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

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## Chapter 3

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

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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  $\geq 80$  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). 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.

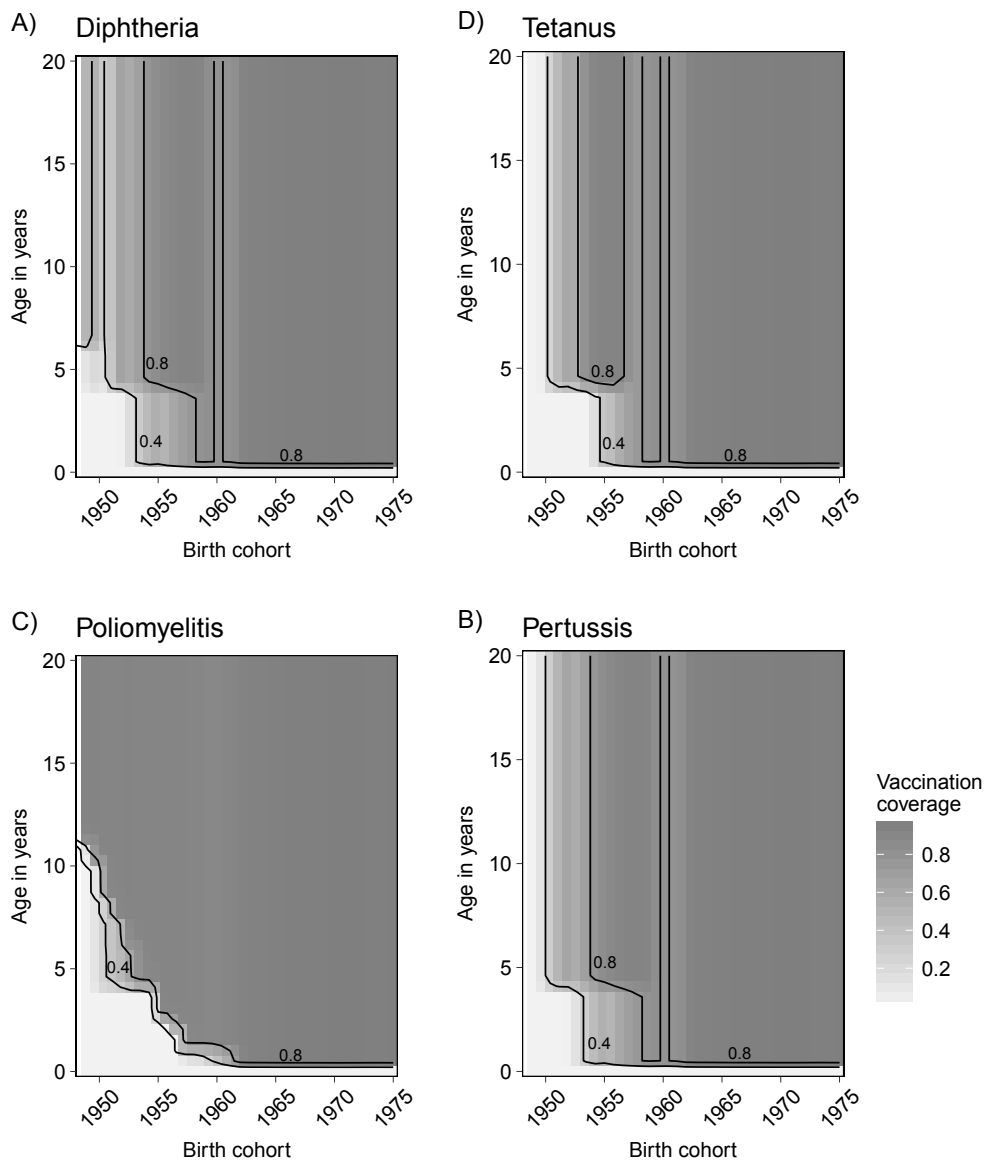
Mass vaccination with the diphtheria toxoid vaccine started in 1953 in the Netherlands. Prior to the start of the mass vaccination programme against diphtheria in

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 re-sampling of pre-vaccination period  $p_{i,a,r}$  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).

