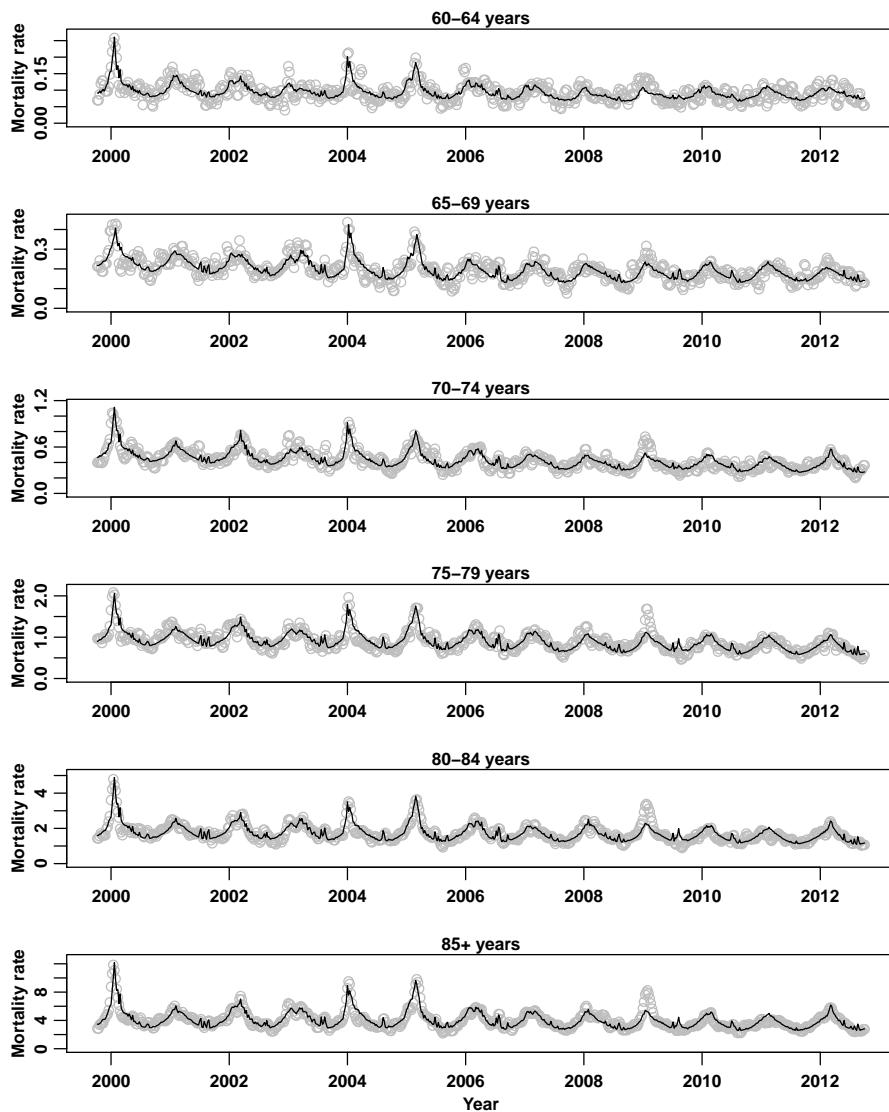
YLL: Years of life lost.



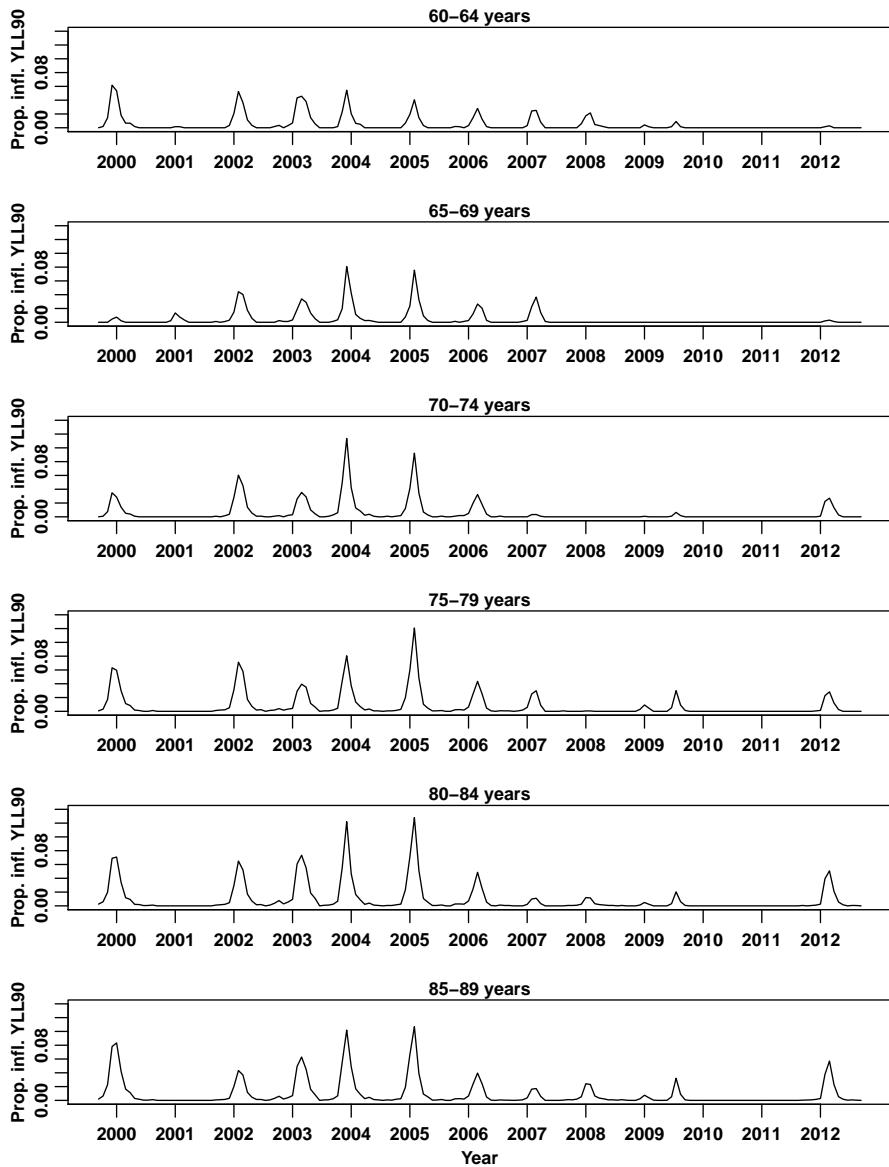
**Supplementary Figure 4.3: Poisson regression model fit to weekly all-cause mortality, the Netherlands, seasons 1999/2000 through 2012/2013.** Mortality rates per 10 000 persons (circles) for each age-group are shown as separate panels. The observed mortality rate data were smoothed using a 3-week moving average.



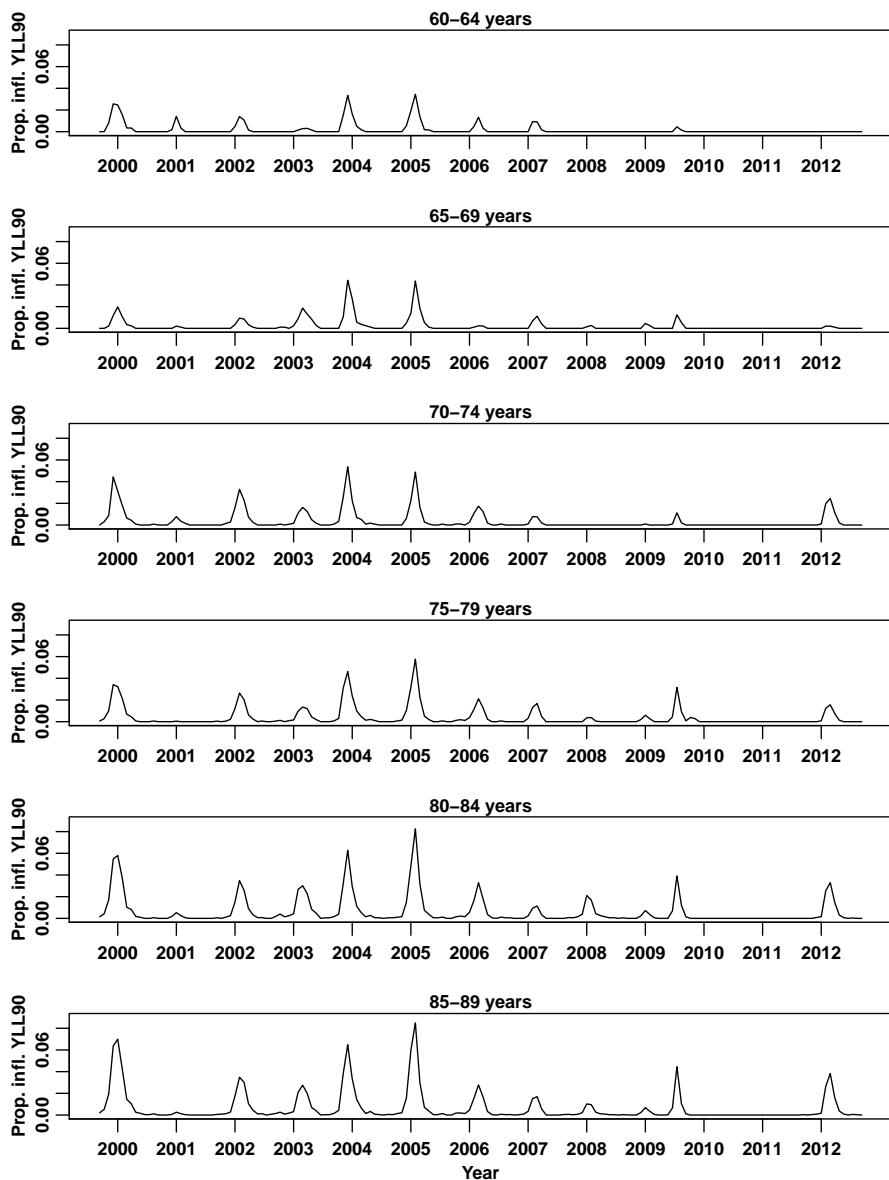
**Supplementary Figure 4.4: Poisson regression model fit to weekly mortality from a circulatory or respiratory underlying cause, the Netherlands, seasons 1999/2000 through 2012/2013.** Mortality rates per 10 000 persons (circles) for each age-group are shown as separate panels. The observed mortality rate data were smoothed using a 3-week moving average.



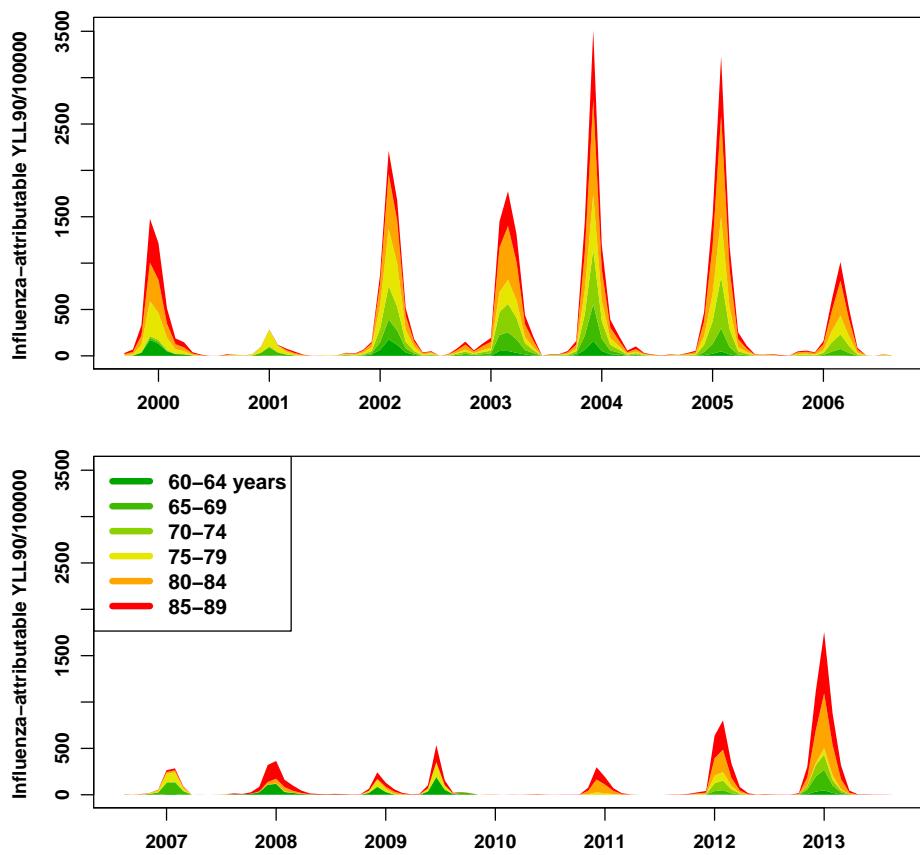
**Supplementary Figure 4.5: Poisson regression model fit to weekly mortality from respiratory underlying causes only, the Netherlands, seasons 1999/2000 through 2012/2013.** Mortality rates per 10 000 persons (circles) for each age-group are shown as separate panels. The observed mortality rate data were smoothed using a 3-week moving average.



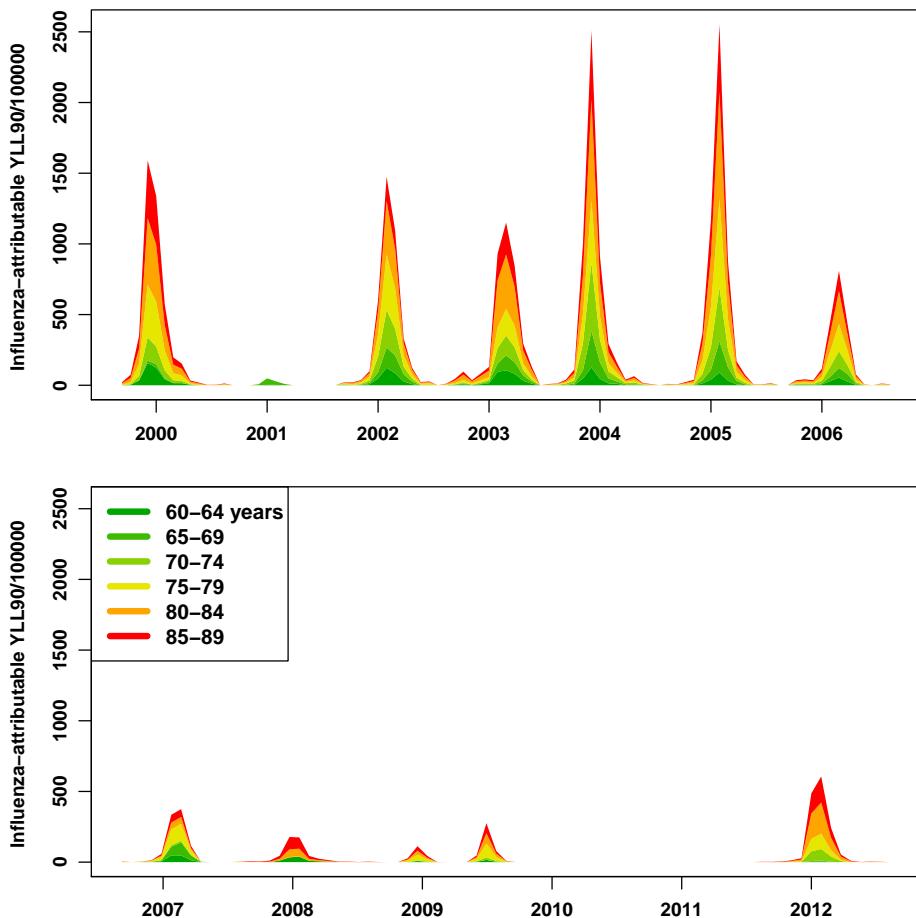
**Supplementary Figure 4.6:** Contribution of influenza to total YLL90 by age-group using mortality from a circulatory or respiratory underlying cause, the Netherlands, seasons 1999/2000 through 2012/2013. Proportion of total YLL90 attributable to influenza aggregated to 4-week intervals for the period 1999/2000 through 2012/2013. Each age-group is shown as a separate panel.



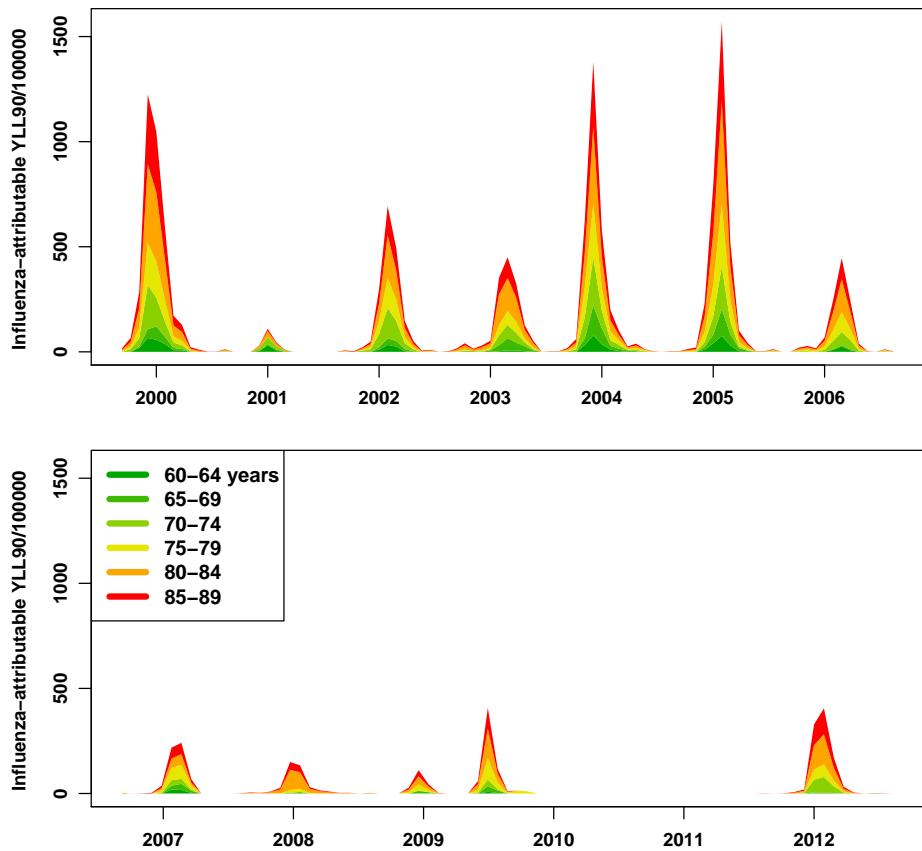
**Supplementary Figure 4.7: Contribution of influenza to total YLL90 by age-group using mortality from respiratory underlying causes only, the Netherlands, seasons 1999/2000 through 2012/2013.** Proportion of total YLL90 attributable to influenza aggregated to 4-week intervals for the period 1999/2000 through 2012/2013. Each age-group is shown as a separate panel.



