



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

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## Summary

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

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

**Findings** In the prevaccination era, the contribution to mortality burden was fairly constant for diphtheria (1·4%), pertussis (3·8%), and tetanus (0·1%). Around the start of mass vaccinations, these contributions to the mortality burden decreased rapidly to near zero. We noted similar patterns for poliomyelitis, mumps, and rubella. The number of deaths due to measles around the start of vaccination in the Netherlands were too few to detect an accelerated rate of decrease after mass vaccinations were started. We estimate that mass vaccination programmes averted 148 000 years of life lost up to age 20 years (95% prediction interval 110 000–201 000) among children born before 1992. This corresponds to about 9000 deaths averted (6000–12 000).

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

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## Introduction

The 20th century showed rapid decreases in childhood mortality and a resultant increase in life expectancy around the world. A large part of the reduction in childhood mortality is attributed to the successful prevention of infectious diseases.<sup>1–3</sup> One of the foremost preventive measures has been the introduction of mass-vaccination programmes.<sup>3–8</sup> However, a precise quantification of the contribution of vaccinations to the fall in childhood mortality burden is not available. Such a quantitative assessment of the effect of vaccination programmes would help parents to reach an informed decision about vaccinating their children, and would inform the debate about the effectiveness of such programmes.<sup>9</sup>

An assessment of the contribution of vaccination programmes to the decrease in mortality is challenging, because it needs reliable historical data about both vaccination coverage and mortality for infectious diseases. A second difficulty is that mortality was falling well before the introduction of mass vaccination; hence,

care should be taken before attributing any change in mortality rates solely to the introduction of mass vaccination.<sup>1,2,10</sup>

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

## Methods

### Mortality data

We obtained detailed cause-specific mortality data for the Netherlands from 1903 to 2012 (for Dutch birth cohorts born from 1903 to 1992). For the first part of this period, 1903–40, we transcribed the data from archived annual reports of the national census bureau (Statistics Netherlands). For the second part of this period, 1941–2012, we decoded the data from a database, provided by Statistics Netherlands, with individual mortality records where the cause of death was coded according to the International Classification of Diseases (ICD). The mortality records over this period covered

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**Research in context****Evidence before this study**

We searched MEDLINE on Sept 2, 2015, for English-language or Dutch historical or comparative studies of the contribution of vaccines to the reduction in vaccine-preventable disease mortality or morbidity (without date restrictions). We used the search terms for the infections of interest ("diphtheria", "pertussis", "tetanus", "measles", "rubella", "polio", or "mumps"), for the intervention of interest ("vaccination programme"), for the outcome of interest ("mortality" or "deaths averted"), and for the kind of study ("comparative study" or "historical article"). We allowed for common variations on each term (such as "immunization programme") and for names of vaccines against the infections of interest (such as "MMR" and "DTP"). We identified 148 articles this way. We screened articles by title and abstract to identify studies that analysed mortality or morbidity during the prevaccination and vaccination periods. We extended the search by screening the references listed in articles that met our criteria. Our search resulted in 16 relevant articles. Most of these articles focused on the duration between successive epidemic waves or the frequency of fade-outs, and most of these articles used case notifications or the number of cases averted as an outcome measure. Five articles discussed mortality data. Of these, three articles reported on mortality and showed a decreasing trend before introduction of vaccination. None of these articles corrected for this long-term trend.

**Added value of this study**

We characterised the effect of vaccination programmes using the cause-specific contributions to childhood mortality burden—a measure that remains unaffected by any trend in mortality rates. We quantified this measure for Dutch birth cohorts born from 1903 to 1992 (using cause-specific and age-specific historical mortality data from 1903 to 2012) for seven vaccine-preventable diseases: diphtheria, pertussis, tetanus, poliomyelitis, measles, mumps, and rubella. For most of these diseases, no temporal trend was discernible in the contribution to mortality burden before mass vaccination was introduced. We showed that high vaccination coverage for a birth cohort coincided with a low cause-specific contribution to childhood mortality for that birth cohort and estimated that about 9000 deaths in the Netherlands have been averted by mass vaccinations. This finding showed the effect that vaccination programmes had on the burden of mortality due to vaccine-preventable diseases, irrespective of any trend in mortality burden.