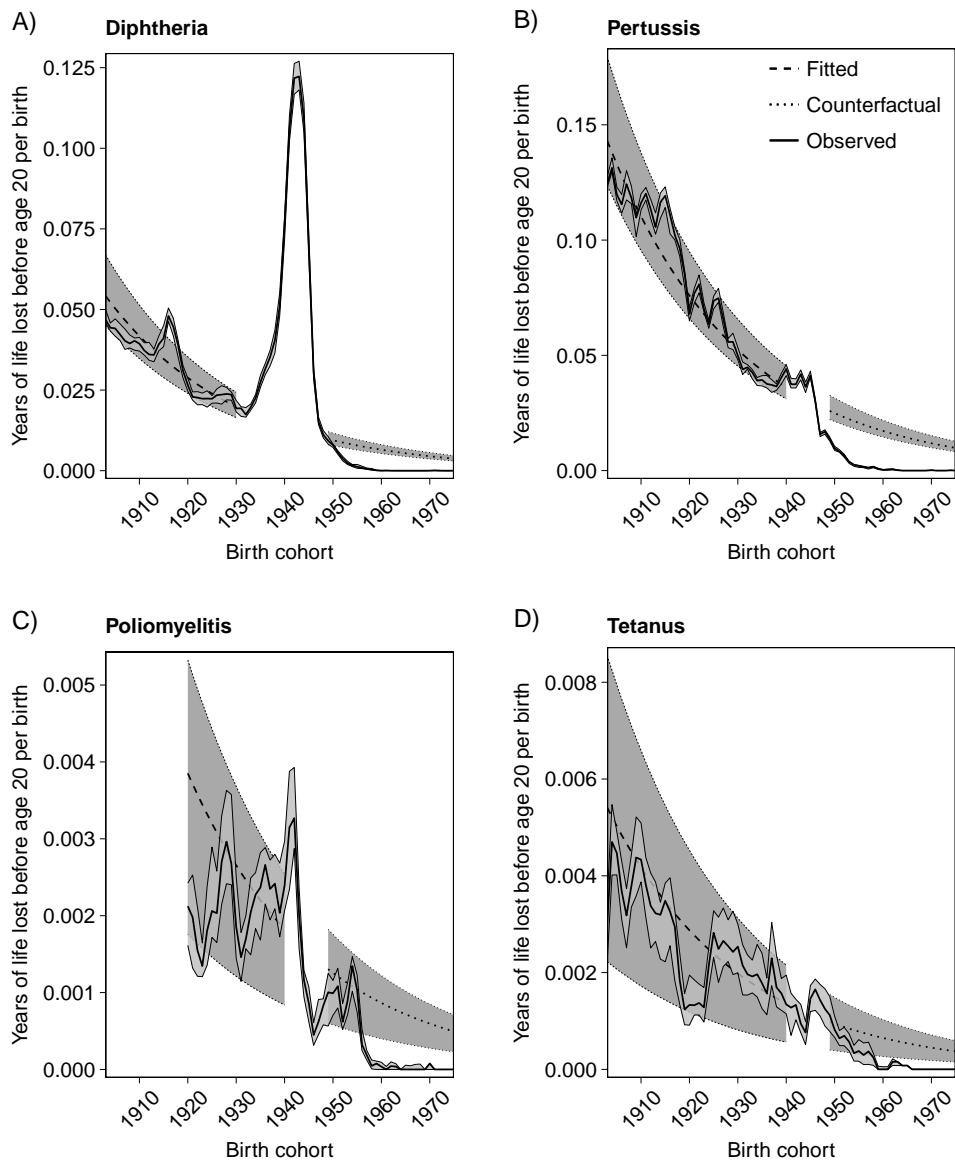
## **Results**

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

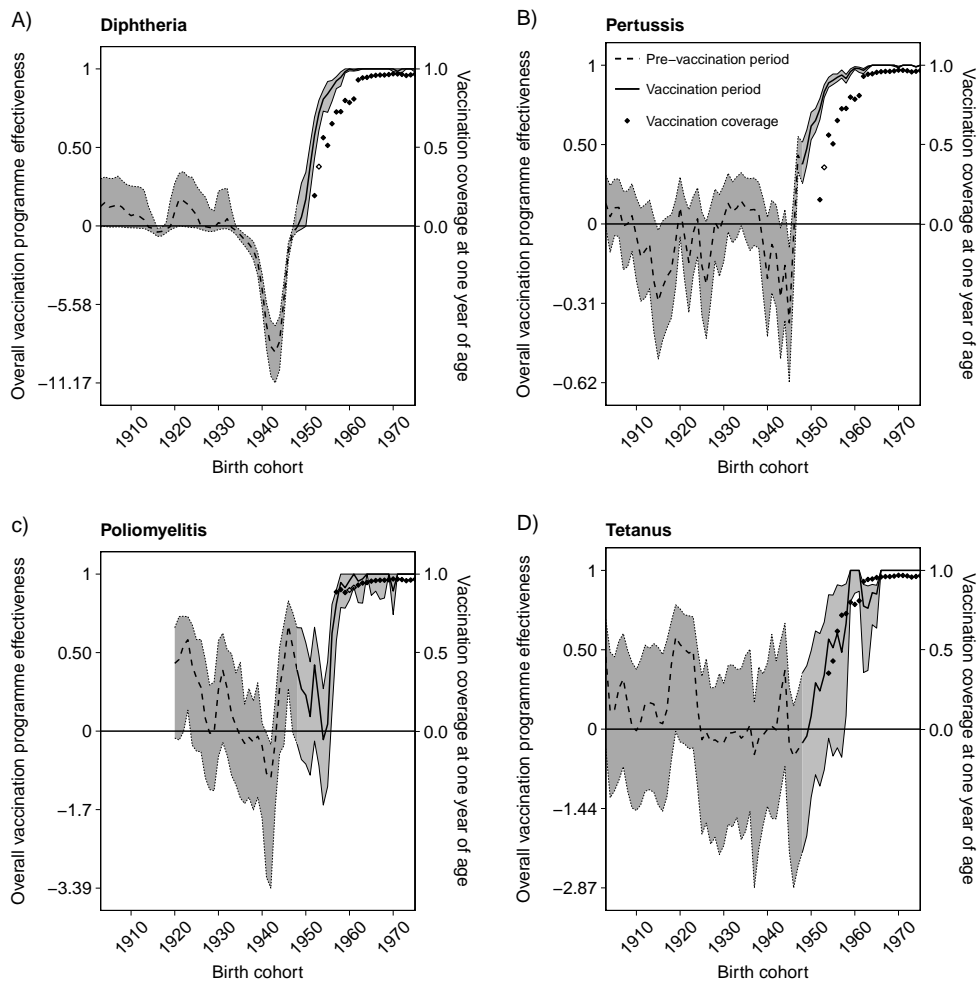
vaccination programmes not been introduced). Our model adequately captures the observed pre-vaccination childhood mortality burden. Upon the start of mass vaccination, the counterfactual and observed childhood mortality burdens rapidly diverge. For pertussis (and to a lesser extent poliomyelitis) this 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.



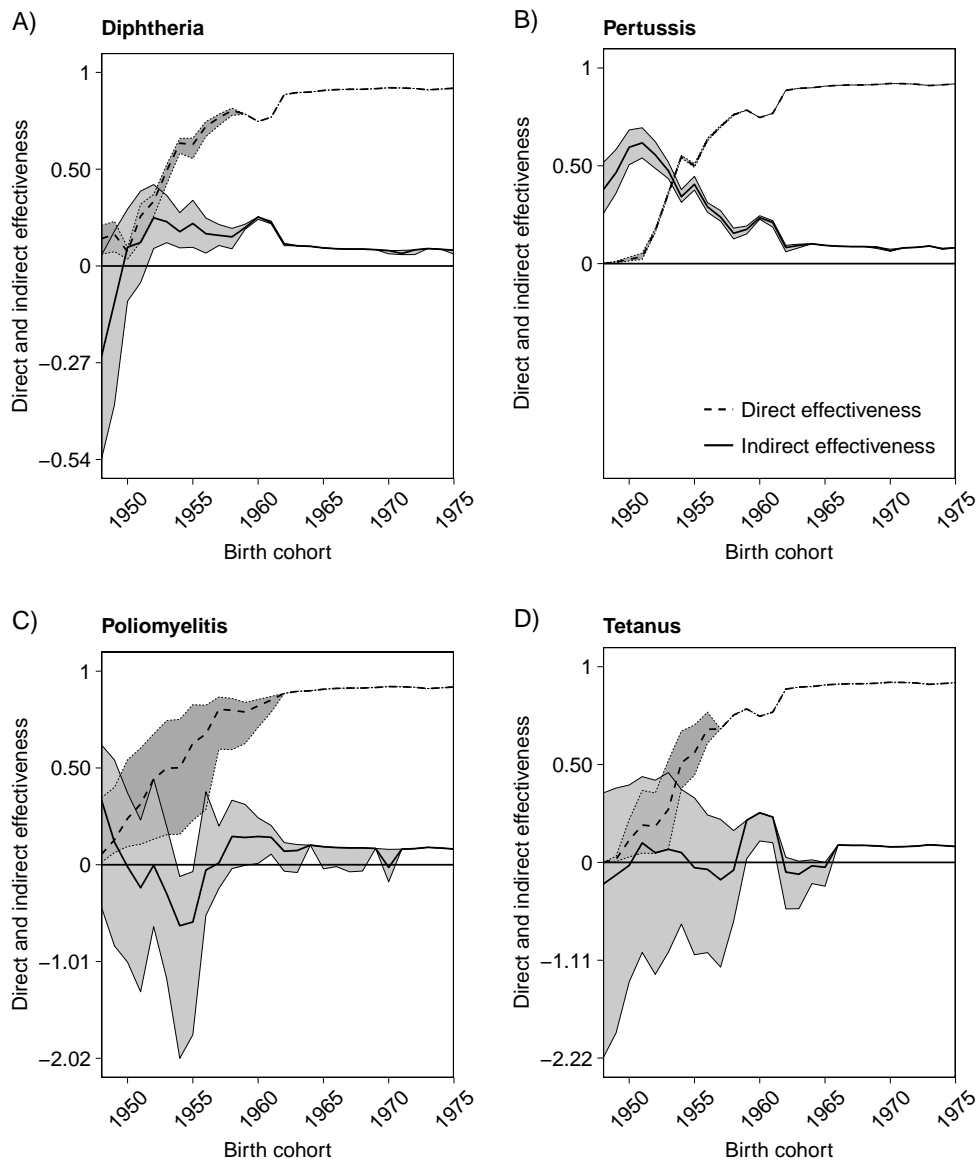
**Figure 3.3: Overall vaccination programme effectiveness and vaccination coverage, the Netherlands, 1903–1975.** Overall vaccination programme effectiveness and vaccination coverage in the Netherlands for (A) diphtheria; (B) pertussis; (C) poliomyelitis; and (D) tetanus. Lines indicate medians and areas 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 (Tuljapurkar 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, HEEdM, 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  $i - a - 1$  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,  $F_j$ , 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).