**Supplementary Figure 4.8: Influenza-attributable YLL90 per 100 000 by age-group, the Netherlands, seasons 1999/2000 through 2012/2013.** Data is based on all-cause mortality and aggregated over 4-week intervals. Age-group-specific mortality burden is represented as stacked coloured regions.



**Supplementary Figure 4.9:** Influenza-attributable YLL90 per 100 000 by age-group using mortality from a circulatory or respiratory underlying cause, the Netherlands, seasons 1999/2000 through 2012/2013. Data is based on mortality from a circulatory or respiratory underlying cause and aggregated over 4-week intervals. Age-group-specific mortality burden is represented as stacked coloured regions.



**Supplementary Figure 4.10:** Influenza-attributable YLL90 per 100 000 by age-group using mortality from respiratory underlying causes only, the Netherlands, seasons 1999/2000 through 2012/2013. Data is based on mortality from respiratory underlying causes only and aggregated over 4-week intervals. Age-group-specific mortality burden is represented as stacked coloured regions.



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# Chapter 5

## **Quantifying the impact of mass vaccination programmes on notified cases in the Netherlands**

The contents of this chapter have been published in Epidemiology & Infection:

### **Quantifying the impact of mass vaccination programmes on notified cases in the Netherlands**

Maarten van Wijhe, Anna D. Tulen, Hester Korthals Altes, Scott A. McDonald, Hester E. de Melker,

Maarten J. Postma, Jacco Wallinga

Epidemiology & Infection, April 6 2018, 146(6):716-722

A shortened translation in Dutch has been accepted for publication in the Dutch Journal of Medicine

(Nederlands Tijdschrift voor Geneeskunde)

## Abstract

Vaccination programmes are considered a main contributor to the decline of infectious diseases over the 20<sup>th</sup> century. In recent years, the national vaccination coverage in the Netherlands has been declining, highlighting the need for continuous monitoring and evaluation of vaccination programmes. Our aim was to quantify the impact of long-standing vaccination programmes on notified cases in the Netherlands. We collected and digitized previously unavailable monthly case notifications of diphtheria, poliomyelitis, mumps, and rubella in the Netherlands over the period 1919–2015. Poisson regression models accounting for seasonality, multi-year cycles, secular trends, and auto-correlation were fit to pre-vaccination periods. Cases averted were calculated as the difference between observed and expected cases based on model projections. In the first 13 years of mass vaccinations, case notifications declined rapidly with 82.4% [95% credible interval (CI): 74.9%, 87.6%] of notified cases of diphtheria averted, 92.9% [95% CI: 85.0%, 97.2%] cases of poliomyelitis, and 79.1% [95% CI: 67.1%, 87.4%] cases of mumps. Vaccination of 11-year-old girls against rubella averted 49.9% [95% CI: 9.3%, 73.5%] of cases, while universal vaccination averted 68.1% [95% CI: 19.4%, 87.3%] of cases. These findings show that vaccination programmes have contributed substantially to the reduction of infectious diseases in the Netherlands.

## Introduction

Mass vaccination programmes are considered to be one of most important public health interventions in human history (Centers for Disease Control and Prevention (CDC), 1999b,a; Hinman et al., 2011). This is evidenced by the dramatic decline in the incidence of vaccine-preventable diseases after the implementation of mass vaccination programmes in many parts of the world. However, even in countries with long-standing vaccination programmes, such as the Netherlands, outbreaks of vaccine-preventable diseases still occur (Greenwood, 2014; Hahne et al., 2009; Knol et al., 2013; Oostvogel et al., 1994; Hanratty et al., 2000). Vaccine-preventable diseases such as measles, pertussis, polio, and mumps, mostly resurge in communities with insufficient vaccination coverage (Muscat et al., 2015; Van der Maas et al., 2013; Van Wijngaarden and van Loon, 1993; Wielders et al., 2011; Sane et al., 2014). In the Netherlands, the national vaccination coverage for the diphtheria-pertussis-tetanus-polioimmunization (DPTP) vaccine has also slightly declined from 95.8% for birth cohort 2011 to 93.5% for birth cohort 2014, the lowest in well over two decades (Van Lier et al., 2017). If this concerning trend continues, these infectious diseases might re-emerge. It is therefore necessary to continue monitoring and evaluating vaccination programmes, including long-standing programmes. Evaluating the effectiveness of long-standing vaccination programmes may help inform health care professionals and parents in a time of increasing vaccine hesitancy.

Evaluation of vaccination programmes is complex as they are often implemented on a large scale and adequate control groups are difficult to identify (Halloran and Struchiner, 1991). Nevertheless, the literature on vaccine impact is extensive, especially for recent vaccines. Few recent studies have evaluated the impact of long-standing vaccination programmes, e.g. against diphtheria, on a population level, in part due to the lack of detailed historical data and analysis methods. Recent literature generally focusses on contemporary (Moore et al., 2015) and potential future mass vaccination programmes (Amirthalingam et al., 2014; Baguelin et al., 2013); long-standing programmes are often neglected and their effectiveness is taken for granted. Studies evaluating the impact of these long-standing vaccination programmes tend to compare pre- versus post-implementation disease occurrence, often many years apart, without taking secular trends into account (Galazka et al., 1999; Roush and Murphy, 2007; Van Panhuis et al., 2013; Van den Hof et al., 1998). More detailed analyses are hampered by a lack of data repositories with a

high temporal and geographic resolution on infectious diseases. Recently, a major effort was put into constructing a comprehensive database on infectious disease notifications in the US, project Tycho (Van Panhuis et al., 2013). Using this extensive historic database, going back to 1888, Van Panhuis et al. (2013) were able to estimate the number of cases averted by mass vaccination programmes in the U.S. Here we extend on their work using more elaborate methods applied to the Netherlands.

Our main objective was to estimate the impact of long-standing mass vaccination programmes in the Netherlands. To take secular trends into account, long time series of infectious disease notifications, including pre-vaccination periods, are required. We constructed a comprehensive database on infectious disease notifications over the past century in the Netherlands. Infectious diseases have been notified to public health authorities in detail since the 19<sup>th</sup> century; these data were previously archived but had not been digitized in databases usable for epidemiologic research. We focused on four infectious diseases: diphtheria, poliomyelitis, mumps, and rubella, and estimated the impact of mass vaccinations in terms of notified cases averted. For these infectious diseases, detailed data are available from both the pre-vaccination and vaccination period, and they are among the first diseases for which mass vaccinations were introduced in the Netherlands.

## Methods

### *Vaccination programmes in the Netherlands*

In the Netherlands, mass vaccination programmes started in 1953 with vaccination against diphtheria, which was combined with pertussis and tetanus (DTP) in 1954. Vaccination against poliomyelitis commenced in 1957 with a staggered catch-up campaign for everyone born since 1945. In 1962 vaccination with the combined diphtheria-pertussis-tetanus-poliomyelitis (DPTP) vaccine started.

Rubella vaccination was initially restricted to 11-year-old girls when vaccination started in 1974, and extended in 1987 with the measles-mumps-rubella (MMR) vaccine to include boys and girls at 14 months of age with a re-vaccination at 9 years of age.

### *Notification data*

We collected data on disease notifications in the Netherlands from 1919 to 1988 from various archived periodic reports by the Health Care Inspectorate (IGZ) and the National Institute for Public Health and the Environment (RIVM). These disease notifications were transcribed in tabular format independently by two researchers. For the period 1988–2015, individual based records were available from databases kept by the RIVM (Van Vliet et al., 2009). The reporting period of notifications varied over the study period, with weekly, 4-weekly, or monthly notifications available for most of the study period. Periods with only weekly or 4-weekly notifications were converted into monthly periods to keep the data in a consistent format. As these periods can cross months, we assumed cases were notified uniformly over a period and redistributed cases to months accordingly.

To estimate the impact of a mass vaccination programme on notified cases, data both prior to, and following the implementation of vaccination programmes are required. We therefore focused on vaccine-preventable diseases for which ample data were available: diphtheria, poliomyelitis, mumps, and rubella. Diphtheria has been notified to public health authorities since 1872, poliomyelitis since 1923, mumps since 1975, and rubella since 1951. For diphtheria we constructed a time series of monthly notified cases from 1919 up to 1915 (earlier data were yet unavailable), for poliomyelitis from 1923 up to 2015, for rubella from 1951 up to 2015, and for mumps from 1976 up to 1998 and from 2008 up to 2015 (mumps was not a notifiable disease from April 1999 to June 2008). We considered including other vaccine-preventable diseases for which mass vaccinations were implemented in the 20<sup>th</sup> century. For pertussis and measles data were available starting 1976. This period does not include the pre-vaccination period (mass vaccinations started in 1954 and 1976 respectively), thus precluding impact estimation. For tetanus data were available starting 1951 and mass vaccination started in 1954. This pre-vaccination period of three years and the notified cases therein were deemed too short and too few for proper analysis. For these reasons, pertussis, measles, and tetanus were not included in the analysis.

### *Poisson regression modelling of notified cases*

A latent process model was fitted to monthly pre-vaccination notification data and projected into the vaccination period to construct a counterfactual. A separate model was fitted to data for each vaccine-preventable disease. To adequately capture

infectious disease dynamics in the pre-vaccination period, each model included a seasonal term and a term for the overall secular trend. Auto-correlation was taken into account using an order-1 auto-regressive term. As some infectious diseases show clear multi-year cycles, we used wavelet analysis and inspected the local and global power spectrum in the pre-vaccination period to investigate the need to include any multi-year harmonic terms (Supplementary Figures 5.1 to 5.5 and Supplementary Tables 5.2 to 5.7). For this we used a Morlet wavelet, after log-transformation and adding a constant of 1 to each observation (Grenfell et al., 2001; Cazelles et al., 2007).

Let  $Y_t$  be the observed number of notifications in month  $t$ ,  $t = 1 \dots n$  and  $n$  is the total number of months in the pre-vaccination period, and follows a Poisson distribution:

$$Y_t = \text{Poisson}(\mu_t)$$

The regression model can then be described as:

$$\log(\mu_t) = \log(p_t) + \beta_0 + \beta_1 t + \sum_{j=1}^k [\alpha_j \sin\left(\frac{2\pi t}{12\tau_j}\right) + \gamma_j \cos\left(\frac{2\pi t}{12\tau_j}\right)] + x_t \quad (5.1)$$

where  $p_t$  is the general population of 0- to 20-year-olds at time  $t$  entered as an offset (the population most at risk of infection),  $\beta_0$  is an intercept term,  $\beta_1$  is the coefficient of the secular trend (transformed to indicate a percentage change:  $\beta_1 = 1 - \exp(\beta_1) \times 100$ ; adding a quadratic term did not improve model fits, data not shown). Seasonality and multi-year cycles are entered as the sum of  $k$  harmonics with frequencies of  $\tau$  years, where  $\tau$  is a set of integers based on the dominant frequencies in the pre-vaccination period (Supplementary Figures 5.1 to 5.5) and at least contains a seasonal term, i.e.  $\tau = 1$ . The term  $x_t$  is the log incidence rate of infection and cannot be observed; as such it describes the latent autocorrelation process defined as:

$$x_{t>1} \sim \text{Normal}(\rho x_{t-1}, \sigma^2)$$
$$x_1 \sim \text{Normal}(0, \sigma^2(1 - \rho^2)^{-1})$$

The model was defined in a Bayesian framework where the priors for the marginal variance and  $\rho$  are defined as:

$$\begin{aligned}\sigma^{-2}(1 - \rho^2) &\sim \text{Gamma}(1, 10^{-5}) \\ \log\left(\frac{1 + \rho}{1 - \rho}\right) &\sim \text{Normal}(0, 0.15)\end{aligned}$$

We assumed vague priors for the unknown coefficients  $\delta = \{\beta_0, \beta_1, \alpha_j, \gamma_j\}$  specified as  $\delta \sim \text{Normal}(0, 10^6)$ . The model was fitted using Integrated Nested Laplace Approximations (INLA); available at [www.r-inla.org](http://www.r-inla.org).

The pre-vaccination period used in the analysis was chosen as the longest possible time-window without destabilizing events that could potentially affect disease incidence, such as World War II (1939–1945). For diphtheria, the model was thus fitted to notified cases in the pre-vaccination period July 1948 to December 1952, after the epidemics during the World War II had died down. For poliomyelitis, this was the period January 1947 to July 1957 (the vaccination programme was implemented throughout the second half of 1957), and for mumps January 1976 through December 1986. The rubella vaccination programme was implemented in two stages: first 11-year-old girls in 1974, followed in 1987 by girls and boys age 14 months and 9 years. Two models were therefore fitted for rubella. The first model was fitted to the period January 1951 through December 1973, when no vaccination took place. The second model was fitted to the period January 1974 through December 1986, when only 11-year-old girls were vaccinated. We varied the length of the pre-vaccination period, and in some instances mode formulation used for fitting our models, to investigate its impact on our results (Supplementary Figure 5.6)

### *Constructing counterfactuals*

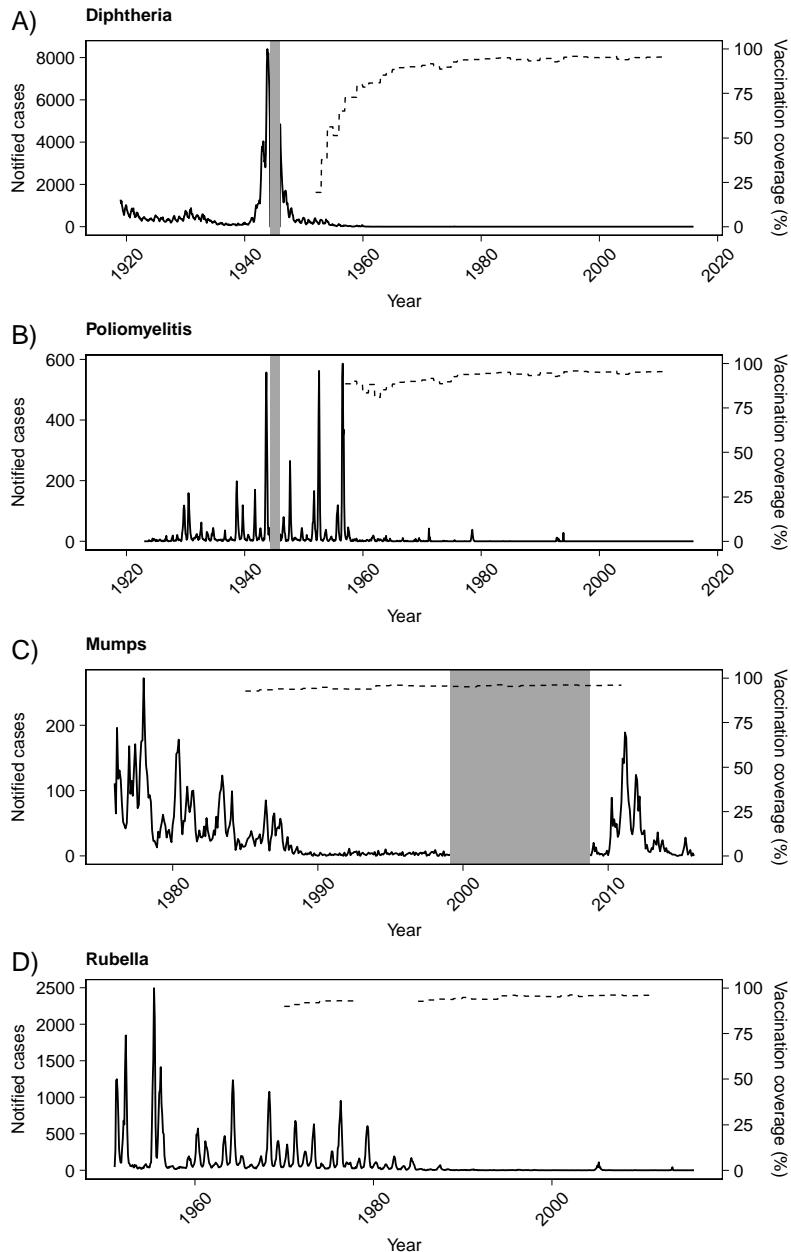
Each model was inspected for statistically significant exponential linear trends (indicated by coefficient  $\beta_1$  in the model). To reduce uncertainty in the counterfactuals, any non-significant trend term was removed and the model refitted. We focused on the impact of vaccination programmes on disease notifications in the first 13 years after a vaccination programme was introduced. We choose 13 years as this is the time between the start of mass vaccination against rubella for 11-year-old girls in 1974 and

the switch to universal vaccination for both boys and girls in 1987 (for mumps the extrapolation period was slightly shorter as mumps was not a notifiable disease from April 1999 until June 2008). The parameter estimates from the fitted models were used to construct counterfactuals (i.e. the situation if no vaccination programme had been implemented) by drawing 10 000 samples from the posterior distributions of the expected value  $\mu_t$  for each month  $t$ . The median and 95% credible intervals were derived from the distributions of posterior samples. All statistical analyses were performed in the R statistical programming environment, version 3.2.0 (R Development Core Team, 2015).