**Implications of all the available evidence**

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

six ICD revisions, which were implemented in 1941 (ICD-5), 1950 (ICD-6), 1958 (ICD-7), 1969 (ICD-8), 1979 (ICD-9), and 1996 (ICD-10). For each revision, we validated the code lists against previous studies (appendix).<sup>11</sup>

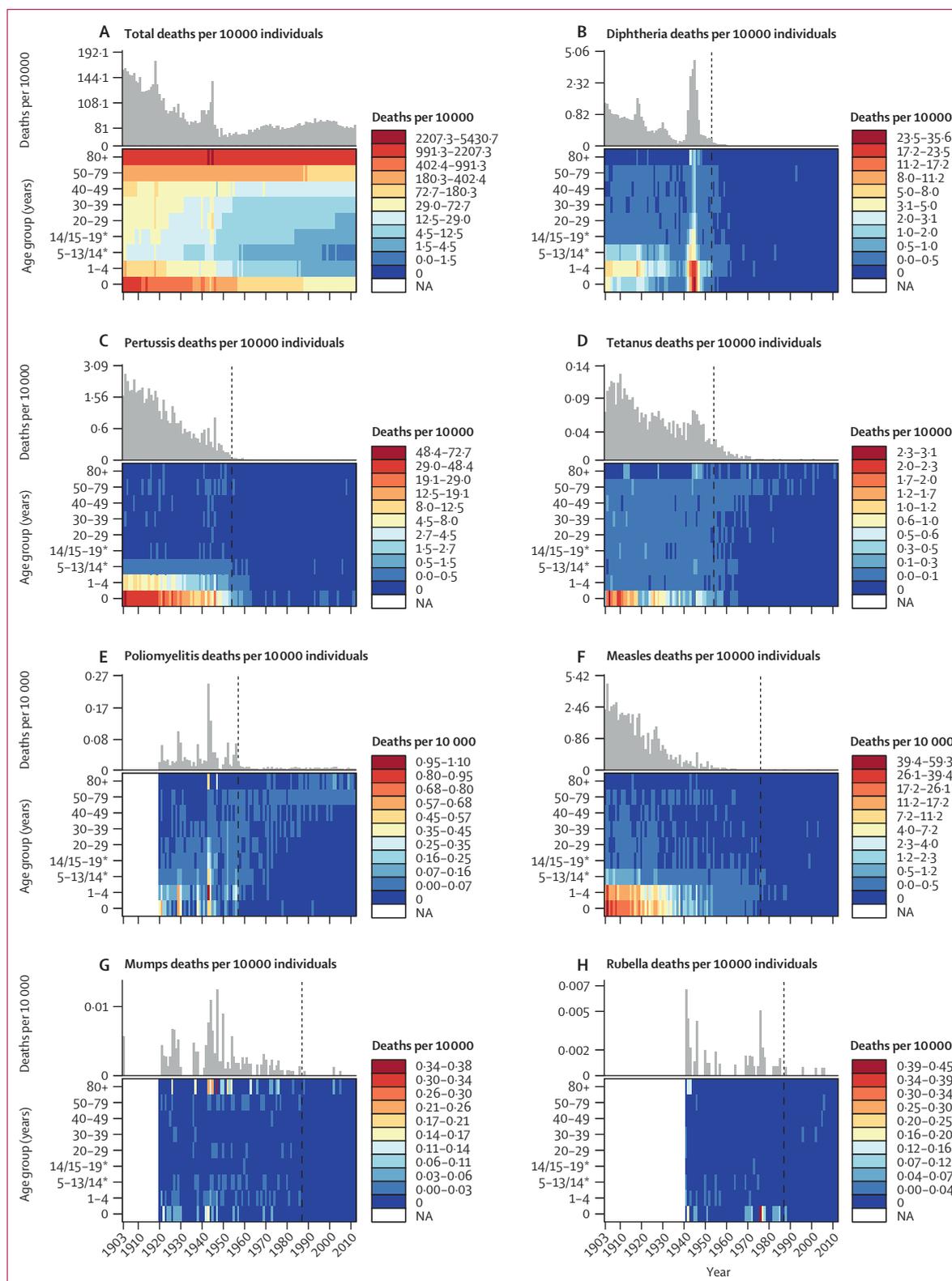
We extracted data about the number of deaths from all causes, and the number of deaths due to diphtheria, pertussis, tetanus, poliomyelitis, measles, mumps, rubella, varicella, and diarrhoea (combined with dysentery and enteritis). Both varicella and diarrhoea served as negative control groups (ie, diseases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