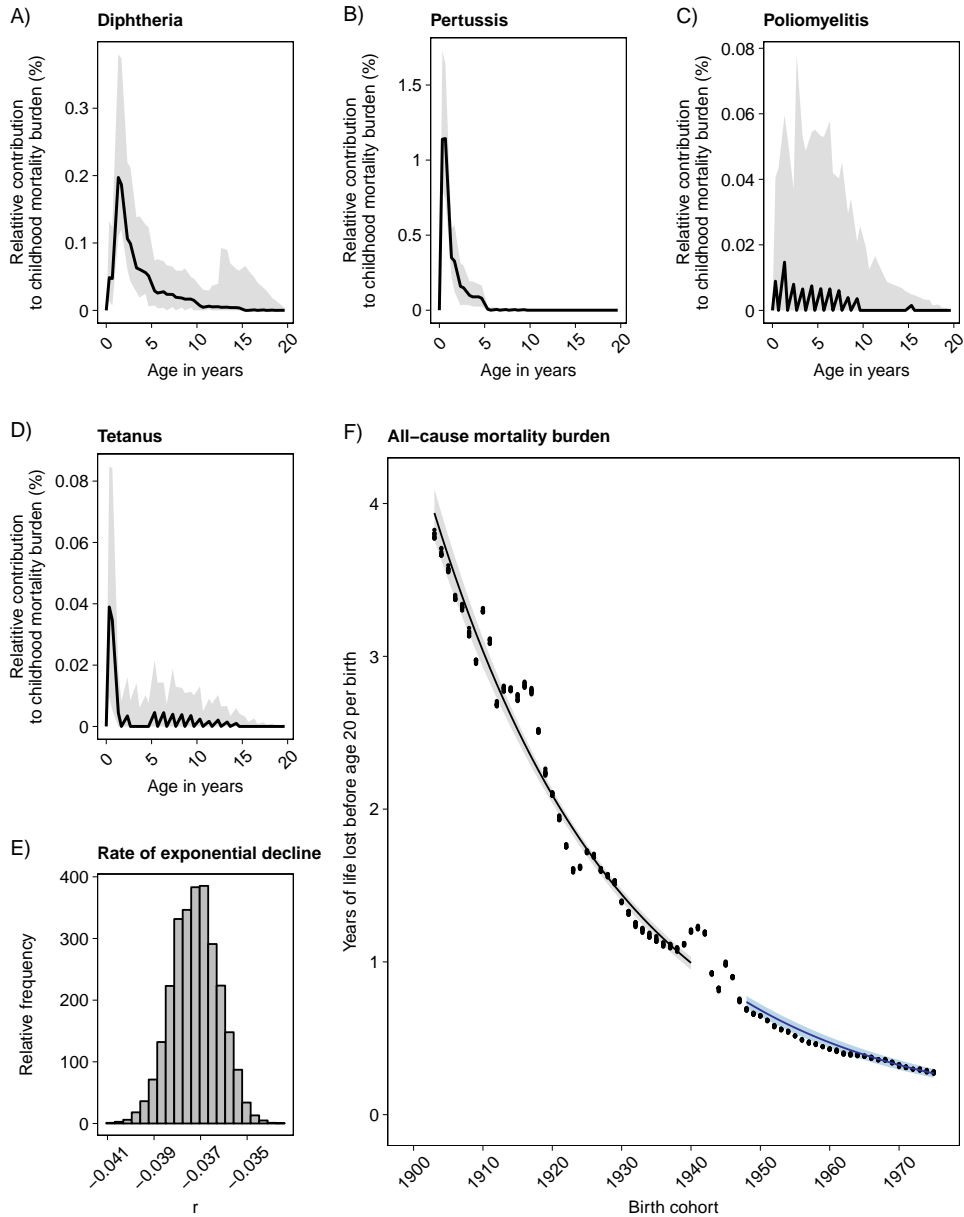
### *Pre-vaccination contribution*

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.