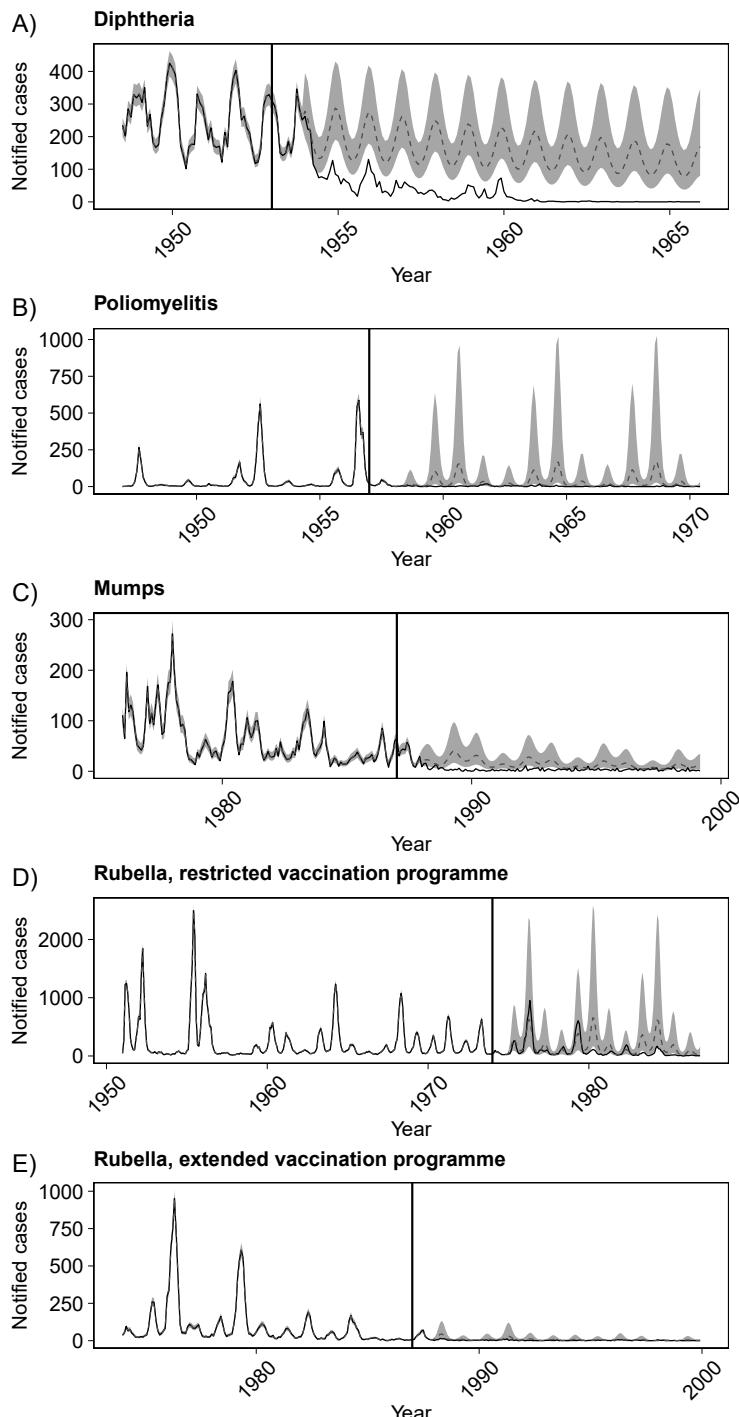
## Results

Figure 5.1 shows the time series of case notification for diphtheria, poliomyelitis, mumps, and rubella, along with the vaccination coverage. Diphtheria showed regular outbreaks each year and the incidence declined prior to World War 2, during which several large outbreaks occurred. After mass vaccination started, notifications declined to near zero. Poliomyelitis showed irregular outbreaks and after the start of mass vaccination few outbreaks occurred. Mumps notifications showed a gradual decline and stabilized at low levels after the start of mass vaccination. In 2010 a resurgence of mumps occurred after mandatory notification resumed in 2008. Similar to poliomyelitis, rubella showed irregular outbreaks, and since the vaccination programme was extended to include boys and girls in 1987 nearly no cases of rubella were reported. For each vaccine-preventable disease, vaccination coverage increased rapidly to well above 90% or was already high at the start of the programme.

Each vaccine-preventable disease showed a seasonal cycle with peaks predominantly during fall and winter (Supplementary Figures 5.1 to 5.5). In the pre-vaccination period, poliomyelitis showed a strong four-year cycle in major epidemics, and mumps showed a three-year cycle. We found a four-year cycle for rubella before mass vaccination; after mass vaccinations started for 11-year-old girls, a three-year cycle became apparent as well. For diphtheria the pre-vaccination period used for fitting was too short to adequately assess the presence of periodicities other than an annual cycle. Using harmonic terms, these annual and multi-year cycles were incorporated in the regression models. The final models are presented in Supplementary Table 5.2 and model selection in Supplementary Tables 5.3 to 5.7.



**Figure 5.1: Monthly notified cases for diphtheria, poliomyelitis, mumps, and rubella, the Netherlands, 1919–2015.** Notified cases for (A) diphtheria; (B) poliomyelitis; (C) mumps; and (D) rubella. Notified cases are shown in black, grey areas represent periods of missing data. Dashed line indicates vaccination coverage and represents the coverage at 11 months of age for diphtheria and poliomyelitis (the primary series and first booster) and at 14 months of age for mumps. For rubella, the dashed line shows the coverage at 11 years of age up to 1977 and the coverage at 14 months of age thereafter; no vaccination data are available for cohorts born prior to 1970 and for the cohorts 1978–1984.



**Figure 5.2: Monthly notified cases, model fits, and counterfactuals for diphtheria, poliomyelitis, mumps, and rubella, the Netherlands.** Notified cases, model fits, and counterfactuals for (A) diphtheria; (B) poliomyelitis; (C) mumps; (D) rubella, vaccination of 11-year-old-girls; and (E) rubella, vaccination of both 14-month- and 9-year-old boys. Notified cases in black, median model fit and 95% credible interval in grey; vertical solid lines indicate start of mass vaccinations. Extrapolated model results are indicated by grey dashed line with 95% credible interval in the vaccination period.

Figure 5.2 show model fits to pre-vaccination notification data as well as the expected notified cases had vaccination programmes not been implemented. Each model showed a good visual fit to the pre-vaccination data. Diphtheria and mumps exhibited an exponential decline in the pre-vaccination period with a median monthly decline of -0.52% [95% credible interval (CI): -0.89%, -0.17%] and -0.90% [95% CI: -1.22%, -0.56%] respectively (Table 5.1). We did not find a trend for poliomyelitis (median monthly decline -0.62%, with a 95% CI: -0.67%, 1.83%). For rubella, no trend was observed before the implementation of mass vaccination for 11-year-old girls (median monthly decline of -0.10%, 95% CI: -0.48%, 0.28%). However, after start of vaccination and before the transition to MMR in 1987, there was a trend with a decline of -1.44% [95% CI: -2.10%, -0.85%]. Posterior distributions for the expected number of notified cases in the counterfactual showed broad credible intervals, but overall mimicked pre-vaccination patterns well.

In the first 13 years after diphtheria mass vaccinations started, a median of 18 900 [95% CI: 12 000, 28 600] notified cases were averted (Table 5.1). For poliomyelitis this was 5000 [95% CI: 2200, 13 500], and for mumps 1800 [95% CI: 1000, 3200]. Vaccination of 11-year-old girls against rubella averted a median 13 700 [95% CI: 1400, 38 300] cases. Switching to the extended programme averted 700 [95% CI: 80, 2300] cases in the first 13 years. In terms of overall effectiveness, 82.4% [95% CI: 74.9%, 87.6%] of cases have been averted by mass vaccination against diphtheria. For poliomyelitis this was 92.9% [95% CI: 85.0%, 97.2%], for mumps 79.1% [95% CI: 67.1%, 87.4%], for the restricted vaccination programme against rubella 49.9% [95% CI: 9.3%, 73.5%], and for the extended programme 68.1% [95% CI: 19.4%, 87.3%]. Varying the pre-vaccination period used for fitting the models for diphtheria, poliomyelitis, and mumps did not substantially impact our results (Supplementary Figure 5.6). For rubella, limiting the fitting period to 1969–1974 and 1976–1987 or shorter resulted in credible intervals for the number of cases averted that overlap with zero.

## Discussion

Our analysis shows a substantial impact of mass vaccination programmes against diphtheria, poliomyelitis, mumps, and rubella on the number of notified cases in the first 13 years following mass vaccinations in the Netherlands. Our findings are in line with other studies on the population-level impact of vaccination programmes in the

**Table 5.1: Impact of vaccination programmes in the first ten years following the implementation of mass vaccination, the Netherlands.** Log-linear Poisson regression models were fit to pre-vaccination notified cases of diphtheria, poliomyelitis, mumps, and rubella. Models took into account secular trends, auto-correlation, and harmonic, seasonal, and multi-annual cycles.

Disease	Start mass vaccination	Pre-vaccination period		Counterfactual period	Vaccination period
		Fitting period	Median monthly change[%] [95% CI]		
Diphtheria	1953	July 1948 – December 1952	-0.52 [-0.89, -0.17]	January 1953 – December 1965	18900 [12000, 28600]
Poliomyelitis	1957	January 1947 – June 1957	0.62 [-0.67, 1.83]	July 1957 – June 1970	5000 [2200, 13500]
Mumps <sup>1</sup>	1987	January 1976 – December 1986	-0.90 [-1.22, -0.56]	January 1987 – March 1999	1800 [1000, 3200]
Rubella <sup>2</sup>	1974	January 1951 – December 1973	-0.01 [-0.48, 0.28]	January 1974 – December 1986	13700 [1400, 38300]
	1987	January 1974 – December 1986	-1.44 [-2.10, -0.85]	January 1987 – December 1999	700 [80, 2300]
					68.1 [19.4, 87.3]

CI: credible interval.

<sup>1</sup> For mumps the counterfactual period is slightly shorter than 13 years as mumps was not notifiable between March 1999 and June 2008.

<sup>2</sup> For rubella two models were fitted: one to the period prior to mass vaccination of 11-year-old girls in 1974 (the restricted programme), and another to the period following this restricted programme but prior to extension with the measles-mumps-rubella vaccine in 1987 to both boys and girls of 14 months of age and re-vaccination at 9 years of age.

Netherlands and other countries in that we show vaccination programmes have been highly effective. Contrary to many pre- versus post-implementation comparisons for long-standing vaccination programmes, we take secular trends into account and thereby provide a more accurate representation of the cases averted by vaccination (Roush and Murphy, 2007; Van Panhuis et al., 2013; Gomes et al., 1999; Peltola et al., 1986).

Notifications of diphtheria and mumps were already declining before the implementation of mass vaccinations. This was not the case for poliomyelitis and rubella. For diphtheria, this decline may be due to unregistered vaccination before the start of mass vaccination; vaccination against diphtheria was already widespread before mass vaccinations started in 1953 (Hoogendoorn, 1954). Despite this early uptake, major diphtheria epidemics swept across the Netherlands during the World War 2 (Figure 5.1). The observed decline in the post-war period may be also due to the aftermath of these war-time epidemics.

Other factors than vaccination could have contributed to the decline in notified cases as well. During the 20<sup>th</sup> century, the Netherlands experienced several socio-demographic, epidemiologic, and economic transitions characterized by improvements in nutritional status, hygiene, housing conditions, and medical care. These changes are reflected in the decrease in mortality from infectious diseases, including vaccine-preventable disease, in the late 19<sup>th</sup> and early 20<sup>th</sup> century (Wolleswinkel-van den Bosch et al., 1997; Van Wijhe et al., 2016; Querido, 1968). However, these factors generally have gradual effects; the sudden and rapid decline in notified cases after the start of mass vaccination, suggests that vaccination played a major role. We are unsure as to why diphtheria and mumps showed a gradual decline over time, whereas polio and rubella did not. Further study of pre-vaccination patterns of these diseases and comparison with other (non-vaccine-preventable) infectious diseases could elucidate this conundrum.

It is unlikely that the pre-vaccination downward trends for diphtheria and mumps would hold on the long-run in the absence of vaccination. As naturally acquired immunity would decline, outbreaks become more likely, and consequently, the incidence of disease may have been higher than our model extrapolations. Similarly, the resurgence of mumps in 2010 is likely due to gradual loss of population-immunity over the preceding period of high vaccination coverage, and cannot be

explained by our model. Had vaccination not been implemented, this resurgence may have been substantially weaker. Such questions would better be addressed with SEIR-type models, trying to unravel the mechanisms of loss of immunity. Because our models do not directly account for the population-immunity we restricted our extrapolation to the early years following vaccine implementation. Nevertheless, the estimated impact of vaccination programmes for diphtheria, mumps, and rubella (after the switch to universal vaccination) is likely underestimated.

We did not take underreporting of cases into account and implicitly assumed a constant reporting rate over time. Although difficult to verify, underreporting may have changed over time, especially around the start of a vaccination programme and the years thereafter. It is possible that underreporting increased as diseases became rarer and people less familiar with them. We would then overestimate the impact of vaccination programmes. The opposite is also possible: underreporting would decline as a result of an increased focus on these diseases. As far as we know, there were no major changes in case definitions or the registration of notifications around the time vaccination programmes started. Because the magnitude and direction of a potential change in reporting rates is unknown, we did not take it into account. More complex mathematical models, tracking the number of infected and susceptible individuals in the population could be used to estimate the amount of underreporting (Wallinga et al., 2003; Metcalf et al., 2009).

We could not take geographic spread of notified cases into account. This may be important as the Netherlands shows regions of distinct vaccination coverage heterogeneity, with areas of low vaccination coverage where people refuse vaccination based on religious beliefs (Knol et al., 2013; Wielders et al., 2011; Van den Hof et al., 1999). It is likely that many of the reported cases in the vaccination era originate from these areas. Our purpose in this study was to quantify the population-level effectiveness of vaccination programmes as a whole, but it would be informative to perform similar analyses on regional data and to stratify the effectiveness by coverage level. Such analyses require detailed information on geographic location of notified cases, which are unfortunately not yet available for the Netherlands.

A future study could focus on the severity of infection and the impact of vaccination programmes on disease burden. For most infectious diseases a major part of the burden is associated with long-term sequelae such as encephalitis, meningitis, and

hearing loss in the case of mumps, paralysis in the case of poliomyelitis, and congenital defects in the case of rubella (Plotkin et al., 2013). Although notified cases tend to be more severe, we lacked access to detailed information on the severity or age of notified cases. We therefore did not assess the morbidity burden averted by vaccination programmes. Recent studies in England showed considerable declines in measles and mumps hospital admissions, encephalitis, and viral meningitis after the introduction of MMR vaccination in 1988 (Iro et al., 2017; Goldacre and Maisonneuve, 2013; Martin et al., 2016). Similar reductions are likely to be present in the Dutch situation as well.

Maintaining high vaccination coverage is important to limit transmission of vaccine-preventable diseases and prevent their resurgence. Continuous monitoring and evaluation of vaccination programmes is therefore important. However, our scientific understanding of the dynamics of disease transmission as well as the evaluation of disease-control programmes and public health education efforts are hampered by a lack of historical infectious disease data repositories with sufficient temporal and geographic resolution (Van Panhuis et al., 2013). In an earlier approach to solve this problem, Van Panhuis et al. (2013) constructed a comprehensive database—aptly named Project Tycho—on infectious disease notifications in the US and estimated the impact of mass vaccination programmes (Van Panhuis et al., 2013). Here we extended on their work for the situation in the Netherlands using a more advanced model taking autocorrelation and secular trends into account.

In summary, we evaluated the early impact of mass vaccination programmes against diphtheria, poliomyelitis, mumps, and rubella in the Netherlands. This study reveals their effectiveness in number of averted cases and provides additional insight in their overall population-level impact and importance to public health.

### Contributors

MvW and ADT obtained, extracted, and analysed the data, searched the scientific literature, and wrote the first draft of the manuscript. MvW, ADT, HKA, SAM, HEdM, MJP, and JW designed the study and revised the manuscript. MvW, MJP, and JW conceived the project.

### Declaration of interests

MJP received grants and honoraria from various pharmaceutical companies, including GlaxoSmithKline, Pfizer, and Sanofi Pasteur MSD, who are potentially interested in the subject matter of this Article.

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## Impact of vaccination programmes on notified cases

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## **Supplementary information to Chapter 5**

**Supplementary Table 5.2: Final models used for the analyses of case notifications.** Model selection was based on statistical relevance of the coefficients and wavelet analysis. Latent process Poisson regression models were fitted to pre-vaccination notified cases of poliomyelitis. Models were fitted in a Bayesian framework using flat priors and assuming a latent auto-correlation process.

Disease	$\beta_1$	Secular trend				Median [95% CI]			
		$\alpha_1$	$\gamma_1$	$\alpha_3$	$\gamma_3$	$\alpha_4$	$\gamma_4$		
Diphtheria	-0.005 [-0.009, -0.002]	0.147 [0.061, 0.233]	-0.374 [-0.459, -0.289]						
Poliomyelitis		-1.287 [-1.528, -1.046]	-0.959 [-1.194, -0.723]					0.981 [0.445, 1.528]	-0.538 [-1.109, -0.002]
Mumps	-0.009 [-0.012, -0.006]	0.392 [0.258, 0.526]	-0.018 [-0.149, 0.114]	-0.171 [-0.359, 0.019]	-0.444 [-0.623, -0.258]				
Rubella <sup>1</sup>									
Pre-vaccination		0.876 [0.775, 0.976]	-0.241 [-0.341, -0.141]					0.913 [0.617, 1.207]	-0.122 [-0.409, 0.166]
Pre-extended programme	-0.015 [-0.021, -0.009]	0.857 [0.729, 0.985]	-0.431 [-0.558, -0.305]	-0.458 [-0.739, -0.173]	-0.236 [-0.532, 0.043]	0.036 [-0.291, 0.377]		-0.534 [-0.857, -0.211]	

CI: credible interval.

<sup>1</sup> For rubella two models were fitted: one to the period prior to mass vaccination of 11-year old girls in 1974 (the restricted programme), and another to the period following this restricted programme but prior to extension with the measles-mumps-rubella vaccine in 1987 to both boys and girls of 14 months of age and re-vaccination at 9 years of age.

**Supplementary Table 5.3: Models fitted to case notifications of diphtheria for the period July 1948 through December 1952.** Final model used for the analyses is highlighted in bold. Model selection was based on statistical relevance of the coefficients and wavelet analysis. Latent process Poisson regression models were fitted to pre-vaccination notified cases of poliomyelitis. Models were fitted in a Bayesian framework using flat priors and assuming a latent auto-correlation process.

Mode	DIC	$\beta_1$	Median [95% CI]			
			Secular trend		Harmonic terms	
		$\alpha_1$	$\gamma_1$	$\alpha_2$	$\gamma_2$	
1.	<b>605.59</b>	<b>-0.005</b>	0.147	-0.374		
		[ <b>-0.009</b> , -0.002]	[0.061, 0.233]	[ <b>-0.459</b> , -0.289]		
2.	605.65		0.145	-0.367		
			[0.045, 0.244]	[ <b>-0.464</b> , -0.268]		
3.	605.55	-0.006	0.145	-0.379	-0.075	-0.041
		[ <b>-0.010</b> , -0.003]	[0.062, 0.226]	[ <b>-0.459</b> , -0.298]	[ <b>-0.165</b> , 0.015]	[ <b>-0.132</b> , 0.049]

CI: credible interval.

**Supplementary Table 5.4: Models fitted to case notifications of poliomyelitis for the period January 1947 through June 1957.** Final model used for the analyses is highlighted in bold. Model selection was based on statistical relevance of the coefficients and wavelet analysis. Latent process Poisson regression models were fitted to pre-vaccination notified cases of poliomyelitis. Models were fitted in a Bayesian framework using flat priors and assuming a latent auto-correlation process.

Model	DIC	$\beta_1$	Secular trend		Harmonic terms				Median [95% CI]
			$\alpha_1$	$\gamma_1$	$\alpha_2$	$\gamma_2$	$\alpha_3$	$\gamma_3$	
1.	779.97	0.003	-1.276 [-1.530, -1.022]	-0.967 [-1.215, -0.719]					
2.	779.94		-1.278 [-1.532, -1.025]	-0.968 [-1.215, -0.720]					
3.	780.39		-1.268 [-1.521, -1.015]	-0.968 [-1.216, -0.721]	0.023 [-0.412, 0.465]	-0.296 [-0.726, 0.136]			
4.	779.24		<b>-1.287</b> [-1.528, -1.046]	<b>-0.959</b> [-1.194, -0.723]			0.981 [0.445, 1.528]	-0.538 [-1.087, -0.002]	
5.	780.79		-1.290 [-1.537, -1.043]	-0.972 [-1.214, -0.731]					[0.789, 0.542] [0.280, 1.596]

C: credible interval.

