The public health impact of vaccination programmes in the Netherlands

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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"Every friend of humanity must look with pleasure on this discovery, by which one more evil is withdrawn from the condition of man; and must contemplate the possibility, that future improvements and discoveries may still more and more lessen the catalogue of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^{th} and early 20^{th} century saw dramatic declines in childhood mortality and rapid increases in life expectancy (Wolleswinkel-van den Bosch et al., 1997; Tuljapurkar 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^{th} 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^{th} century. For a large part, the data used in the following chapters spans most of the 20^{th} 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^{th} century. In the 19^{th} 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* ('hygiënisten' in Dutch), was dedicated to changing the then poor health status of people in larger cities, mainly though 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 20th 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 20th 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-20th century, mortality due to infectious diseases had declined drastically and life expectancy had increased: where in the mid-19th century life expectancy was around 45 years, by the mid-20th 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 19th century to chronic diseases in the 20th 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 Praevention 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[1]	
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	*Haemophilus influenzae* serotype b (Hib).	
1995	Influenza	Start of nationally organised influenza vaccination for risk-groups.[2]
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		DTP-IPV-Hib replaced with DTaP-IPV-Hib.
2006	7-valent pneumoccocal conjugate vaccine (PCV-7)	HepB combined with DTP-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 influenza* 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.

[1] 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.

[2] 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[1]
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.

[1] 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 of 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 20th 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 20th century in the Netherlands.

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