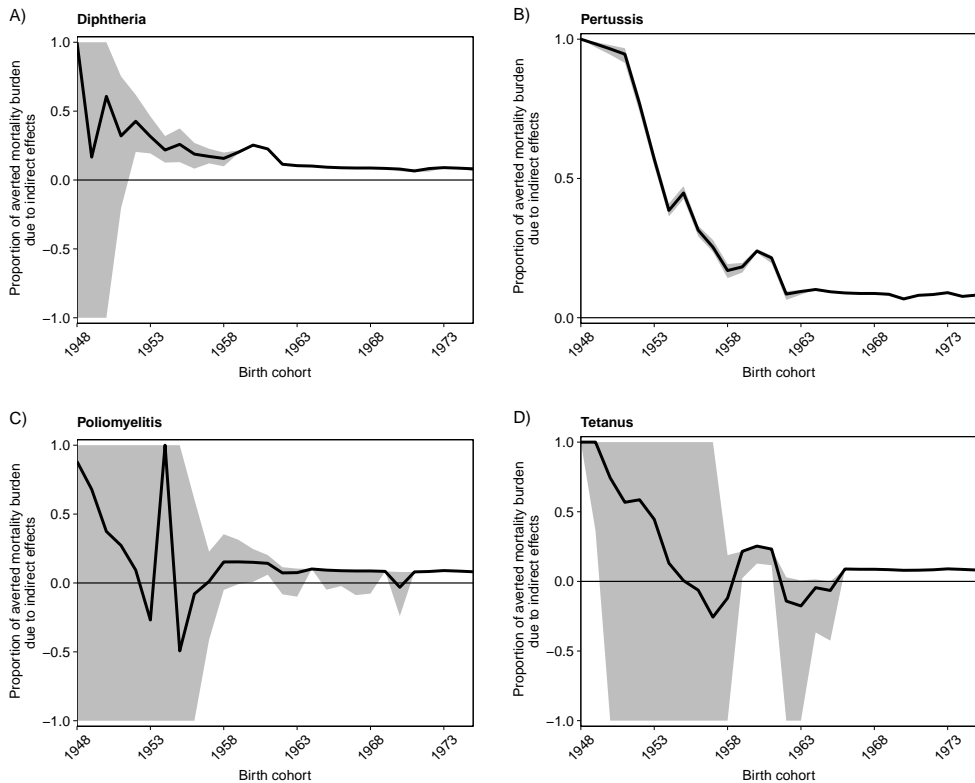
For each cause of death, there were several statistically significant linear trends in the pre-vaccination period. The largest value for the regression coefficient was found for pertussis for the youngest age-group (<1 year): 0.00003 per cohort. This would result in an increase in contribution less than 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,  $p_{I,a,t}$ , 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%.

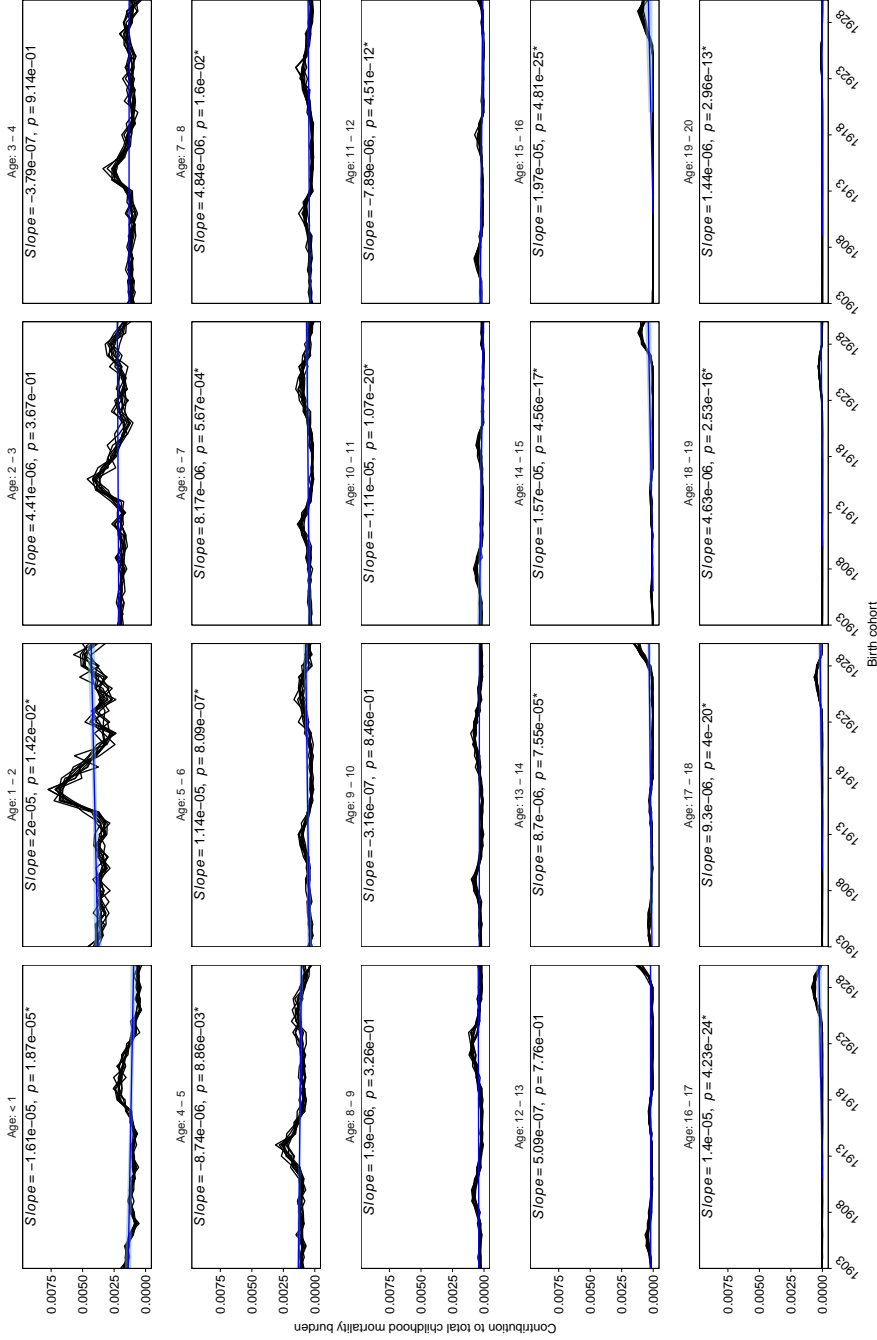
### Results

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.