**Data for population sizes and vaccination coverage**

We obtained age-specific national population estimates for 1903–2012 from Statistics Netherlands (appendix). For 1903–49, we transcribed the estimated population size by 5-year age groups from compiled periodic reports. For 1950–2012, we used an existing database containing age-specific population estimates. We obtained a database containing the number of births for 1903–2012 and migration data from Statistics Netherlands (appendix).

We transcribed historical vaccination coverage data by birth cohort from annual reports by the Dutch Health Care Inspectorate for the 1952–69 birth cohorts. For the birth cohorts 1970–2012, data for coverage were obtained from records held by the Dutch National Institute for Public Health and the Environment. For each birth cohort, we used the national vaccination coverage at age 11 months (the age at which babies should have completed the primary series and received a first booster) for diphtheria, pertussis, tetanus, and poliomyelitis, and the national coverage at age 14 months (the first vaccination) for measles, mumps, and rubella. For birth cohorts with missing coverage data for these two ages (1953 and 1958–61), we interpolated the coverage from adjacent birth cohorts (appendix). The coverage does not include unregistered administration of vaccines and therefore slightly underestimated the actual vaccination coverage.

See Online for appendix



**Figure 1: All-cause and cause-specific mortality rates in the Netherlands from 1903 to 2012**

Figure shows mortality rates for all causes, diphtheria, pertussis, tetanus, poliomyelitis, measles, mumps, and rubella. Top panels show the total number of deaths per 10 000 individuals per year, and bottom panels show age-specific mortality rates. Dashed line in B-H shows the start of mass vaccination. \*In 1920 these age groups changed from 5-13 years to 5-14 years, and from 14-19 years to 15-19 years.

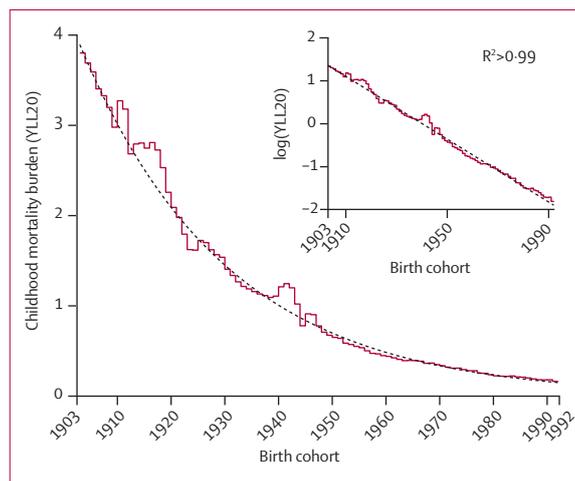
Mass vaccination started in the Netherlands in 1953, when children aged 1–10 years could be vaccinated against diphtheria at the expense of the government. In 1954, the diphtheria vaccine was combined with vaccines for pertussis and tetanus. In 1957, poliomyelitis vaccination was added to the programme, with a catch-up campaign for all children aged 1–5 years. Rubella vaccination started in 1974 for girls aged 11 years. Measles vaccination started in 1976 for children aged 14 months. Since 1987, all children aged 14 months and 9 years were given a combined vaccination against measles, mumps, and rubella, with a catch-up campaign for children aged 9 years born in 1978–82 and children aged 4 years born in 1983–85.

### Outcomes

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

### Statistics

We used the restricted mean lifetime method<sup>12,13</sup> to calculate cause-specific mortality burden among children and young adults for each birth cohort as the number of years of life lost up to age 20 years (YLL20; appendix).<sup>12</sup> We chose the cutoff age of 20 years to enable a fair comparison of mortality burden between birth cohorts born between 1903 and 1992, and excluded migration because it had no effect on the results (migration in this context means the difference between individuals moving into the Netherlands and moving out; appendix).