**Supplementary Table 5.5: Models fitted to case notifications of mumps for the period January 1976 through June 1986.** Final model used for the analyses is highlighted in bold. Model selection was based on statistical relevance of the coefficients and wavelet analysis. Latent process Poisson regression models were fitted to pre-vaccination notified cases of poliomyelitis. Models were fitted in a Bayesian framework using flat priors and assuming a latent auto-correlation process.

Model	DIC	Secular trend		Harmonic terms					Median [95% CI]	
		$\beta_1$	$\alpha_1$	$\gamma_1$	$\alpha_2$	$\gamma_2$	$\alpha_3$	$\gamma_3$	$\alpha_4$	
1.	1073.77	-0.008 [-0.014, -0.003]	0.396 [0.242, 0.551]	0.024 [-0.176, 0.128]						
2.	1073.63		0.404 [0.245, 0.563]	-0.022 [-0.179, 0.135]						
3.	1073.78	-0.008 [-0.014, -0.003]	0.396 [0.241, 0.551]	-0.026 [-0.178, 0.127]	-0.104 [-0.344, 0.136]	0.096 [0.138, 0.330]				
4.	<b>1075.16</b>	-0.009 [-0.012, -0.006]	0.392 [0.238, 0.526]	-0.018 [-0.149, 0.114]			-0.171 [-0.359, 0.019]	-0.444 [-0.623, -0.258]		
5.	1073.76	-0.008 [-0.014, -0.002]	0.397 [0.240, 0.553]	-0.024 [-0.178, 0.130]				0.019 [-0.319, 0.359]	0.002 [-0.315, 0.322]	

CI: credible interval.

**Supplementary Table 5.6: Models fitted to case notifications of rubella for the period January 1951 through December 1973.** This model was fitted to the period prior to the start of vaccination of 11-year-old girls. Final model used for the analyses is highlighted in bold. Model selection was based on statistical relevance of the coefficients and wavelet analysis. Latent process Poisson regression models were fitted to pre-vaccination notified cases of poliomyelitis. Models were fitted in a Bayesian framework using flat priors and assuming a latent auto-correlation process.

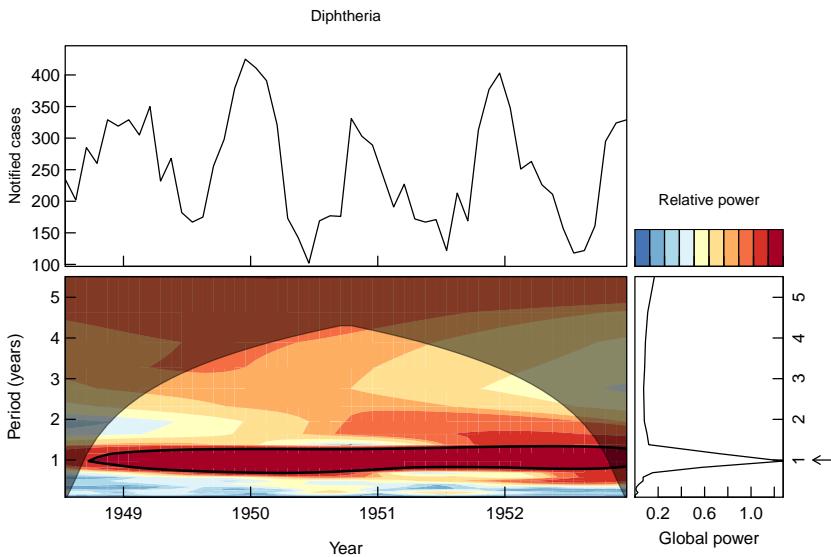
Model	DIC	$\beta_1$	Secular trend				Harmonic terms				Median [95% CI]
			$\alpha_1$	$\gamma_1$	$\alpha_2$	$\gamma_2$	$\alpha_3$	$\gamma_3$	$\alpha_4$	$\gamma_4$	
1.	2405.25	-0.002	0.872	0.241							
			[0.008, 0.004]	[0.767, 0.977]							
2.	2405.21		0.873	-0.241							
				[0.767, 0.978]							
3.	2405.27		0.873	-0.241	0.095		-0.067				
				[0.767, 0.978]	[0.106, 0.295]		[0.266, 0.132]				
4.	2404.93		0.837	-0.240				0.050	-0.315		
				[0.768, 0.977]				[0.234, 0.333]	[0.593, -0.036]		
5.	2403.82		0.876	-0.241						-0.122	
				[0.775, 0.976]					[0.617, 1.207]		[0.409, 0.166]

C: credible interval.

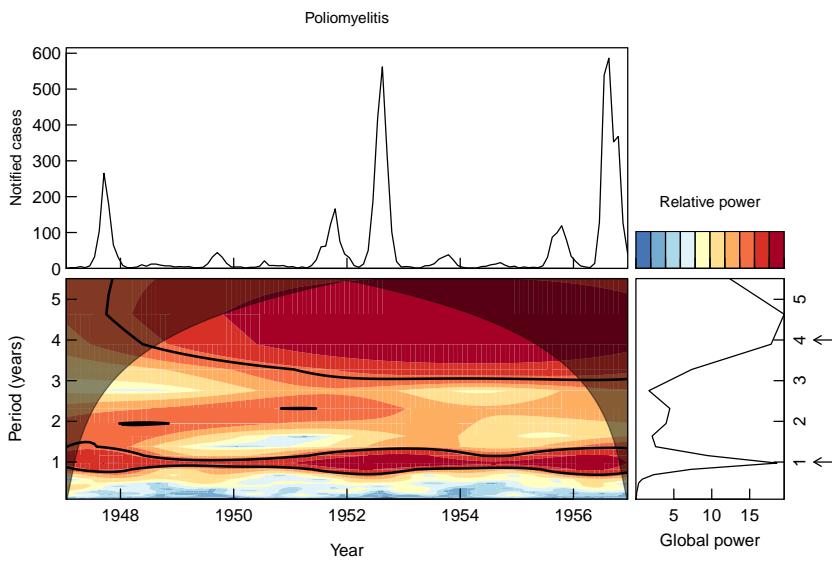
**Supplementary Table 5.7: Models fitted to case notifications of rubella for the period January 1974 through December 1986.** This model was fitted to the period prior to the start of vaccination of 14-month and 9-year-old boys and girls. Final model used for the analyses is highlighted in bold. Model selection was based on statistical relevance of the coefficients and wavelet analysis. Latent process Poisson regression models were fitted to pre-vaccination notified cases of poliomyelitis. Models were fitted in a Bayesian framework using flat priors and assuming a latent auto-correlation process.

Model	DIC	$\beta_1$	Secular trend		Harmonic terms				Median [95% CI]
			$\alpha_1$	$\gamma_1$	$\alpha_2$	$\gamma_2$	$\alpha_3$	$\gamma_3$	
1.	1207.49	-0.012 [0.021, -0.001]	0.845 [0.798, 0.962]	-0.129 [-0.564, -0.294]	-0.426 [-0.561, -0.291]				
2.	1207.74		0.849 [0.713, 0.985]						
3.	1207.81	-0.012 [0.021, -0.001]	0.846 [0.708, 0.983]	-0.429 [-0.566, -0.293]	0.027 [-0.224, 0.277]	0.088 [-0.160, 0.334]			
4.	1207.51	-0.014 [-0.022, -0.005]	0.851 [0.719, 0.983]	-0.433 [-0.563, -0.303]			-0.481 [-0.794, -0.165]	-0.309 [-0.623, 0.003]	
5.	1207.63	-0.014 [-0.022, -0.006]	0.851 [0.777, 0.984]	-0.428 [-0.560, -0.297]					0.013 [-0.610, -0.239]
6.	1208.05	-0.015 [0.021, 0.009]	0.857 [0.729, 0.985]	-0.431 [-0.558, -0.305]			-0.458 [-0.739, -0.173]	-0.236 [-0.532, 0.043]	

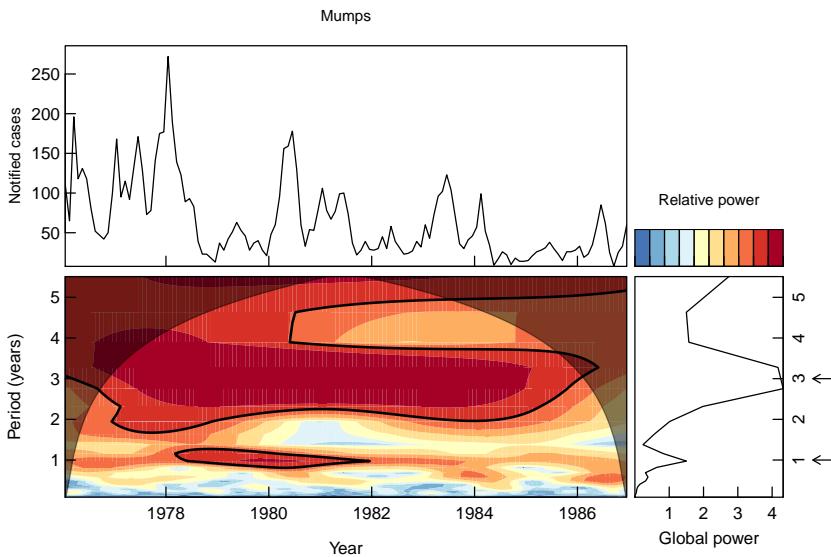
CI: credible interval.



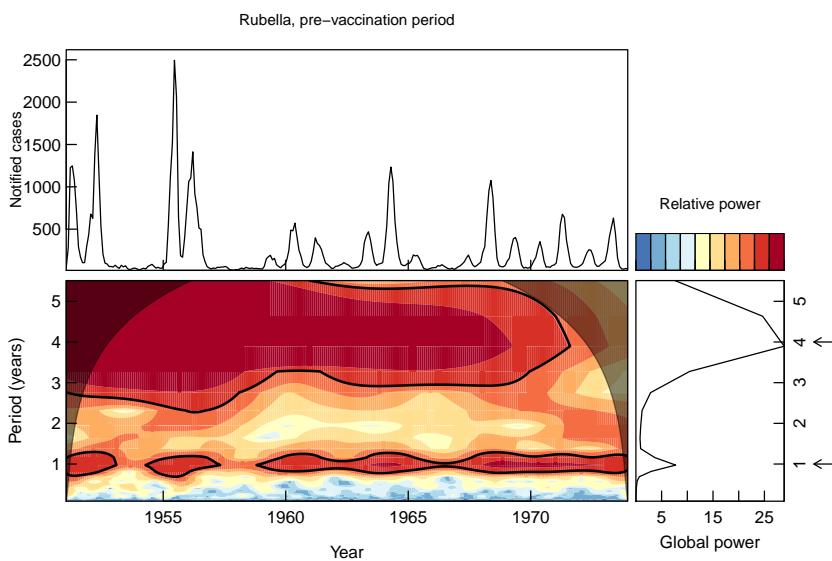
**Supplementary Figure 5.1:** Wavelet time series analysis of monthly notified cases of diphtheria in the pre-vaccination period July 1948 through December 1952, the Netherlands. Top panel shows the monthly notified cases of diphtheria. Bottom panel shows the local wavelet power spectrum; colour code is shown at the top right. Bottom right panel shows the global wavelet power spectrum; arrow indicates the predominant signal.



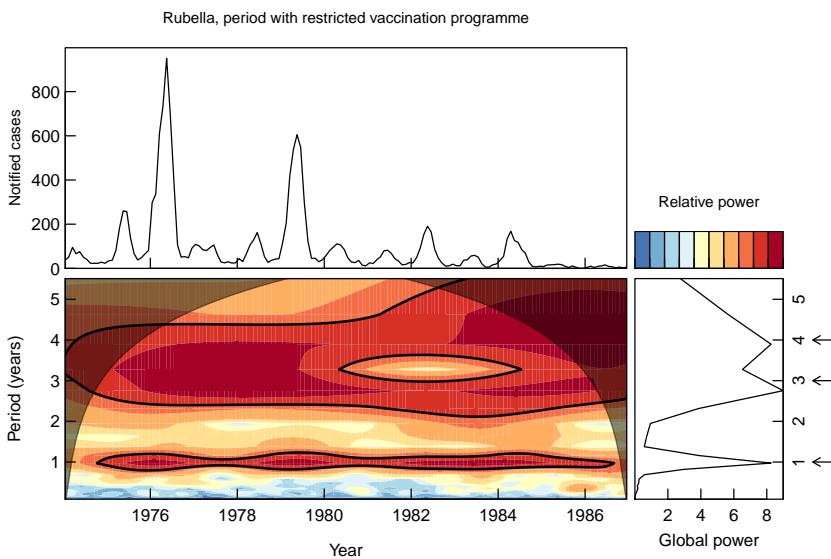
**Supplementary Figure 5.2:** Wavelet time series analysis of monthly notified cases of poliomyelitis in the pre-vaccination period January 1947 through June 1957, the Netherlands. Top panel shows the monthly notified cases of poliomyelitis. Bottom panel shows the local wavelet power spectrum; colour code is shown at the top right. Bottom right panel shows the global wavelet power spectrum; arrows indicate the predominant signals.



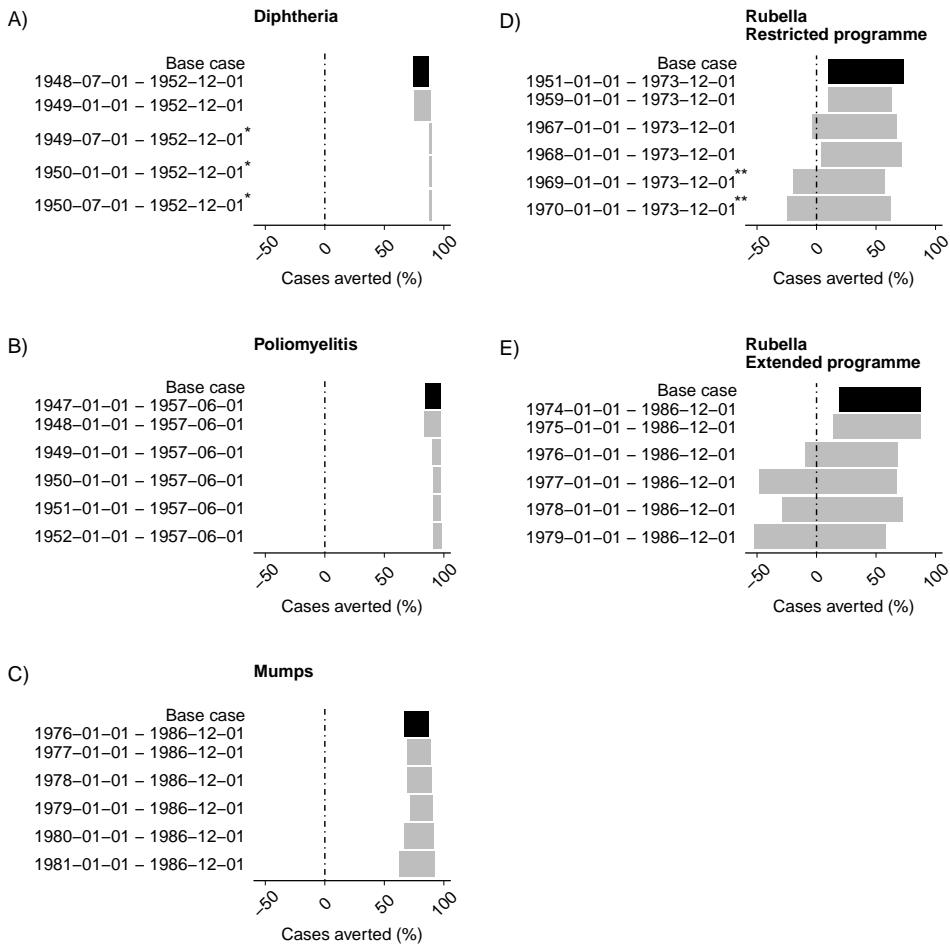
**Supplementary Figure 5.3: Wavelet time series analysis of monthly notified cases of mumps in the pre-vaccination period January 1967 through December 1986, the Netherlands.** Top panel shows the monthly notified cases of mumps. Bottom panel shows the local wavelet power spectrum; colour code is shown at the top right. Bottom right panel shows the global wavelet power spectrum; arrows indicate the predominant signals.



**Supplementary Figure 5.4:** Wavelet time series analysis of monthly notified cases of rubella in the pre-vaccination period January 1951 through December 1974, the Netherlands. Top panel shows the monthly notified cases of rubella. Bottom panel shows the local wavelet power spectrum; colour code is shown at the top right. Bottom right panel shows the global wavelet power spectrum; arrows indicate the predominant signals.



**Supplementary Figure 5.5:** Wavelet time series analysis of monthly notified cases of rubella in the period with a restricted vaccination programme for 11-year-old girls January 1974 through December 1986, the Netherlands. Top panel shows the monthly notified cases of rubella. Bottom panel shows the local wavelet power spectrum; colour code is shown at the top right. Bottom right panel shows the global wavelet power spectrum; arrows indicate the predominant signals.



**Supplementary Figure 5.6: Estimated percentage of cases averted due to vaccination programmes under various fitting periods.** Estimated percentage of cases averted due to vaccination programmes under various fitting periods for (A) diphtheria; (B) poliomyelitis; (C) mumps; (D) rubella for the restricted vaccination programme of 11-year-old girls; and (E) rubella for the extended vaccination programme of both boys and girls at 14 months and 9 years of age, the Netherlands. Pre-vaccination periods used for fitting the regression models are indicated on the left. Base cases as presented in the main text are represented by the black bar. Except for several scenarios, models were of an identical form as the base case. For diphtheria three scenarios did not include a term for secular trend (\*); for rubella two scenarios included a term for a two-year cycle rather than a four-year cycle (\*\*).



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# **Chapter 6**

## **Financing vaccination programmes in the Netherlands from a macro-economic perspective: a historical analysis**

The contents of this chapter have been submitted for publication:

**Financing vaccination programmes in the Netherlands from a macro-economic perspective:  
a historical analysis**

Maarten van Wijhe, Pieter T. de Boer, Herman J. de Jong, Hans van Vliet, Jacco Wallinga,  
Maarten J. Postma

## Abstract

### *Background*

Health economic evaluations are often required before implementation of a vaccination programme. Such evaluations should be viewed in the context of the history of vaccination programmes. Here we aim to provide an overview of the financial history of vaccination programmes in the Netherlands and to reflect government expenditures on these programmes to demographic and macro-economic developments.

### *Methods*

Previously uncatalogued historical expenditures on the Dutch National Immunisation Programme (NIP) and influenza vaccination were obtained from various official reports. All costs were adjusted for inflation using Consumer Price Indices and expressed in Euro of 2016.