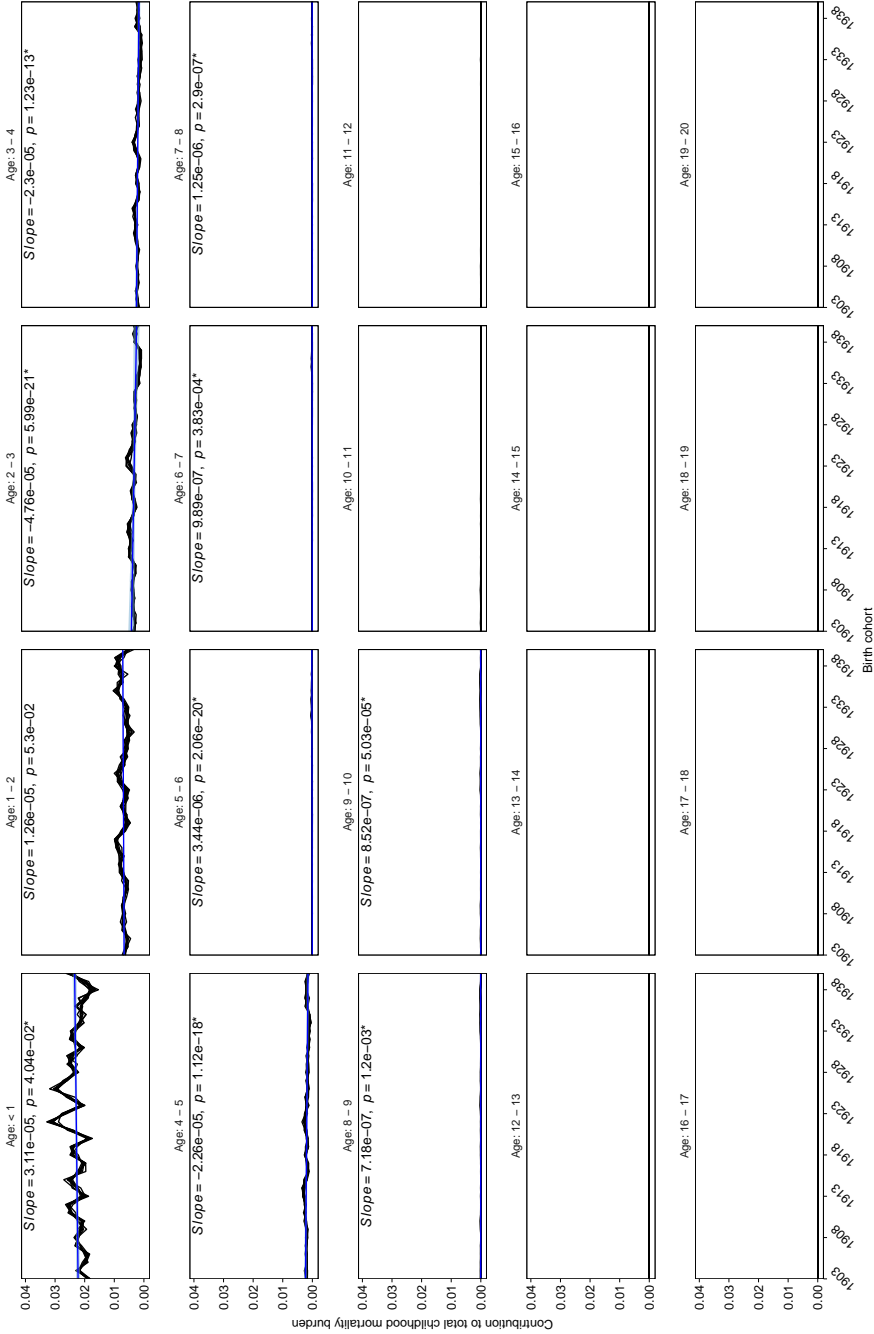
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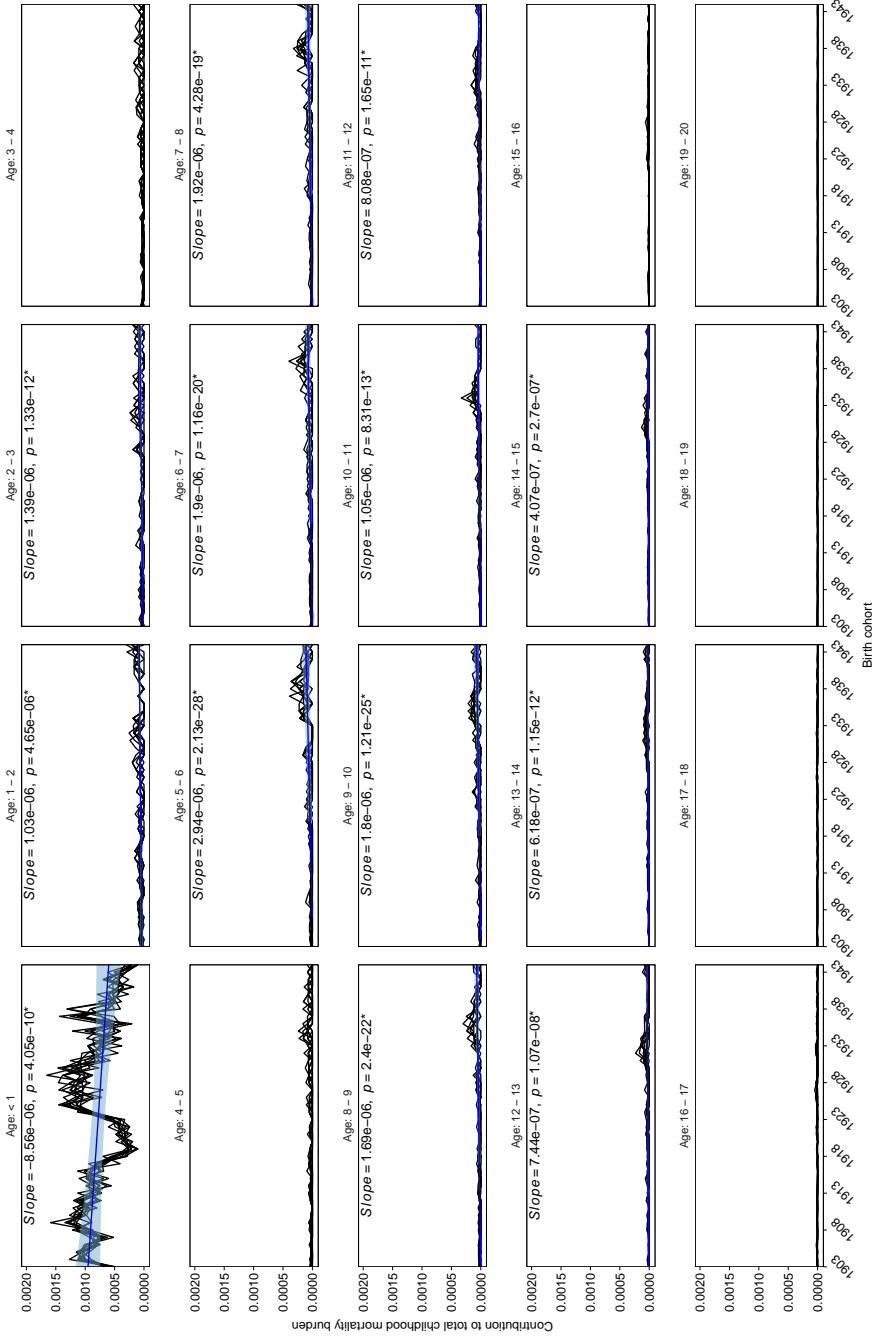


**Supplementary Figure 3.3: Proportion all-cause childhood mortality burden due to diphtheria by birth cohort and by age, the Netherlands, 1903–1930.** Solid black lines represent the realisation of ten imputations. Solid blue line represents the fitted values of the OLS linear regression. Blue area's 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.