**Figure 2:** All-cause mortality burden in years of life lost up to age 20 years per livebirth in the Netherlands

Data are years of life lost up to age 20 years (YLL20) per livebirth in Netherlands for birth cohorts from 1903 to 1992 (solid line) with best-fit exponential reduction (dotted line). Inset shows the log-transformed YLL20 (solid line) and the corresponding best linear fit (dotted line).

The age-specific, all-cause mortality rates fell throughout the 20th century, and this decreasing trend is also noted with many cause-specific mortality rates.<sup>1,2,14,15</sup> To correct for this long-term trend, we focused on the cause-specific contributions to the all-cause number of years of life lost (ie, total childhood mortality burden). For each birth cohort and each infectious disease, we calculated these contributions as the ratio of cause-specific years of life lost before age 20 to all-cause years of life lost before age 20 (appendix). We restricted the analysis to birth cohorts for which we have complete data on cause-specific mortality rates for all age ranges. This means that for poliomyelitis and mumps we restricted the analysis to cohorts born since 1920, for rubella to cohorts born since 1941, and for varicella to cohorts born since 1936. For all other infections the analyses covered all cohorts born since 1903.

The mortality burden averted because of vaccination was obtained by extrapolating the prevaccination mortality burden and subtracting the actual mortality burden over the vaccination period (appendix).

### Role of the funding source

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

### Results

From 1903 to 2012, all-cause mortality rates showed a strong and persistent reduction in most age groups, especially in children aged 0–4 years (figure 1). All-cause mortality decreased from 156 deaths per 10000 individuals per year in 1903 to 84 deaths per 10000 individuals per year in 2012. This trend of decreases was interrupted during World War 1 (1914–18) and World War 2 (1939–45). Cause-specific mortality for each of the specific childhood infections shows a decreasing trend among the youngest age groups and fell to near zero after the launch of mass-vaccination programmes (lower panels in figure 1; appendix).

The all-cause number of life-years lost decreased with year of birth from 1903 to 1992 (figure 2). The decrease is well approximated by an exponential decay, with a halving time of 19 years (figure 2 inset,  $R^2 > 0.99$ ). Children born in 1903 lost, on average, 3.80 years of life before age 20, those born in 1952, on average, 0.59 years of life, and those born in 1992 lost, on average, 0.16 years of life.

Breaking down the life-years lost by vaccine-preventable disease (appendix), we estimated that a newborn baby in 1903 would lose, on average, 0.34 years of life (8.8% of 3.80 all-cause life-years lost) because of diphtheria, pertussis, tetanus, or measles before age 20 years. A newborn baby in 1952, just before mass vaccination was introduced, would lose, on average, 0.01 years (2.5% of 0.59 all-cause life-years lost) because of diphtheria,