### *Results*

Expenditure on the NIP increased from €5 million in 1957 to €93 million in 2014. Since the mid-1980s, expenditure increased nearly five-fold due to the introduction of new vaccines, specifically 7-valent pneumococcal conjugate vaccine. Expenditure reached €5.54 per capita and €533 per birth in 2014. Spending on specific vaccines tended to decline over time. The contribution of the NIP to total healthcare expenditure remained small, ranging between 0.05% and 0.14%. Spending on influenza vaccination increased from €37 million in 1996 to €52 million in 2014, while spending relative to total healthcare expenditure decreased from 0.069% to 0.055%. Together, 0.022% of the Dutch Gross Domestic Product and 0.15% of healthcare expenditure was spent on vaccination programmes in 2014.

### *Conclusion*

While government expenditure on vaccination programmes increased substantially, the contribution to overall healthcare expenditure remained small. The financial evolution of vaccination programmes provides the context for today's decision making.

## Introduction

Currently, health economic evaluations of vaccines are a common part of vaccine research. In the Netherlands, the introductions of new vaccines are generally discussed by a special committee of the Health Council of the Netherlands on several criteria before they are considered for inclusion in the National Immunization Programme (NIP). These criteria include the severity of the disease, effectiveness and safety of the vaccine, its acceptability, whether the public health issue is urgent enough, and the cost-effectiveness of the vaccine (Houweling et al., 2010). With the last criterion the economic considerations explicitly come into play.

Cost evaluations were not always part of the decision making process. The merits of Edward Jenner's vaccine against smallpox were measured on its safety and efficacy, not its costs. Similarly, the inclusion of diphtheria, pertussis, tetanus, poliomyelitis, measles, mumps, and rubella, were not evaluated on their cost-effectiveness or cost-saving potential before they were introduced (Black, 2013). In general, considerations on healthcare costs were by far not as prominent as they are nowadays. Also, the first vaccination programmes were introduced in a time with higher infectious disease morbidity and mortality as compared to today, which may have led to an easier decision on implementation of preventive measures. Decision makers focused on whether the disease was severe enough to warrant a vaccination programme and whether the vaccines themselves were efficacious.

The economic aspects of vaccinations have only begun to play an important role in decision making over the past several decades, partially due to the substantial increase in healthcare expenditure in most high income countries (Anderson et al., 2003). In addition, recently introduced vaccines such as the pneumococcal vaccines and the vaccines against human papillomavirus are much more complicated to produce, have a higher price, and their benefits are sometimes less visible than the older vaccines (Hinman et al., 2004; Davis, 2010). For a government with restricted budgets, these developments have led policy makers to focus on health economic analyses of medical and preventive interventions including vaccines (Meltzer, 2008).

Health economic evaluations of a new vaccine that is considered for inclusion in the NIP should be viewed in the context of the vaccination programme as a whole along with its history. Understanding the history of vaccination programmes may help to properly evaluate the benefits and costs of old and new vaccines.

To provide such an understanding, we review the financial history of vaccination programmes in the Netherlands up to the year 2014, with a focus on childhood and influenza vaccinations. Rather than look at the potential future expenditure on new vaccines, we take a look at how much existing vaccination programmes have costed throughout the years from a government perspective. We will briefly discuss the history of the Dutch vaccination programmes and how they were financed, followed by an analysis of the developments in government expenditure on these programmes since implementation. In particular, and to provide further context, we examine whether the expenditure on vaccination programmes have increased relative to other measures such as total healthcare expenditure and Gross Domestic Product (GDP).

## **Organisation and funding of vaccination programmes**

### *Childhood vaccination programmes*

Table 6.1 provides a brief overview of the development of vaccination programmes in the Netherlands. Officially, the Dutch NIP was launched in 1957 with the start of mass vaccinations against poliomyelitis, but already in 1953 mass vaccinations against diphtheria were implemented. Although a toxoid-vaccine against diphtheria was available since the mid-1920s, diphtheria vaccinations in the Netherlands were not widespread before 1953, with only 4% to 13% of the population being vaccinated in the early 1940s (Hoogendoorn, 1954). Vaccinations were generally provided by local private healthcare providers or government bodies and administered by general practitioners to children aged between 4 and 9 years, while most cases of diphtheria occurred in younger children. The potential impact of these vaccinations was thus limited. The vaccines were paid for by parents, private or social health insurances, charities, or other local funding organisations, but there was no coherence between regions or a central coordination of vaccination efforts (Vos and Richardus, 2004a).

In the early 1950s the Health Care Inspectorate increased their efforts to get more children vaccinated and at a lower age. To do so, financial support was offered to Child Welfare Centers by providing a reimbursement of 1 Dutch Guilder for each registered vaccination starting in 1951. This was done through a local and government financed fund called the 'Praeventiefonds', which was tasked to provide

financial support to organisations and groups to improve public health and combat disease. In 1953, the government extended its support by providing the vaccines free of charge. Vaccines were produced or bought by the National Institute for Public Health and provided through the Health Care Inspectorate. During this time, vaccines against pertussis and tetanus became available and were provided for free through the same structure. This marks the start of the developments that would eventually lead to the organized vaccination programme we know today.

Providing financial support and consolidating the organisation of vaccination efforts increased vaccination coverage (coverage of the diphtheria vaccine for infants increased from 20% in 1953 to over 50% in 1955 (Van Wijhe et al., 2016)), but it became clear that in order to reach more children, closer collaboration between municipalities and healthcare workers was required. To unite the organisations involved in vaccinations, the first so-called 'entgemeenschap' was launched in 1955. Within this collaborative framework, Child Welfare Centers, local general practitioners, Health Organisations, municipal health services, and local governments worked together to coordinate vaccination efforts (Vos and Richardus, 2004b).

At the same time, it was recognized that a uniform registration system of vaccination was needed to monitor the progress and success of the vaccination campaigns. Since the 19<sup>th</sup> century a register of smallpox vaccinations was already kept by municipalities and was now extended with the new vaccines. At birth, children received a card on which all vaccinations was registered. With each vaccination (generally administered at Child Welfare Centers or schools), healthcare workers would send a note to the local municipality where the vaccination was recorded.

All efforts of the preceding years came together with the mass vaccination against poliomyelitis in 1957 which sparked an increased public interest in vaccination. A major nationally coordinated vaccination campaign, staged over multiple years, was organised in which all children born since 1945 were invited to be vaccinated against poliomyelitis. This catch-up vaccination programme was executed from 1957 until 1962 and reached more than 2.6 million children. It also marked the launch of the new registration system as well as the start of the expansion of the collaborative framework of 'entgemeenschappen' to the rest of the Netherlands. The mass vaccination campaign against poliomyelitis is therefore seen as the official start of the Dutch NIP (Vos and Richardus, 2004b).

The Praeventiefonds continued to financially support the NIP until 1963, when the Ministry of Social Affairs and Public Health took over the complete funding of the vaccination programme, now containing the vaccines against smallpox and the combined DTP-IPV-vaccine (diphtheria-pertussis-tetanus-inactivated poliomyelitis). Since 1974, funding was provided through the collective and government funded social health insurance (the 'Algemene Wet Bijzondere Ziektekosten'; AWBZ) which covered every Dutch citizen. All subsequent vaccines that were added to the NIP were financed in this way until 2015 when the AWBZ was abolished. In 2018, the childhood vaccination programmes will be incorporated in the Public Health Act. Currently, the NIP is coordinated by the National Institute for Public Health and the Environment (RIVM) which is also responsible for communication on the NIP, and the registration, purchase, storage, and distribution of vaccines.

### *Influenza vaccination programme*

The first successful influenza vaccine was developed in the early 1940s and used by the US military in 1944 and 1945. In the following two decades it became clear that the influenza virus mutates rapidly and that the vaccine needs to be reformulated regularly to match it with the expected strain of influenza, although an occasional mismatch does occur (Hannoun, 2013).

Like the NIP, initially there was no national programme for influenza vaccination in the Netherlands. Vaccinations were distributed by pharmacies and administered by and at general practitioners and targeted towards risk groups. The Health Council of the Netherlands reported each year on which risk groups should be vaccinated. These groups included patients with respiratory or heart problems, patients with diabetes mellitus, patients with HIV, and other groups with medical conditions that impair an adequate immune response. Individuals belonging to the risk groups were invited each year by the general practitioner to receive the influenza vaccine.

In 1991 the vaccination coverage among high risk groups in the general population was estimated at around 28%, while coverage among the risk groups visiting hospitals may have been as high as 56% (Meynaar et al., 1991; Perenboom and Davidse, 1996). Vaccination was ongoing in earlier years but little to no data are available (vaccination coverage was likely around 5% (Beyer and Masurel, 1983)). Reasons for this low vaccination coverage were that part of the target group refused

vaccination because of doubts about efficacy, fear of side-effects, and because they thought it was not necessary. In addition, physicians also had doubts about the efficacy of the vaccine, side effects, the target groups to be vaccinated and how to reach them, and the need to vaccinate. Finally, practical reasons about access and availability may have resulted in lower uptake, as patients were requested to get the vaccine at the general practitioner (Davidse et al., 1994).

In the early 1990s, the government and other organisations decided to actively intervene and increase the coverage of influenza vaccination. This was initially attempted by reaching out to the risk groups through media campaigns. In 1992 and 1993 the Dutch Ministry of Health, Welfare and Sport, as well as other organisations including pharmaceutical companies and the National Organisation of General Practitioners, financed a national campaign, including television commercials, to inform risk-groups on the annual influenza vaccination (Sprenger and Masurel, 1992). The next step was achieved in 1995 when a national vaccination campaign was organised by the National Organisation of General Practitioners. This programme was extended in 1996 to also include everyone over 65 years of age, a strategy which was shown to be favourable in cost-effectiveness research (Postma et al., 1999). Similar to the NIP, the influenza vaccination campaign was to be financed by public funds through government funded social health insurance. Although funded similarly, influenza vaccinations are not part of the NIP but organised as a separate programme. Reason for this separation is that the vaccination needs to be repeated each year and target specific risk groups and the elderly rather than focussing on children in general.

In 1997 the programme became officially known as the National Programme Influenza Prevention and in 2008 the target age was further extended to everyone over 60 years of age in addition to risk-groups. Currently, the programme is co-ordinated by the RIVM that also buys and distributes the vaccines. In recent years the vaccination coverage has been declining steadily from 71.5% in 2008 to 53.5% in 2016; possibly due to an increase in healthy elderly within the target population who perceive lower risks of influenza and are less willing to vaccinate. (Tacken et al., 2015; Heins et al., 2017).

**Table 6.1: Short history of the Dutch National Immunization Programmes.**

Year	Vaccine	Target group	Modifications and other remarks on funding and organisation
1799	Smallpox	There was no specific target group at this time.	
1823	Smallpox	School-going children and infants under 1 year of age.	
1951			Start financial support of Child Welfare Centers by the Praeventiefonds.
1953	Diphtheria	Infants under 1 year of age.	Government starts providing vaccines for free.
1954	DTP	Infants under 1 year of age.	Diphtheria combined with tetanus and pertussis in DTP.
1955			Start first 'entgemeenschap'.
1957	Poliomyelitis	Catch-up campaign: everyone born since 1945 (3 doses). Routine vaccination: 3-, 4-, 5- and 11-month-olds (4 doses), 3-, 4-, 5-, 11-month-olds (4 doses)	Official start of Dutch NIP.
1959	DTP		Catch-up vaccinations for 4 and 9-year-olds.
1962	DTP-IPV	3-, 4-, 5-, 11-month-olds (4 doses).	'Entgemeenschappen' extended over the rest of the Netherlands.
1963			DTP combined with inactivated poliomyelitis vaccine in DTP-IPV.
1965	DT-IPV	4- and 9-year-olds.	Complete funding of the NIP provided by the government.
1974	Rubella	11-year-old girls.	Smallpox vaccination discontinued. Funding provided through social health insurance.
1976	Measles	14-month-olds.	
1987	MMR	14-month-old and 9-year-old boys and girls.	Measles combined with mumps and rubella in MMR.
1993	<i>Haemophilus influenza</i> serotype b (Hib)	3-, 4-, 5-, 11-month-olds (4 doses).	As a separate vaccination. Government and other organisations funded a national campaign to inform risk-groups of influenza vaccination.
1995	Influenza	Risk groups. <sup>1</sup>	Start of nationally organised influenza vaccination for risk-groups.
1996	Influenza	65-year-olds and over.	Influenza vaccination extended to 65-year-olds and over and financed through social health insurance.
1999	DTP-IPV and Hib	Starting age for DTP-IPV and Hib one month earlier, at 2, 3, 4, and 11 months.	

Table 6.1: Continued.

Year	Vaccine	Target group	Modifications and other remarks on funding and organisation
2001	Acellular pertussis (aP)	4-year-olds.	As a separate vaccine.
2002	Meningococcal serotype C (MenC)	Catch-up campaign: everyone up to 18 years old. Routine vaccination: 14-month-olds.	
2003	Hepatitis B (HepB)	2-, 3-, 4-, and 11-month-old children with parents from high risk countries and children from mothers who carry hepatitis B-virus (4 doses).	
2005	DTP-IPV-Hib		Hib combined with DTP-IPV in DTP-IPV-Hib.
2006	7-valent pneumococcal conjugate vaccine (PCV-7)	2-, 3-, 4-, and 11-month-olds (4 doses).	PERTUSSIS component in DTP-IPV-Hib for infants replaced with acellular pertussis. Coordination of influenza vaccination handed to the RIVM.
	HepB	Directly after birth for children from mothers who carry hepatitis B-virus.	HepB combined with DTP-IPV-Hib for risk groups.
	DTaP-IPV		Acellular pertussis for 4-year-olds now combined in DTaP-IPV. 'Entgemeenschappen' integrated in RIVM.
2007	DTaP-IPV-Hib-HepB	Children with down syndrome.	
2008	Influenza	60-year-olds and over.	Target age for influenza vaccination lowered to 60 years from 65.
2009	Human papilloma virus (HPV)	Catch-up campaign: everyone born between 1993 and 1996.	
2010	HPV	Start Routine vaccination: 12-year-old girls (3 doses).	
2011	PCV-10	DTaP-IPV-Hib-HepB	PCV-10 replaces PCV-7.
		2-, 3-, 4-, and 11-month-olds.	Now as a combination vaccine for all children.
2013	PCV-10		Change from four to three doses of PCV-10, at 2, 4, and 11 months.
2014	HPV		Change from three to two doses of HPV.
2018	MenACWY	14-month-olds	MenACWY replaces MenC. Catch-up campaign: everyone born between 1-5-2018 and 31-12-2018.

RIVM: National Institute for Public Health and the Environment. NIP: National Immunisation Programme.

Vaccine key: aP: acellular-pertussis; DTP: diphtheria-tetanus-pertussis; IPV, inactivated poliomyelitis vaccine; Hib, *Haemophilus influenzae* serotype b; HepB, hepatitis B; MenC, meningococcal serotype C; MenACWY, meningococcal serotype A, C, W, and Y; MMR, measles-mumps-rubella; PCV, pneumococcal conjugate vaccine; HFV, human papillomavirus.

<sup>1</sup> Risk groups for influenza vaccinations were defined by the Health Council of the Netherlands.

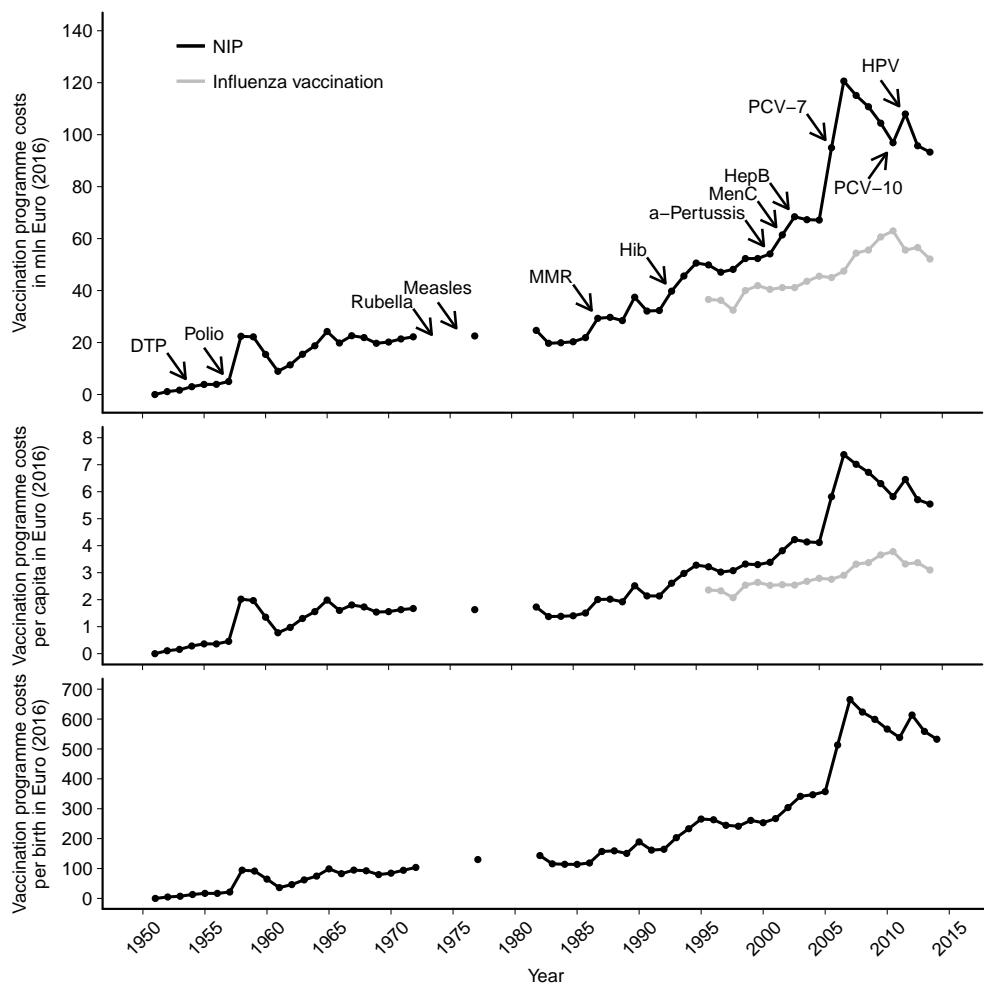
## Price development of vaccination programmes

### *Data and methods*

We obtained previously uncatalogued historical expenditure data on the NIP from 1951 up to 2014, from various official reports ranging from annual reports of the Praeventiefonds, the Dutch Ministry of Health, Welfare and Sport, and Sports and her predecessors, and other official publications. For the periods 1973–1976 and 1978–1981 no data were available. We also obtained the expenditure on influenza vaccinations from 1996 up to 2014. These expenses reflect the government expenditure on the NIP and influenza vaccination, and include vaccine costs, costs of administration, personnel costs, and overhead costs, but may not contain all costs associated with vaccination programmes, such as catch-up campaigns. For most periods these costs were not separately specified. Expenditure on specific vaccinations in the NIP from 1995 to 2013 were obtained from databases of the Dutch Health Authority. Data prior to 1987, from 1991–1994, and for 2001 were unavailable. For influenza vaccination, no specific expenditures were available for the period 2004–2008 and cost for this period were based on available subsidies as reported in the ‘Staatscourant’ (the official Dutch Government Gazette).