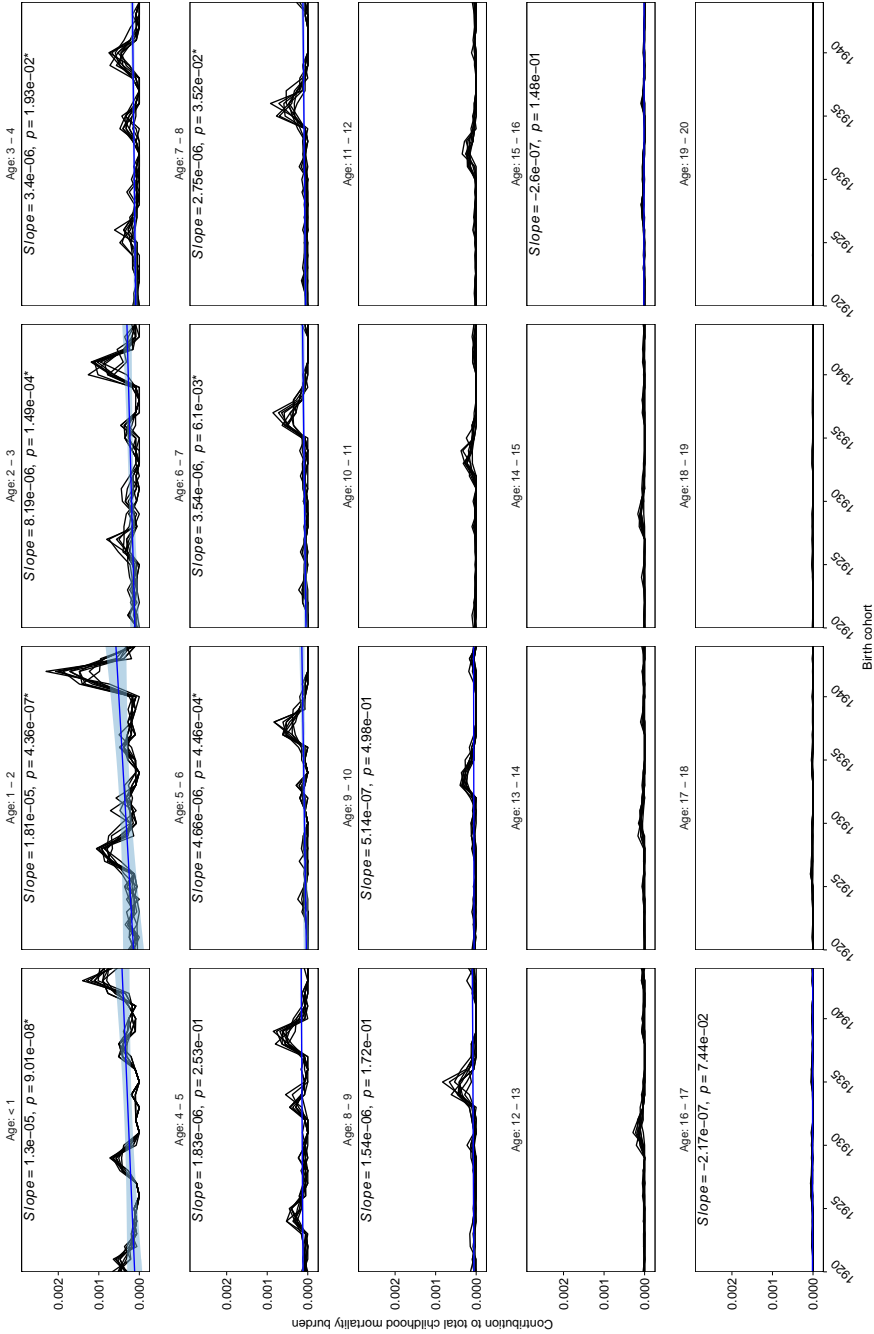




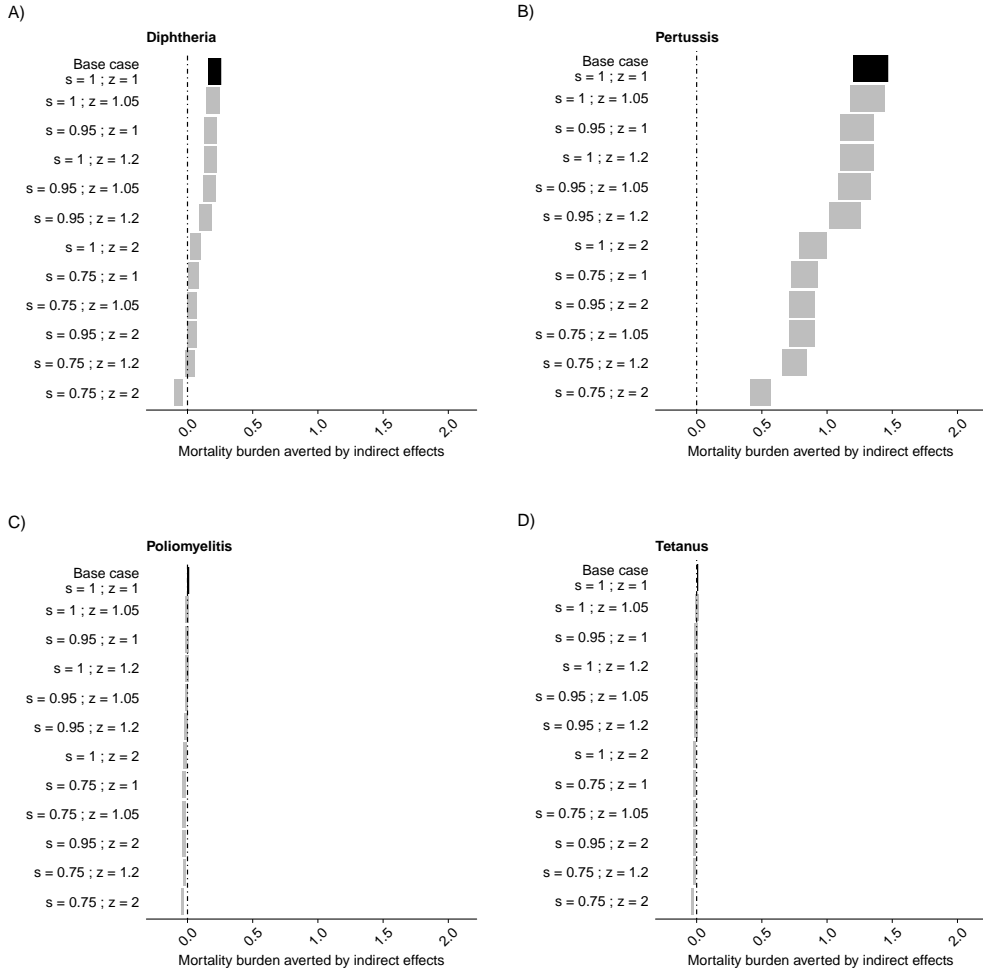
**Supplementary Figure 3.4: Proportion all-cause childhood mortality burden due to pertussis by birth cohort and by age, the Netherlands, 1903–940.** Solid black lines represent the realisation of ten imputations. Solid blue line represents the fitted values of the OLS linear regression. Blue area's 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.



