The public health impact of vaccination programmes in the Netherlands

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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 20th 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 20th 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 20th 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 20th 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

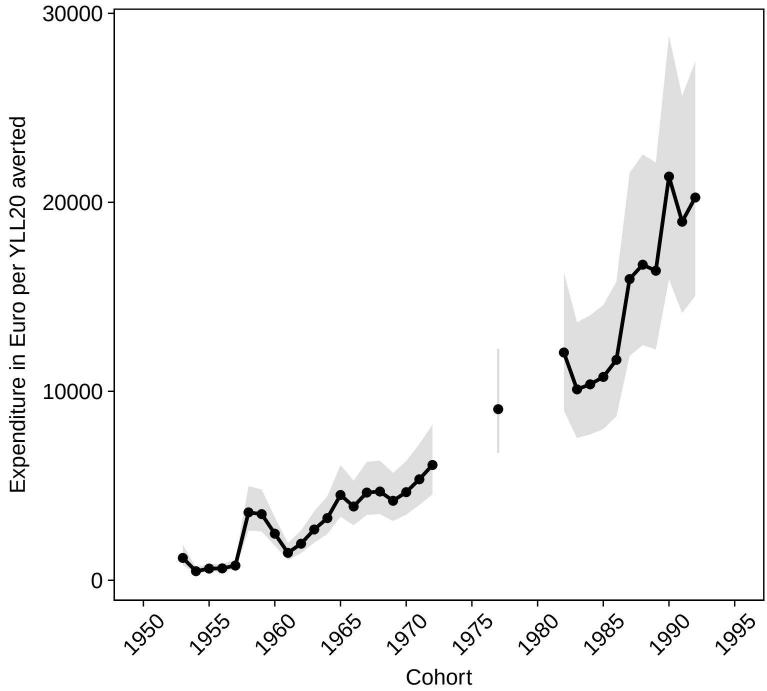

Figure 7.1: Government expenditure on the Dutch National Immunisation Programme (NIP) per year of life lost up to age 20 years (YLL20) averted, birth cohorts 1953–1992, the Netherlands. This graph combines the results from Chapter 2 and Chapter 6. The black line indicates expenditure on the NIP per YLL20 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$^{\text{th}}$ 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 (Tuljapurkar 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 20th 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 19th 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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