We obtained the number of births, population size, as well as overall healthcare expenditure from Statistics Netherlands (Statistics Netherlands (CBS), 2017b,c). For the overall healthcare expenditure, no data were available prior to 1972. Gross Domestic Product was obtained from the Netherlands Bureau for Economic Policy Analysis (Netherlands Bureau for Economic Policy Analysis (CPB), 2017).

We adjusted the development of expenditures of the Dutch NIP, influenza vaccination, GPD, and overall healthcare costs for inflation using the Consumer Price Index (CPI) published by Statistics Netherlands (Statistics Netherlands (CBS), 2017a). By adjusting for the general price development of a basket of consumer goods and services, the movements in the expenditures on the NIP are the combined result of changes in the volumes and the specific price movements of vaccinations only. The expenditures were expressed in prices of 2016 (in Euro) and data prior to 2002 were converted to Euro from Dutch Guilders where €1 = 2.20371 Dutch Guilder. We expressed the expenditure on the NIP and influenza vaccination programme relative to demographic (population and births) and macro-economic changes (total healthcare expenditure and GDP).



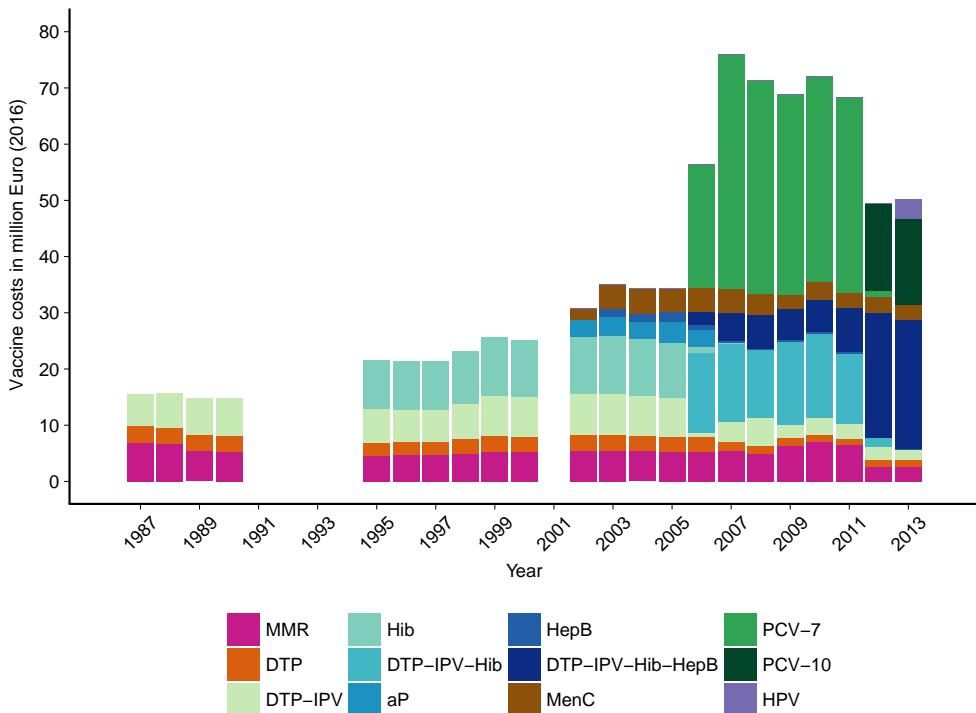
**Figure 6.1: Government expenditure on the Dutch National Immunisation Programme (NIP) and influenza vaccination programme, 1951–2014, the Netherlands.** Black lines indicate expenditure on the NIP, grey lines indicate the expenditure on the influenza vaccination programme. Arrows indicate when new vaccines are included in the Dutch NIP. All costs are expressed in Euro of 2016 adjusted for inflation using Consumer Price Indexes. All prices express government expenditure according to various official reports. Data for the periods 1973–1976 and 1978–1981 were unavailable. Vaccines key: DTP-IPV, diphtheria-tetanus-pertussis-inactivated poliomyelitis; rubella, only for 11-year-old girls up to 1987; MMR, measles-mumps-rubella, for both boys and girls of 14 months and 9 years of age; Hib, *Haemophilus influenzae* serotype b; a-Pertussis, acellular-pertussis; MenC, meningococcal C; HepB, hepatitis B; PCV-7, 7-valent pneumococcal conjugate vaccine; PCV-10 10-valent pneumococcal conjugate vaccine; HPV, human papillomavirus.

## Results

Figure 6.1 shows the total, per birth, and per capita expenditure on the Dutch NIP and influenza vaccination programme. In general, the expenditure on the NIP increased gradually over time from €5 million (mln) in 1957 to €93 mln in 2014. Government expenditure increased in particular since the end of the 1980s. The increase in costs is mainly due to the addition of new vaccines such as the measles-mumps-rubella (MMR) vaccine in 1987, the vaccine against *Haemophilus influenza* in 1993, acellular pertussis in 2001, meningococcal C in 2002, and hepatitis B for risk groups in 2003. The expenditure on the NIP increased again in 2006 with the inclusion of the pneumococcal conjugate vaccine (PCV); from €67 mln in 2005 to €120 mln in 2007. The per capita and per birth expenditure on the NIP followed a similar trend, increasing from €0.46 to €5.54 per capita and €21 to €533 per birth between 1957 and 2014. At its peak in 2007 the NIP costed €7.37 per capita and €665 per birth. Since 2007, the costs of the vaccination programme have been declining. Similar to the NIP, the expenditure on the influenza vaccination programme increased, from €37 mln in 1996 to €52 mln in 2014. In total, the government spent €145 mln (€8.65 per capita) on the NIP and influenza vaccination programme in 2014.

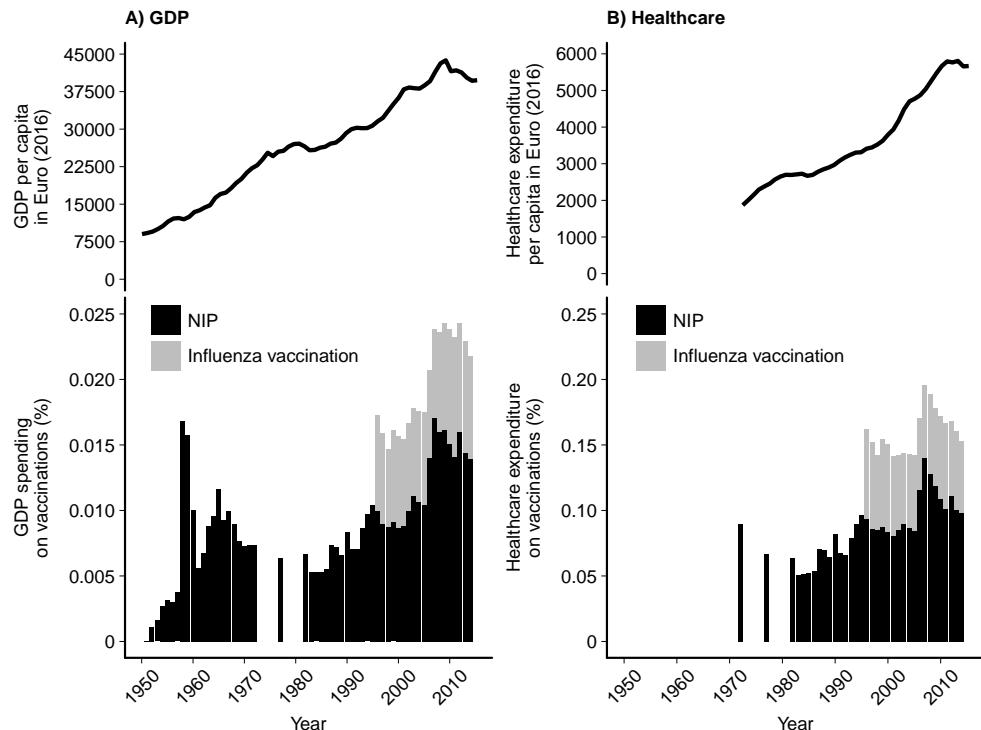
A breakdown of the costs of the NIP by vaccine is shown in Figure 6.2. While the total expenditure on vaccinations increased substantially when a new vaccine was introduced, the costs of a specific vaccine seemed to decline over time. For example, expenditure on the MMR vaccine declined from €6.9 mln in 1987 to €2.6 mln in 2013. Reformulations of vaccines (such as combining DTP-IPV-Hib with the hepatitis B vaccine) did not substantially impact total expenditure. The main cause of the increase in costs in 2007 was the inclusion of the PCV-7 vaccine. In 2012, the expenditure on PCV declined dramatically due to better pricing for the PCV-10 vaccine.

Figure 6.3 shows the expenditure on the NIP and influenza vaccinations as proportions of the GDP and healthcare expenditure. Overall, expenditure relative to GDP and healthcare expenditure increased as more mass vaccination programmes were implemented in the Netherlands. The proportion of healthcare expenditure spent on the NIP ranged between 0.05% and 0.14%. Similar to the overall developments in vaccination expenditure, the proportionate expenditure on the NIP increased up to



**Figure 6.2: Breakdown of costs by vaccine from 1987 to 2013.** All costs are expressed in Euro of 2016 adjusted for inflation using Consumer Price Indexes. Data prior to 1987, from 1991–1994, and for 2001 were unavailable. Due to differences in data sources, the timing of costs specified here may not correspond exactly to those in Figure 6.1 or changes in the programme listed in Table 6.1. HPV vaccination was officially launched in 2010 for 12-year-old girls but until 2012 the HPV programme was funded directly by Dutch Ministry of Health, Welfare and Sport and expenditures were confidential. Vaccines key: aP, acellular-pertussis; DTP, diphtheria-tetanus-pertussis; IPV, inactivated poliomyelitis; Hib, *Haemophilus influenza* serotype b; HepB, hepatitis B; MenC, meningococcal C; MMR, measles-mumps-rubella; PCV-7, 7-valent pneumococcal conjugate vaccine; PCV-10 10-valent pneumococcal conjugate vaccine; HPV, human papillomavirus.

2007, after which a steady decline was observed. Meanwhile, relative healthcare expenditure on influenza vaccination showed a decrease from 0.069% in 1996 to 0.055% in 2014. In total, 0.022% of GDP and 0.15% of healthcare expenditure was spent on vaccination programmes in 2014.



**Figure 6.3: Government expenditure on vaccination programmes relative to macro-economic developments.** Government expenditure relative to (A) Gross Domestic Product (GDP) for 1951–2014; and (B) relative to total healthcare expenditure for 1972–2014. Top panels show the per capita GDP and total healthcare expenditure, bottom panels show percentages expended on the National Immunisation Programme (NIP) and the influenza vaccination programme. All costs are expressed in prices of 2016 adjusted for inflation using Consumer Price Indexes. Data on cost of the NIP for the periods 1973–1976 and 1978–1981 were unavailable; no data were available on healthcare expenditure from 1951–1971.

## Discussion

Vaccines are often hailed as one of the most effective public health methods in preventing infectious diseases. As the cost of new vaccines increase and in time where policy makers are confronted with limited resources and budget constraints, a historic perspective and good understanding of the evolution of the expenditure on vaccination programmes may help give context to today's decision making problems. Here we explored the organizational and financial history of vaccination programmes in the Netherlands.

The expenditure on the Dutch National Immunisation Programme has increased substantially over time, with a near five-fold increase since the mid-1980s and a near doubling since the early 2000s. We found that, both absolute and relative expenditure spiked whenever a new vaccine was introduced, but that expenditures tend to stabilise or decline when a vaccination programme covered the same vaccines.

There are two main reasons for the increase in vaccination expenditure on the long term. First, the number of included vaccines has increased. Nowadays, the Dutch NIP includes vaccines against 12 infectious diseases. Second, new vaccines are introduced at progressively higher prices. The current low costs of vaccines included in the early days of the Dutch NIP sharply contrast the new generation of vaccines which have much higher price tags. These vaccines are more complex to manufacture and thus cost more in the early years of implementation.

Over time the costs of each specific vaccination, including the more recent vaccinations, declined. The expenditure on the MMR-vaccination for example declined by more than 60% between 1987 and 2014. This was partially due to tendering for better prices and a decline in the number of births. That expenditure on specific vaccinations declines over time is likely to be true for the newer vaccines as well as evidenced by the decline in expenditure on PCV after 2011. Vaccination against PCV-7 started in 2006 and dramatically increased the expenditure on the NIP. However, with the shift to PCV-10 in 2011, which was much cheaper, prices dropped considerably.

Contrary to the childhood vaccination programmes, the expenditure on the national influenza vaccinations has not seen a drastic increase since 1996. However, as

more universal influenza vaccines are being developed (Berlanda Scorza et al., 2016) and the elderly population is poised to increase in the coming decades due to the ageing population, an increase in the expenditure on influenza vaccinations is to be expected.

Although the total government expenditure on vaccination programmes has increased substantially, overall the impact on total healthcare expenditure is very small. An earlier analysis showed that spending on vaccinations in 2003 was €8.96 per capita (1.17% of total spending on prevention in the Netherlands); compared to €6.77 in our study (De Bekker-Grob et al., 2007). Although the approaches differ and included expenditure on screening, they broadly corroborate our results. Compared to other European countries, the Netherlands spends relatively little of its healthcare budget on vaccination programmes, accounting for only 0.15% in 2014, and this has been decreasing since 2007. In an analysis of seven other European countries spending on vaccine procurement in 2014 ranged from 0.25% (Spain) of healthcare budget to 0.47% (Germany) (Ethgen et al., 2016). In part this difference is due to differences in the vaccines included (the Netherlands is slow to implement new vaccines) and in differences in financing of healthcare between European countries, and thus differences in total healthcare spending. In 2014, the Netherlands ranked 15<sup>th</sup> in the world rankings of highest expenditure on healthcare as percentage of GDP (9<sup>th</sup> on rankings per capita), spending 10.9% of its GDP on healthcare; Germany ranked 10<sup>th</sup> with 11.3% while Spain ranked 40<sup>th</sup> (World Health Organization (WHO), 2017).

The costs reported here may not include all costs that are related to vaccination. It is often unclear what is actually included in the reported government expenditure on vaccination programmes. For example the reported numbers may not include expenses related to catch-up campaigns. For example, the meningococcal catch-up campaign is estimated to have costed at least €76 mln (Welte et al., 2004). Although substantial, these are one-time expenses. In addition, while vaccines are generally considered as safe, they might cause adverse reactions, such as swellings at the injection site. These side-effects may result in healthcare utilization and thus vaccine-related healthcare costs. These costs were not taken into account here. Nevertheless, the government expenditure on vaccination programmes we reported here gives an indication of the order of magnitude on how much these programmes have costed and how the expenditures have developed over time.

While we have provided an overview of the development in government expenditure on the NIP, these expenditures should be considered in view of the benefits. Vaccination programmes are often considered amongst one of the most effective public health interventions and highly effective in preventing infectious disease morbidity and mortality (Van Wijhe et al., 2016; Roush and Murphy, 2007; Van Panhuis et al., 2013; Centers for Disease Control and Prevention (CDC), 1999; Hinman et al., 2011). By preventing disease and mortality, vaccines also avert medical cost incurred due to treatment of those diseases, costs associated with productivity loss by parents tending to stricken children, as well as other costs due to long-term sequelae. As these costs associated with disease can be substantially higher than the costs of vaccination, many vaccines are cost saving (Chabot et al., 2004; Zhou et al., 2014). Some studies have suggested that the benefits of vaccination programmes extend to other areas such as lifetime income, increasing overall well-being, better school attendance of children due to increased health, and as a consequence of these other benefits gains in productivity and longevity (Bloom, 2011; Rappuoli, 2014; Bloom, 2015). Evidence for such broader impacts remain unclear however (Jit et al., 2015).

For the near future, vaccination costs will increase further due to the implementation of new vaccines or extending the target group of already implemented vaccines. The Dutch Ministry of Health, Welfare and Sport recently decided that in 2018 the meningococcal vaccination against serotype C will be replaced with the vaccine against serotypes A, C, W, and Y. Moreover, the Health Council of the Netherlands recommended vaccination against rotavirus for newborns with high-risk conditions (mainly pre-term infants, infants with a low birth weight, or infants with birth defects). Interestingly, they also stated that vaccination of all children against rotavirus would only be recommended when the cost-effectiveness was beneficial, i.e. the vaccine price was low enough (Health Council of the Netherlands, 2017a). In the near future, the Health Council of the Netherlands is expected advise on a new vaccine against herpes zoster for the elderly. In addition, new target-groups of existing vaccines are under consideration, such as maternal pertussis vaccination (positive recommendation by the Health Council of the Netherlands in 2015), pneumococcal vaccination for elderly, HPV vaccination for boys, combined hepatitis A and B vaccination for children, and influenza vaccination for children (Health Council of the Netherlands, 2017b).

The success of a vaccination programmes is inherently tied to the willingness of policy makers to finance the purchase and delivery of vaccines, the monitoring of their effects in terms of coverage, adverse events, and the occurrence of the target diseases (Hinman et al., 2004; Verweij and Houweling, 2014). Because vaccination programmes are implemented on a large scale, targeting entire birth cohorts, it is easy to perceive them as costly endeavours. Using a historical perspective, we have shown that vaccination programmes only constitute a small portion of the government spending on healthcare and their total costs, although increasing, are relatively low. However, inclusion of a new vaccine might result in an increase in expenditure. Such jumps in expenditure should always be substantiated by additional health gains. Moreover, the expenditure on these vaccines should always be viewed in context with the history of vaccination programmes as a whole; evaluations of the costs and effects of old and new vaccines should not be done in isolation. Understanding the evolution of vaccination programmes both in an organization and financial perspective may help put context to the budgetary impact of future vaccines.

Our historical perspective on the financial developments of vaccination programmes shows that while vaccination programmes have become more expensive, they have a relatively low impact on overall healthcare expenditure. Nevertheless, recent vaccines are progressively more expensive, which may put strain on the willingness of policy makers to finance these programmes. The financial evolution of vaccination programmes provides the context for today's decision making.

### **Contributors**

MvW obtained, extracted, and analysed the data, searched the scientific literature, and wrote the first draft of the manuscript. MvW, PTB, HJJ, HV, JW, and MJP designed the study and revised the manuscript. MvW, MJP, and JW conceived the project.

### **Declaration of interests**

MJP received grants and honoraria from various pharmaceutical companies, including GlaxoSmithKline, Pfizer, and Sanofi Pasteur MSD, who are potentially interested in the subject matter of this Article.