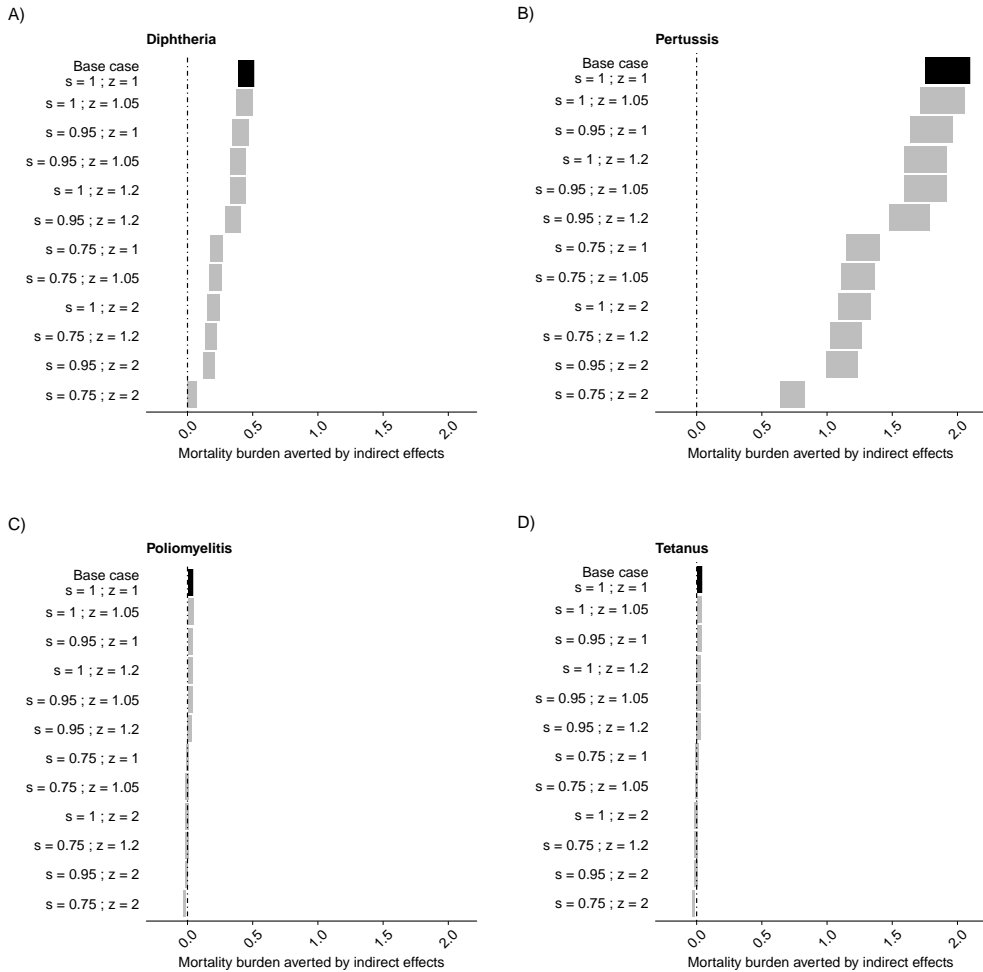
**Supplementary Figure 3.5: Proportion all-cause childhood mortality burden due to poliomyelitis stratified by birth cohort and by age, the Netherlands, 1920–1944.** Solid black lines represent the realisation of ten imputations. Solid blue line represents the fitted values of the OLS linear regression. 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.



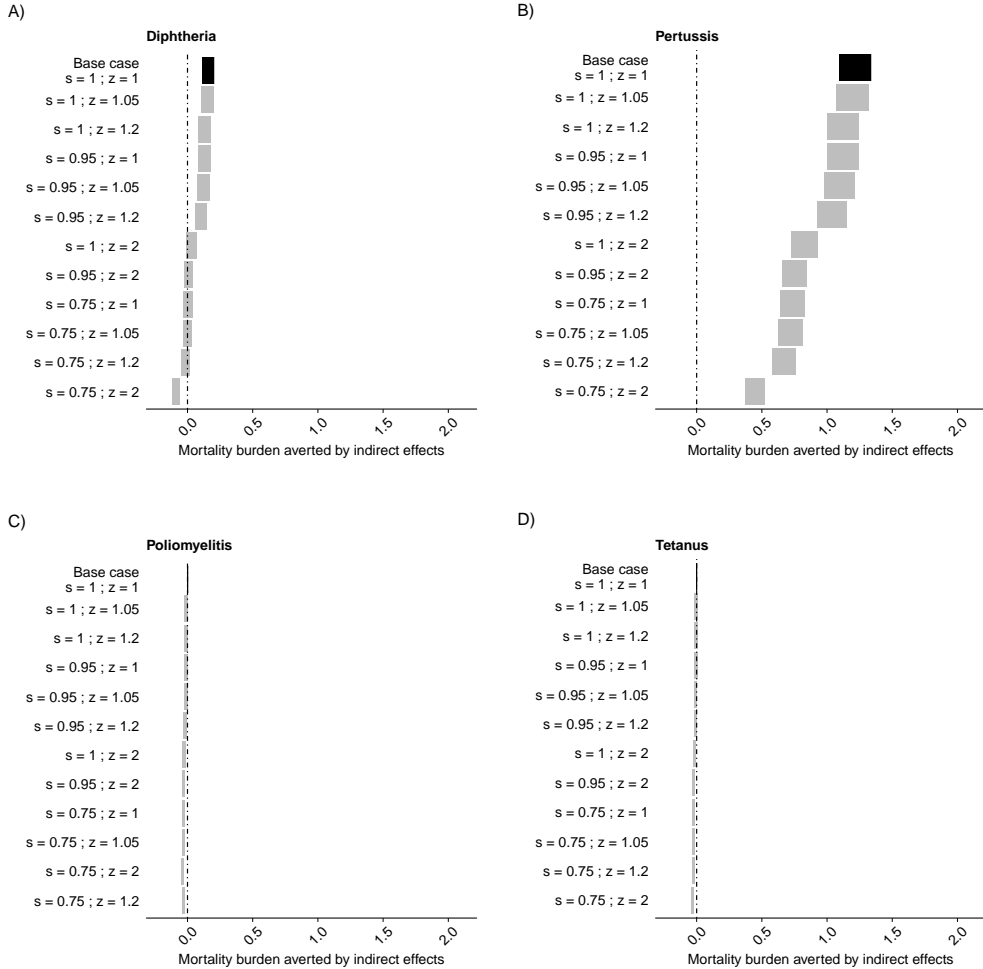
**Supplementary Figure 3.6: Proportion all-cause childhood mortality burden due to tetanus stratified by birth cohort and by age, the Netherlands, 1903–1944.** Solid black lines represent the realisation of ten imputations. Solid blue line represents the fitted values of the OLS linear regression. Blue 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.