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# **Chapter 7**

## **General discussion**

*"It's the questions we can't answer that teach us the most. They teach us how to think. If you give a man an answer, all he gains is a little fact. But give him a question and he'll look for his own answers." — Patrick Rothfuss, *The Wise Man's Fear*, 2011*

The objective of this thesis was to provide a comprehensive and quantitative overview of the impact of long-standing vaccination programmes over the 20<sup>th</sup> century in the Netherlands. The data used throughout this thesis were to a large extend previously unavailable and collected from archived documents and digitized by hand. The methods we used go beyond the standard pre- versus post-comparisons common in literature, by taking secular trends and competing risks into account. In Chapter 2, we used long time series of cause-specific mortality along with novel methods borrowed from demographic and survival analyses to investigate the impact of vaccination programmes on childhood mortality burden. In Chapter 3 we expanded on this work by dissecting the impact of vaccination programmes into its component parts, the direct and indirect effects. Chapter 4 showed the added benefit of using competing risk analysis in mortality burden estimations in the case of influenza. In Chapter 5 we estimated the impact of vaccination programmes on case notifications. Finally, in Chapter 6 the developments in government expenditure on vaccination programmes in the Netherlands were explored.

The results in this thesis provide new approaches for estimating the impact of vaccination programmes and new insights in the context in which the impact of these programmes should be viewed. Our analysis of cause-specific childhood mortality burden in Chapter 2 showed that most of the mortality decline had already happened well before mass vaccination programmes were implemented. This is not a novel finding; the 20<sup>th</sup> century saw dramatic declines in childhood mortality around the world, including reductions in childhood mortality due to vaccine preventable diseases (Viner et al., 2011; Ahmad et al., 2000; Tuljapurkar et al., 2000). A large part of this decline is due to improvements in nutrition, hygiene, housing conditions, and new medical technologies. Our analysis, however, revealed that regardless of this decline, mass vaccinations have contributed to further lowering mortality burden and have averted a substantial number of deaths. The impact on mortality was most pronounced in the early years of mass vaccination, but as overall childhood mortality gradually declined, the absolute impact of vaccination programmes on mortality also declined. Nowadays, the potential impact of these programmes on mortality burden is considerably less than in the early years of mass

vaccinations. This also has consequences for the evaluation of contemporary and future vaccination programmes, as a one-on-one comparison with past achievements is unfair; regarding to mortality burden, contemporary and future vaccination programmes cannot compete with the historical impact of long-standing vaccination programmes. On a similar note, mathematical models employed for estimating the effectiveness of new vaccinations often assume a constant case fatality rate (the number of deaths divided by the number of cases) for a given infectious disease. This is unlikely to be accurate because the mortality due to infectious diseases declined rapidly in the 20<sup>th</sup> century, more so than the number of notified cases (see Figure 2.1 and Figure 5.1). Using historical data to inform modelling approaches for new vaccines will help obtain better parameter values and more realistic estimates of the (expected) effectiveness of future vaccination programmes.

Building on the results in Chapter 2, we showed that vaccination programmes can have substantial indirect effects on mortality burden. Indirect effects of vaccination programmes are well described but are difficult to establish in practice (Fine, 1993). While we lacked specific information on the vaccination status of each death to directly account for indirect effects, the substantial overall programme effectiveness we estimated cannot easily be explained by direct effects alone. Especially in the early years of a vaccination programme when vaccination coverage is still limited, these indirect effects are considerable. Indirect effects are an important phenomenon of vaccination programmes as they extend the impact to those individuals that are not vaccinated, such as very young infants and those that cannot be vaccinated due to medical reasons.

The methods used in Chapters 2 and 3 are novel in a sense that they combine long time series of cause-specific mortality with a cohort approach to mortality burden estimation, while taking competing risks and secular trends into account. In survival analysis, competing risks are events that change the probability of the outcome of interest. For example, we were interested in mortality due to vaccine-preventable diseases, and in this case, a competing event would be mortality due to other causes that preclude our events of interest. Often these competing events are censored and ignored in the analysis, resulting in overestimation of the years of life lost (Lai and Hardy, 1999). While there are other methods that account for competing risks (Andersen et al., 2012; Fine and Gray, 1999), the advantage of the methods we used is that they directly construct cumulative incidence curves for each cause of death

(Andersen, 2013). In Chapter 4 we used this approach to estimate influenza mortality burden among the elderly. The main mortality burden associated with influenza was in elderly 80 years and over; suggesting that this group may benefit from additional prevention measures. We also showed that ignoring competing risks results in considerable overestimation of the mortality burden associated with influenza. Such overestimation may influence decision makers' prioritisation of certain intervention strategies over others. It is therefore important that estimates of the mortality burden are as accurate as possible and always account for competing risks.

While mortality can be seen as the most severe outcome of an infectious disease, it is perhaps not where most of the benefits of vaccination programmes have been achieved. Our analysis of notified cases in Chapter 5 shows that in the first years following vaccination programmes, a large number of cases have been averted. In the absence of vaccination, our extrapolations are likely not sustainable up to present time; extending the time frame of our analysis would not produce reliable results. This is further corroborated by epidemics that occurred regardless of an established vaccination programme, such as poliomyelitis (Oostvogel et al., 1994), rubella (Hahne et al., 2009), and measles (Knol et al., 2013). The exact mechanisms underlying the dynamics of these diseases, their resurgence, and interaction with vaccination programmes requires more detailed statistical and mathematical models than those presented in this thesis. Although not on a mechanistic level, our results do indicate the likely effectiveness in the early years of vaccination. Furthermore, since we focussed on notified cases only, the real impact (including cases that were not notified) is much larger.

When evaluating any public health intervention, the associated costs are important. In Chapter 6 we focused on the government expenditure on vaccination programmes and described their developments over time. With considerable effort we could trace the expenditures back to the start of mass vaccinations, although some gaps in the data remain. Our analysis of the expenditures showed that while expenditure increased over time, the impact on total health care expenditure is minimal. Interestingly, while new vaccines are progressively more expensive, the expenditure on specific vaccines seemed to decline over time. This seems to be part of the natural development of prices, when at initial launch a product may be expensive, over time prices drop as more competitors join the market. It is likely that this will be true for future programmes as well. We showed that expenditures on the

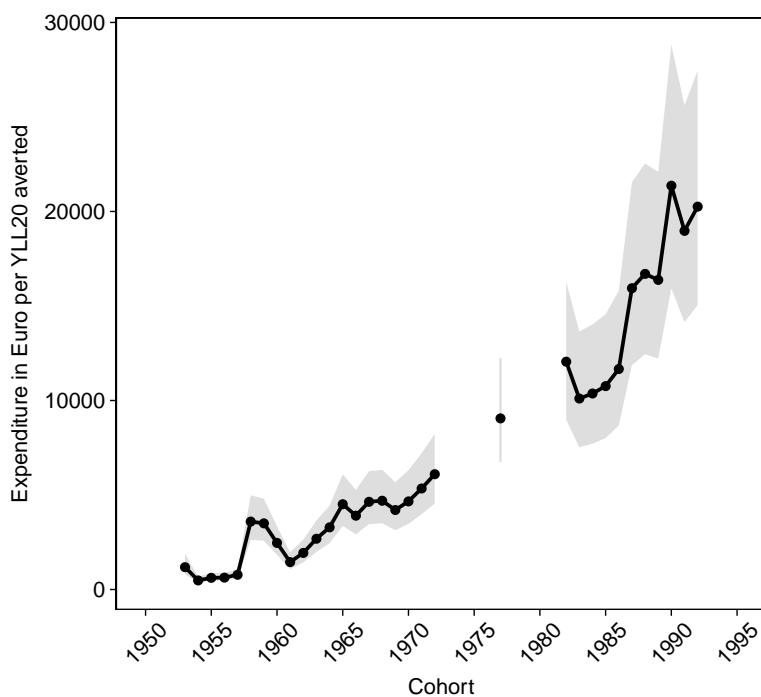
influenza vaccination programme have been relatively stable so far. These expenses on influenza vaccination are likely to increase in the near future due to the ageing of the population which increases the number of people 60 years and older eligible for vaccination. This expected rise in costs may however be partially recouped by the worrying decline in vaccination coverage among the elderly. Policy makers should be aware of these past and expected future economic and demographic developments as they plan the implementation of future vaccines.

## The cost per life-year gained

Integrating the results from Chapters 2 and 6 we can conclude that vaccination programmes have been highly cost-effective: for cohorts born between 1953 and 1992, €5 thousand [95% confidence interval: €4, €7] was spent for every year of life lost (up to age 20) averted (see Figure 7.1), corresponding to €89 thousand [95% confidence interval: €68, €120 thousand] per death averted. Of note is that the cost per life-year lost averted are increasing over successive birth cohorts due to declining mortality. These estimates only use expenditures and do not include any costs saved, nor are they representative of the total burden averted as they only include life-years lost and not the more extensive QALY measure which also incorporates loss of quality of life (for example paralysis due to poliomyelitis infection during childhood). All-in-all, these estimates do, however, indicate a high cost-effectiveness of long-standing vaccination programmes.

## Diminishing returns

The exponential decline in mortality throughout the 20<sup>th</sup> century is reminiscent of a process of *diminishing returns*: with everything else constant, additional input in terms of resources will eventually result in a lower gain per unit. When we look at the history of public health interventions, including vaccination programmes, this is understandable. In public health, resources and attention are generally spent in proportion to the perceived importance. The first public health interventions were targeted towards what was then perceived as the main causes of mortality and morbidity: poor drinking water, sanitation, personal hygiene, nutrition, and housing conditions. Following interventions in these areas, vaccines were developed against major health threats such as diphtheria, tetanus, pertussis, polio, etc. These



**Figure 7.1: Government expenditure on the Dutch National Immunisation Programme (NIP) per year of life lost up to age 20 years (YLL20) averted, birth cohorts 1953–1992, the Netherlands.** This graph combines the results from Chapter 2 and Chapter 6. The black line indicates expenditure on the NIP per YLL20 averted by vaccination programmes, grey area indicates the 95% confidence interval. All costs are expressed in Euro of 2016 adjusted for inflation using Consumer Price Indexes. All prices express government expenditure according to various official reports. Data for the periods 1973–1976 and 1978–1981 were unavailable.

infectious diseases were major killers in the first half of the 20<sup>th</sup> century. As these ‘low-hanging-fruits’ were harvested, other infectious diseases emerged as the next health threat, such as measles. These diseases required more innovative, and more expensive, methods and technologies. Over time, progressively more complex diseases and those with lower burden, like pneumococcal disease, were targeted. With each step, the potential benefits, compared to previous endeavours, were naturally less. All the while, the resources required to achieve additional health gains through vaccination programmes increased, as seen in Chapter 6 and Figure 7.1.

As new vaccines targeted diseases more difficult to prevent, potentially warranting more expensive vaccines, the costs of vaccination programmes increased. It is thus not surprising that the balance between resources invested and their marginal returns is reflected in increasing costs of vaccination programmes and an exponential decline in mortality burden (Tulapurkar et al., 2000). Furthermore, as most of the 'low-hanging-fruits' have been picked, the potential benefits of new vaccines are less visible. This implies that contemporary and future vaccination programmes cannot be expected to provide the same impact as past vaccination programmes and direct comparisons are unfair. Policy makers and public health care workers should be aware of these effects that act over a long period; a good understanding of the history of vaccination programmes can help give context to today's and tomorrow's decisions regarding new vaccines and potentially other preventive programmes.

## New possibilities

While in this thesis we attempted to provide an overview of the impact of vaccination programmes in the Netherlands, many questions remain unanswered and issues unexplored. This thesis is limited to long-standing vaccination programmes, from diphtheria up to the measles-mumps-rubella vaccine. Other vaccines, such as those against *Haemophilus influenzae* and meningococcal disease, have generally been studied in more detail and are not covered here. Although we would have liked to extend our efforts to include these more recent vaccines, there was unfortunately no time to do so. Data availability was also a constant problem. For some vaccine-preventable diseases there were no mandatory notifications prior to the start of mass vaccinations, such as for measles and pertussis. To assess their impact, pre-vaccination disease incidences need to be reconstructed, possibly based on backward projections, or demographic-based estimations. Particularly in the case of measles, where the main benefit of vaccination likely lies in the averted morbidity and not mortality, such reconstruction of the incidence of disease in the pre-vaccination period will further substantiate the impact of vaccinations. Unfortunately, we did not have the time to do such a formal analysis and this remains a topic for further study.

Another topic for future research is the impact of vaccinations on morbidity burden as estimated by measures such as the QALY. While in Chapter 5 we provided estimates of the number of notified cases averted, this does not include more detailed estimation of the actual burden in terms of quality of life. Many infectious diseases

can have serious long-term sequelae, such as paralysis after poliomyelitis infection or long-term disabilities due to encephalitis. An inventory of notified cases averted is valuable but does not paint a complete picture of averted morbidity burden.

While we have shown that vaccination programmes resulted in a further decline in childhood mortality and case notifications, we did not explore in depth the impact of other interventions, such as antibiotics. Our methods, in part, account for these other factors, but we could not quantify these specifically. It will be difficult to do so since many developments overlap—hygiene and nutrition likely improved simultaneously—and quantitative methods that are able to distinguish between factors are lacking. In addition, data on these developments may be difficult to identify, if available at all. For instance, while we know roughly when new antibiotics were introduced in the Netherlands, there was no registry for the prescription of these drugs. Perhaps information can be gleamed from detailed hospital records, if they have been kept. This issue illustrates the difficulty of such historic research.

Another issue left unexplored in our work is the heterogeneity in mortality, morbidity, and vaccination coverage across regions. In the Netherlands there are distinct regions with lower vaccination uptake, known as the ‘bible-belt’. It would be interesting to see the development of vaccination coverage and the occurrence of infectious diseases by region. This would further inform the impact of vaccines. In our current studies these regions have been aggregated to the national level, thus potentially masking some of the impact of vaccination. It is likely that our estimates, specifically the estimates of direct and indirect effects in Chapter 3, underestimate the true effectiveness. Regional data for both vaccination coverage and notified cases are available and just await further digitization.

Next to the direct and indirect effects of vaccination, there may also be so-called non-specific effects. Non-specific effects are, as the name implies, non-specific, or ill defined, and indicate that a vaccine may have more general effects than just inducing immunity to the target disease. Non-specific effects have been described for the BCG-vaccine (Aaby and Benn, 2012), DTP-vaccine (Aaby et al., 2012), and measles-containing vaccines (Benn et al., 2013). One example of non-specific effects of vaccinations was recently described for measles by Mina et al. (2015). Infection with the measles virus potentially increases susceptibility to other infectious diseases. It is

not clear how this happens, one theory suggests a sort of measles induced immune-amnesia where the memory cells responsible for eliciting a quick and adequate immune response, suffer from 'short-term memory loss' after measles infection. This *immunomodulation* may last for up to three years and increases the risk of non-measles infectious disease mortality (Mina et al., 2015). Vaccination against measles may thus prevent measles infection, subsequent immune amnesia, and the associated increase in non-measles mortality. We investigated this hypothesis for the Netherlands using similar methods as Mina et al. (2015). We could, however, not detect a statistically significant effect. If these indirect effects are present, their impact will be limited. Non-specific effects of vaccines are still poorly understood, but it is important to realise these effects may exist and that the impact of vaccinations may be larger than expected based solely on the impact on the diseases they target (Breiman et al., 2004; Aaby and Clements, 1989).

## A broader interdisciplinary perspective

The benefit of vaccinations may also extend to other areas such as lifetime income, increasing overall well-being, better school attendance of children, and by extension gains in productivity and longevity (Rappuoli, 2014; Bloom et al., 2017). Some vaccines may also delay the development of antibiotic resistance by reducing the need for antibiotics (Callaway, 2014). The improvement in health, in its broadest meaning, due to vaccines, also implies a utilitarian value difficult to express in financial gain. Thus, by extension, vaccinations may help shape the overall health and wealth of a region (Bloom, 2015). These economic and societal benefits are difficult to quantify and extend over long periods of time but failing to consider them can lead to undervaluation of current and future vaccination programmes. A broader view on the impact of vaccination programmes becomes more important when the direct benefits of vaccinations become less visible in standard surveillance and research methods (due to the overall decline in mortality, and the more complex disease dynamics targeted by new vaccines). A more interdisciplinary and integrated approach to valuing vaccinations may help evaluate the extend of these suggested additional benefits.

Furthermore, disease and health are not the sole domain of epidemiologist and medical doctors but also of other fields like demography, history, and social sciences. An interdisciplinary approach including these fields may lead to new insights on the

broad health impact of vaccinations. The field of 'historical epidemiology' should not remain a fringe science but should become an established field characterized by its interdisciplinary focus, where these fields work together to provide answers to modern public health issues utilizing the power of historical data. This area of study is yet relatively unexplored and should be a consolidated in future research efforts.

## The value of historical data

Throughout the projects described here, we have repeatedly sought out data in archived reports, documents, and repositories, both physical and digital. We have thus collected a sizeable amount of information, including all tables of officially notified cases of infectious diseases in the Netherlands over the 20<sup>th</sup> century (by week and for a large part by municipality). In 2016 and 2017 we started a project where we digitize these data in computable format (excel and R-data files). While at the time of writing nearly 40% of over 3000 tables have been digitized, much more can be done. Specifically, the digitization of these data should be continued and extended to also include data from the 19<sup>th</sup> century. These data are already available in tabular format and require only a one-time investment of time and money to digitize.

If we do not secure these historical data from archives, they may soon be lost and along with them a part of our national history. A prime example is the vaccination coverage in the Netherlands, which was not available at the National Institute for Public Health and the Environment (RIVM) for the years prior to 1970. We managed to obtain these missing records from periodic reports kept by regional coordinators (thank you Louis Labohm and Gida Koevoets) who had kept them with the motto (I paraphrase here): "might be useful one day". This example indicates the fragility of these historical records. The value of these datasets for research cannot be overstated.

The history of infectious diseases contained within these old records is an essential part of the story of public health in the Netherlands and have intrinsic value as such. It should be a responsibility of institutes like the RIVM and Statistics Netherlands to collect and curate historical data on infectious diseases as well as facilitating their availability to other researchers. In this age of digitization where massive datasets containing information on population demography, mortality, hospitalizations, and infectious disease notifications become available, it is paramount that the historical

context of infectious diseases is highlighted more. As health and disease today are a culmination of past achievements, a strong focus on the history of disease in public health research and education is only natural.

The work presented in Chapters 2, 3, 5 and 6 shows the added value of a historical perspective on public health. I have found that such a perspective is important to give context to how and why vaccination programmes, and other public health initiatives, came about and to understand their role and impact today. Ideas of today are all too often incorrectly and unilaterally applied to past events and vice versa—a historical view of public health may help put them into perspective, and for that, historical data are of paramount importance.

## Concluding remarks

Contemporary and future vaccination programmes should not be seen in isolation but in the context of the National Immunisation Programme as a whole, as well as its past achievements. It is important to realise that as the public health context in which vaccination programmes are introduced changes over time, the impact of these programmes (Chapters 2 and 5) and their associated costs (Chapter 6) develop and change as well. Nowadays and in the future, a smaller gain is achieved by the prevention of deaths and more by the prevention of illness, severe complications, hospitalisation, and long-term sequelae. Policy-makers, communicators, and health care workers should realize that the rationale of vaccinations is dynamic. Communication strategies to (future) parents and the general public, as well as education programmes, should reflect these changes. While we should not forget that vaccination programmes have saved and continue to save many lives and avert much suffering, we should also recognise that past achievements are not representative for current and future expected value. This is ever more important in a time of increasing vaccine-hesitancy. As the risk perception of many vaccine-preventable infectious diseases declines and the diseases fade from memory, attention shifts from the concern of infection to concern about the possible adverse events of vaccinations and the need for vaccines. Continuously monitoring the impact of vaccination programmes and highlighting their importance to public health is paramount.

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## **Supplements**

**Summary**

**Nederlandse samenvatting**

**Acknowledgements**

**About the author**

**Research Institute SHARE**

## Summary

The last century has seen a dramatic decline in morbidity and mortality due to infectious diseases. This is partially due to improvements in nutrition and sanitation, access to clean water, the introduction of antimicrobial drugs, and vaccination programmes. Vaccinations are often considered the most important public health intervention of the 20<sup>th</sup> century. But how effective have they been? The impact of long-standing vaccination programmes in the changing epidemiological landscape of infectious diseases in the 20<sup>th</sup> century is poorly studied. Most research focusses on contemporary and future vaccinations, and the effectiveness of long-standing programmes, such as vaccinations against diphtheria and poliomyelitis, are often taken for granted. Evaluating the impact and effectiveness of long-standing vaccination programmes becomes increasingly important as vaccination hesitancy increases.

What was the actual impact of vaccinations? How many deaths have vaccinations averted? And how many cases? In this thesis we asked ourselves these questions. To help answer them, we focused on the somewhat obvious question 'What if a vaccination programme had not been introduced?'. Such a question requires considerable amounts of data, both before and after implementation of a vaccination programme. We have scoured various archives both digital and analogous to gather historical data spanning the entire 20<sup>th</sup> century; most of these data were previously unavailable.

As a whole, this thesis attempts to provide a comprehensive overview of the impact of long-standing vaccination programmes in the Netherlands. We take a closer look at the impact on mortality, morbidity, and health care spending. We mainly focus on vaccination programmes for diphtheria up to the measles-mumps-rubella vaccinations and the influenza vaccination. We hope this, and similar evaluations, will help parents and policy makers reach more informed decisions regarding vaccinations.

Chapter 2 presents the first part of our answers. Here, we explored the impact of vaccination programmes on mortality due to diphtheria, pertussis, tetanus, poliomyelitis, measles, mumps, and rubella among children and young adults. We wanted to determine the number of deaths averted by vaccination programmes taking pre-existing declines in mortality into account. To do so, we used a

'competing risk' approach to estimate childhood mortality burden associated with these diseases. Childhood mortality already declined drastically in the first half of the 20<sup>th</sup> century, before vaccination programmes started. However, the contribution of vaccine-preventable diseases remained relatively constant. Extrapolating these pre-vaccination trends into the vaccination era we created a 'counterfactual', a scenario where vaccination programmes had not been implemented. Comparing this to the actual vaccination era trends we estimated that between 6 and 12 thousand deaths have been averted by mass vaccinations in birth cohorts 1953–1992.

We further specify the impact of vaccination programmes in Chapter 3, where we estimate the direct and indirect effects of vaccination programmes on mortality burden. Indirect effects arise when vaccination reduces circulation of a disease, and consequently reduces the risk of infection among unvaccinated individuals. Using the observations in Chapter 2, along with vaccination coverage data, we partitioned the overall effectiveness of vaccination programmes on mortality burden into the expected direct and indirect effects. We show that a considerable part of the mortality burden averted by vaccination programmes can be ascribed to indirect effects, especially in the early years of a vaccination programme when the coverage is still relatively low.

In Chapter 4 we estimate the mortality burden for influenza among the elderly. In the Netherlands, those over 60 years-of-age and other specific risk groups can receive an influenza vaccine each year. Because of the relatively high mortality among these groups it is important to take other causes of death into account when estimating mortality burden. Especially for policy making, when funding of intervention programmes is (partially) determined by the ranking of health problems based on such estimates. In our analysis, the burden of mortality due to influenza was highest in those of 80 years and older. Most notably, we also show that not accounting for competing risks may lead to substantial over-estimation: up to 82% of the mortality burden. This keenly emphasizes the importance of 'competing risks' in mortality burden estimation.

In Chapter 5 we examine the impact of vaccination programmes on morbidity, or: case notifications. We fitted time series regression models to pre-vaccination periods and constructed counterfactuals for the first years after the implementation of mass vaccinations. We also accounted for seasonal patterns, multiannual cycles and

secular trends. We see that in the first years following the implementation of mass vaccination programmes for diphtheria, poliomyelitis, mumps, and rubella 78.4%, 90.0%, 79.0%, and 49.5% of cases were averted respectively. Thus, apart from their impact of mortality, vaccination programmes have had a considerable curbing effect on morbidity.

When evaluating the impact of vaccination programmes, the expenditures on these programmes should also be considered. We discuss the financial evolution of mass vaccination programmes in the Netherlands in Chapter 6. The government expenditure on vaccination programmes has increased substantially, from €5 million in 1957 to €93 million in 2014 (recalculated to prices of 2016). The increase was especially large in the past three decades with the introduction of new and expensive vaccines, such as vaccines against pneumococcal disease. However, in the total healthcare expenditure vaccines are only a minor expense. In addition, while each new vaccine naturally increased the total spending on vaccination programmes, the costs for specific vaccinations in the National Immunisation Programme tended to decline over time, e.g. the expenditure on MMR vaccination declined from €6.9 million to €2.6 million between 1987 and 2013. Expenditure on vaccination programmes is likely to increase in the future as new and more complex vaccines are being considered for implementation. However, their total expense will only ever play a small role in overall healthcare spending.

Mass vaccination programmes have contributed greatly to the (further) decline in mortality and morbidity due to infectious diseases with only little impact on government expenditure. Continuously monitoring and evaluating vaccination programmes, both old and new, is important to highlight their successfulness in preventing disease and mortality. This becomes especially important in a time of increasing vaccine hesitancy, as maintaining a high vaccination coverage is paramount in limiting the transmission of vaccine-preventable diseases and preventing their resurgence. The results from our research also suggest that the prevention of deaths will play an increasingly smaller role in the rationale for continuing existing and implementing new vaccination programmes. A higher emphasis should be on the prevention of illness, severe complications, hospitalisation, and other long-term consequences of disease. Communication strategies and education programmes should reflect these changing priorities.

Throughout this thesis we have focused on collecting and using long time series of infectious disease mortality, case notification, vaccination coverage, and vaccination programme spending. For the most part, these data were hitherto unavailable. Currently, the digitisation of more detailed data on notifiable diseases (by week and municipality) is still in progress and when completed will be openly accessible. As the work presented here demonstrates, such data are a treasure trove for understanding current and predicting future events. Securing, digitising, and curating as well as making publicly available historical data on public health in its broadest sense, for current and future needs, should be a priority. Failure to do so will result in the eventual loss of these data, along with any insights and foresights they might have offered.

Our historical perspectives on the impact of vaccination programmes in terms of mortality burden, cases averted, as well as reflecting on financial developments of vaccination programmes, provides the context for today's decision making and shows the value, importance, and necessity of historical epidemiological research. Current and future vaccination programmes should not be seen in isolation but within the context of the vaccination programme as a whole and along with its history. Only from a historical perspective can we understand and value the impact of vaccination programmes today and in the future.

## Nederlandse samenvatting

In de afgelopen eeuw is het aantal ziekte- en sterfgevallen voor diverse infectieziekten drastisch afgenomen. Enkele verklaringen hiervoor zijn verbeteringen in voeding, sanitaire voorzieningen, toegang tot schoon drinkwater, antimicrobiële middelen en tenslotte vaccinatieprogramma's. Vaccinaties worden daarbij gezien als een van de belangrijkste ontwikkelingen in de publieke gezondheid in de 20<sup>e</sup> eeuw. Echter, hoeveel vaccinatieprogramma's daadwerkelijk hebben bijgedragen aan de veranderende epidemiologie van infectieziekten is beperkt onderzocht. De meeste onderzoeken richten zich op huidige en toekomstige vaccinaties terwijl de effectiviteit van de oudere vaccinatieprogramma's, zoals die tegen difterie en polio, vaak als vanzelfsprekend worden gezien. Het evalueren van de impact en effectiviteit van deze oudere vaccinatieprogramma's wordt steeds belangrijker door de toenemende weerstand tegen vaccinaties in recente jaren. Zulke evaluaties kunnen ouders en beleidsmakers helpen onderbouwde beslissingen te nemen omtrent wel of niet vaccineren en het beleid daaromheen.

Dit proefschrift biedt een overzicht van de impact van vaccinatieprogramma's in Nederland. We behandelen hoe vaccinatieprogramma's hebben bijgedragen aan het reduceren van de sterfte onder kinderen en jongvolwassenen, de effectiviteit van vaccinaties in het voorkomen van ziekten en de kosten van deze programma's. We richten ons met name op de Nederlandse vaccinatieprogramma's onder kinderen tegen difterie, kinkhoest, tetanus, polio, bof, mazelen, en rodehond en vaccinaties tegen influenza voor ouderen. Om de impact van deze vaccinatieprogramma's te schatten stellen we steeds de vraag: "Wat zou er zijn gebeurd als een vaccinatieprogramma niet was geïmplementeerd?". Het opstellen van dit alternatieve scenario is complex omdat we rekening moeten houden met diverse trends die speelden voor de invoering van een vaccinatieprogramma. Daarnaast zijn aanzienlijke hoeveelheden gegevens nodig van zowel vóór als ná de invoering van een vaccinatieprogramma.

Voor elk onderzoek hebben we steeds gezocht naar gearchiveerde historische gegevens, zowel digitaal als op papier, van de 20<sup>e</sup> eeuw. Veel van de gebruikte data waren niet gemakkelijk beschikbaar of bij elkaar gebracht voor onderzoek.

In Hoofdstuk 2 is onderzocht in welke mate vaccinaties hebben bijgedragen aan het reduceren van sterfte aan difterie, kinkhoest, tetanus, polio, bof, mazelen en

rodehond onder kinderen en jongvolwassenen in Nederland. Dit is gedaan met een concurrerende risico overlevingsanalyse. Hiermee schatten we hoeveel levensjaren door deze ziekten zijn verloren tot het 20<sup>e</sup> levensjaar. Uit de analyses blijkt dat de algemene sterftelast onder kinderen en jong volwassenen sterk afnam in de 20<sup>e</sup> eeuw. Echter, het aandeel dat werd veroorzaakt door de boven genoemde ziekten bleef relatief constant (met uitzondering van mazelen dat sneller daalde). Door de trends in de prevaccinatie periode te extrapoleren konden we schatten dat onder iedereen geboren tussen 1953 en 1992, tussen de 6 en 12 duizend sterfgevallen zijn voorkomen dankzij vaccinatieprogramma's.

Een belangrijk aspect van vaccinaties zijn de potentiële indirekte effecten. Indirecte effecten ontstaan wanneer de circulatie van een ziekte wordt verstoord door immunititeit in de bevolking. Hierdoor wordt het risico op infectie onder ongevaccineerden minder en kunnen ook zij profiteren van vaccinaties. Dit fenomeen wordt ook wel groeps-immunititeit genoemd. In Hoofdstuk 3 bestuderen we de indirekte populatie-effectiviteit van vaccinatieprogramma's op de sterftelast. Door gebruik te maken van de resultaten uit Hoofdstuk 2 konden we de totale effectiviteit opdelen in de verwachte directe en indirekte effecten. De analyses laten zien dat een aanzienlijk deel van de sterftelast die is voorkomen met vaccinaties kan worden toegeschreven aan indirekte effecten. Dit speelde met name een rol in de eerste jaren nadat een vaccinatieprogramma was geïntroduceerd en de vaccinatiegraad nog relatief laag was.

In Hoofdstuk 4 bepalen we de sterftelast door influenza onder ouderen. In Nederland kunnen 60-plussers en andere specifieke doelgroepen elk jaar een vaccinatie tegen influenza krijgen. Het is belangrijk om andere doodsoorzaken (concurrerende risico's) mee te nemen wanneer we de sterftelast berekenen voor groepen met relatief hogere sterfte. In onze analyses vonden we de hoogste sterftelast voor influenza onder de 80-plussers. Toen we geen rekening hielden met concurrerende risico's, werd de sterftelast substantieel overschat, tot wel 82%. Dit kan met name gevlogen hebben voor beleid wanneer het wel of niet subsidiëren van een interventieprogramma deels afhankelijk is van de ordening van aandachtsgebieden op basis van dit soort schattingen. Hiermee tonen we het belang aan van concurrerende risico's voor het schatten van sterftelast.

## Supplements

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In Hoofdstuk 5 bestuderen we de impact van vaccinatieprogramma's op het aantal gemelde ziektegevallen. We gebruikten daarvoor tijdreeks regressiemodellen geschat op de pre-vaccinatie perioden. Hierbij hielden we rekening met seizoenspatronen, meerjaarlijkse cycli en algemene lange termijn trends. Onze analyses laten zien dat vaccinatieprogramma's zeer succesvol zijn geweest in het voorkomen van ziekten: in de eerste jaren hebben vaccinaties tegen difterie, polio, bof en rodehond respectievelijk 78.4%, 90.0%, 79.0% en 49.5% van de ziektegevallen voorkomen. Vaccinatieprogramma's hebben niet alleen bijgedragen aan een daling in sterfte maar ook in ziektegevallen.

De evaluatie van de impact van vaccinatieprogramma's is niet volledig zonder ook naar de uitgaven aan deze programma's te kijken. In Hoofdstuk 6 gaan we dieper in op de financiële geschiedenis van vaccinatieprogramma's in Nederland. De overheidsuitgaven aan vaccinatieprogramma's zijn geleidelijk toegenomen van € 5 miljoen (omgerekend naar kosten in 2016) tijdens de officiële start van deze programma's in 1957, tot € 94 miljoen in 2014. Vooral in de laatste drie decennia zijn de kosten sterk gestegen door de invoering van duurdere vaccins tegen bijvoorbeeld pneumokokken. In verhouding tot de totale gezondheidszorguitgaven zijn de kosten van vaccinatieprogramma's minimaal en laten de laatste jaren zelfs een dalende trend zien. De kosten van afzonderlijke vaccins lijken over de tijd ook af te nemen. Zo daalden de totale uitgaven aan vaccinaties tegen bof, mazelen en rodehond van € 6.9 miljoen in 1987 tot € 2.6 miljoen in 2013. Uitgaven aan vaccinatieprogramma's zullen in de toekomst waarschijnlijk toenemen wanneer nieuwe en complexere vaccins worden toegevoegd aan het vaccinatieprogramma. Relatief gezien zullen de uitgaven aan vaccinatieprogramma's echter een kleine rol blijven spelen.

Vaccinatieprogramma's hebben substantieel bijgedragen aan het (verder) reduceren van de ziekte- en sterftelast door infectieziekten in Nederland met minimale overheidsuitgaven. Het is belangrijk om het succes van zowel oudere als nieuwe vaccinatieprogramma's te blijven evalueren. Dit belang wordt extra benadrukt door de toenemende weerstand tegen vaccinaties. Het in stand houden van een hoge vaccinatiegraad is belangrijk om de verspreiding en wederopkomst van infectieziekten tegen te gaan of te beperken. De resultaten die in dit proefschrift worden gepresenteerd suggereren dat tegenwoordig, en in de toekomst, het voorkomen van sterfgevallen een steeds kleinere rol zal spelen in beslissingen over het doorzetten

van reeds bestaande en het introduceren van nieuwe vaccinatieprogramma's. Steeds meer nadruk zal komen te liggen op het voorkomen van ziekte, ernstige gevolgen, ziekenhuisopnamen en andere lange-termijn gevolgen. Communicatiestrategieën zouden deze veranderingen in prioriteiten moeten reflecteren.

In dit proefschrift is veel aandacht besteed aan het verzamelen en analyseren van lange tijdreeksen van gegevens over sterfte, gemelde ziektegevallen, vaccinatiegraad en overheidsuitgaven. Een groot deel van de gegevens is niet eerder op deze manier bij elkaar gebracht. Terwijl ik dit schrijf, is de digitalisatie van gedetailleerdere gegevens over gemelde ziektegevallen (per week en per gemeente) nog in volle gang en deze zullen op den duur openbaar beschikbaar worden gesteld. Het verzamelen, digitaliseren, waarborgen en beschikbaar maken van dit soort historische gegevens over publieke gezondheid is essentieel, niet alleen om studies zoals hier beschreven mogelijk te maken, maar ook om een deel van onze nationale geschiedenis veilig te stellen. Als dit niet systematisch wordt gedaan zal deze informatie uiteindelijk verloren gaan.

Ons historisch perspectief over de impact van vaccinatieprogramma's in termen van sterftelast en voorkomen ziektegevallen en onze reflectie op de financiële ontwikkeling van deze programma's, laat het belang zien van historisch epidemiologisch onderzoek en geeft context aan de beslissingen waar beleidsmakers tegenwoordig voor staan. Hedendaagse en toekomstige vaccinatieprogramma's kunnen niet afzonderlijk van elkaar worden beoordeeld maar moeten in de context van het Rijksvaccinatieprogramma en haar geschiedenis als geheel worden gezien. Inzicht in de waarde en impact van vaccinatieprogramma's van vandaag en de toekomst, is alleen mogelijk vanuit een historisch perspectief.

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Like most things in life, my thesis also took several unexpected turns. I started on this project, perhaps a bit naively, expecting that we could construct a uniform model to estimate disease burden averted by vaccinations. This proved to be much more challenging. However, I can hardly deny that we have made some progress. The last several years have been a delight both scientifically and personally. In the end, I can be satisfied with the work that we have accomplished. While at times I have felt a bit alone working on this topic, it could not have been done without the support of so many people.

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## About the author

Maarten van Wijhe was born on June 29<sup>th</sup>, 1989 in Malden, the Netherlands. From an early age he was interested in infectious diseases, spurred on by movies like Outbreak (1995). After graduating from secondary school he studied Biomedical Sciences at the Radboud University in Nijmegen. He continued his studies in epidemiology at the same university. He did two internships, one at the Municipal Health Service in Den Bosch, with a more consultancy focus, and one at the National Institute for Public Health and the Environment (RIVM) with a pure research focus. In 2013, he obtained his Master's degree Cum Laude at the Radboud University and several months thereafter, he started his PhD at the University of Groningen in collaboration with the RIVM. During his PhD he gave multiple talks at national and international conferences and symposia, such as Epidemics (2015) and the 'VastePrik-dag' (2017). He also developed a strong interest in historical outbreaks of infectious diseases, and is currently continuing along this path as a post-doctoral research fellow under the guidance of Lone Simonsen at the Roskilde University in Denmark.

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