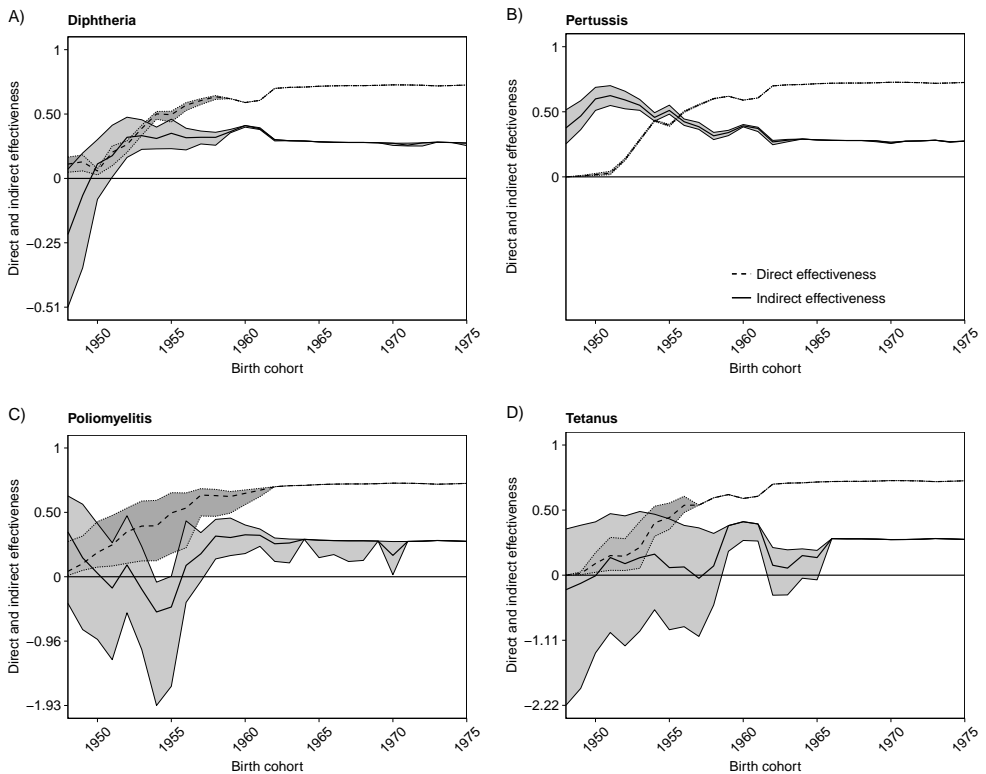
**Supplementary Figure 3.7: Sensitivity analysis for total indirect effects with vaccine effectiveness at 95%.** Sensitivity analysis over birth cohorts 1948–1975 when taking antibiotics into account for (A) diphtheria; (B) pertussis; (C) poliomyelitis; and (D) tetanus. We assume antibiotics lower the 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%.



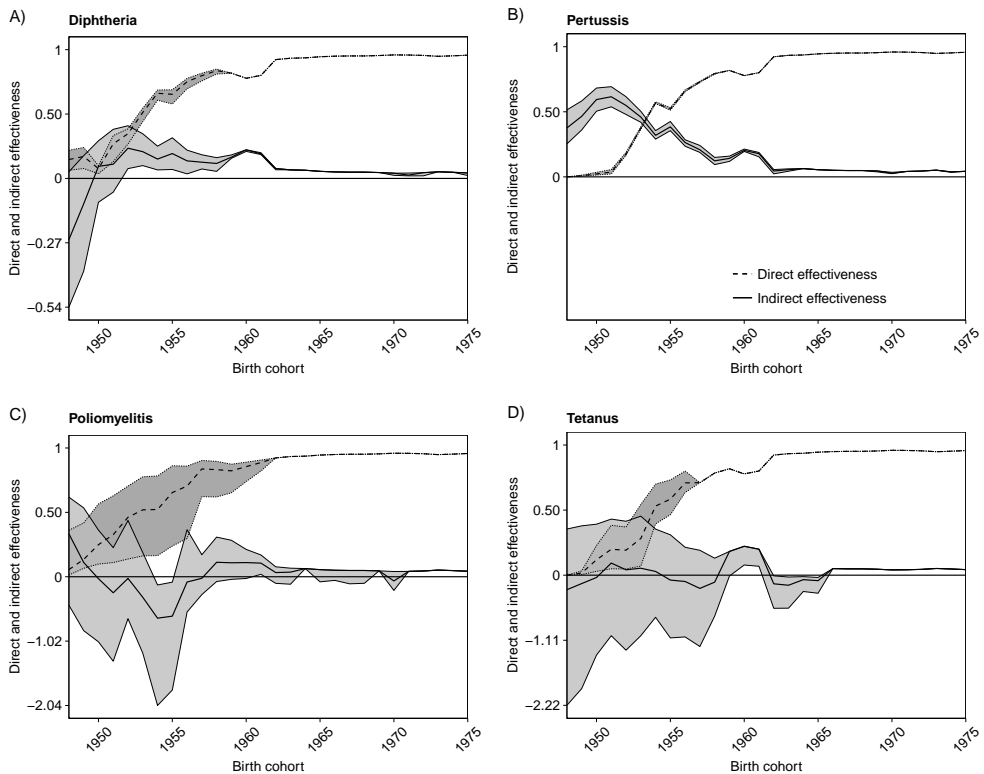
**Supplementary Figure 3.8: Sensitivity analysis for total indirect effects with vaccine effectiveness at 75%.** Sensitivity analysis over birth cohorts 1948–1975 when taking antibiotics into account for (A) diphtheria; (B) pertussis; (C) poliomyelitis; and (D) tetanus. We assume antibiotics lower the 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%.