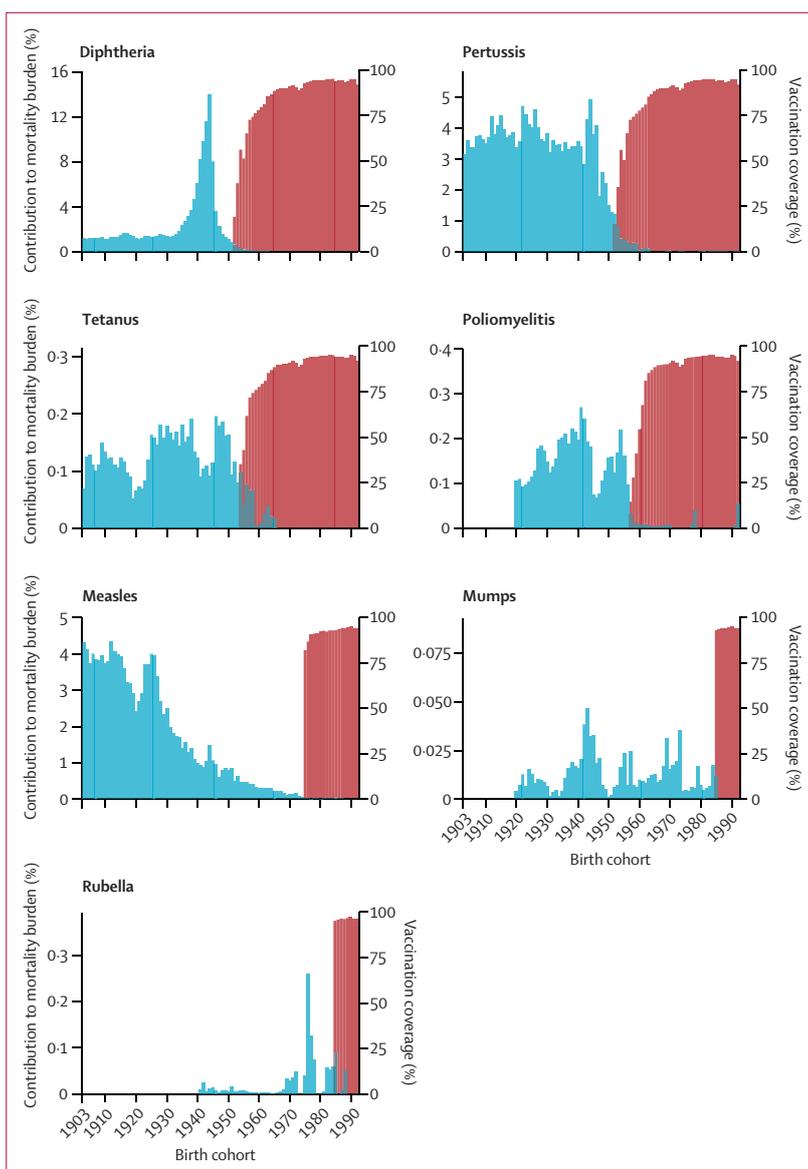
pertussis, tetanus, or measles before the age of 20, and another 0.001 years (0.1% of all-cause life-years lost) because of poliomyelitis, mumps, or rubella. A newborn baby in 1992 would lose, on average, 0.0001 years, or roughly 1 h (0.1% of 0.16 all-cause life-years lost) from vaccine-preventable childhood diseases, with only pertussis and poliomyelitis contributing.

For most vaccine-preventable diseases, the contribution to the overall mortality burden before age 20 years (after correction for long-term trends in life-years lost) was constant in the prevaccination period (figure 3, table). For diphtheria, this constant contribution was around 1.4%; for pertussis around 3.8%, and for tetanus around 0.1%. For poliomyelitis, the contribution to life-years lost varied between 0.07% and 0.27%. The irregularity was due to recurrent epidemics and the small number of deaths of individuals younger than 20 years. For each of these vaccine-preventable diseases, the contribution to the total mortality burden fell rapidly towards zero when mass vaccinations started.

For measles, the contribution to overall mortality steadily fell from 4.3% for the birth cohort born in 1903 to 0.02% for the birth cohort born in 1975, just before the start of mass vaccination against measles (figure 3). For mumps, the contributions to overall mortality in the prevaccination period varied between 0.01% and 0.05%. For rubella, the contribution to life-years lost was about 0.01% for birth cohorts born in 1941–71, before mass vaccination of girls aged 11 years was introduced (figure 3). The number of deaths due to measles around 1975 in the Netherlands was too small to detect an accelerated rate of decrease after the introduction of mass vaccination. For birth cohorts born after 1987—the start of mass vaccination with the combined measles–mumps–rubella vaccine—the contributions of mumps and rubella to the mortality burden fell to zero.

Each vaccine programme achieved a high coverage within a few years after its introduction into the national immunisation programme (figure 3). The coverage of vaccination against diphtheria, pertussis, and tetanus exceeded 80% within 10 years after introduction in 1953. The coverage of vaccination against poliomyelitis exceeded 80% within 6 years of introduction; for measles coverage exceeded 80% at the start of the programme; and for mumps and rubella coverage exceeded 80% since the start of the combined measles–mumps–rubella vaccination programme. We noted that for all the diseases considered, except measles, the rapid increase in vaccination coverage against a particular infection coincided—within a timeframe of a few years—with a rapid decrease of this disease's contribution to life-years lost before age 20.

For varicella, for which no vaccination programme exists in the Netherlands, the contribution to mortality burden was around 0.06%. For diarrhoea (combined with dysentery and enteritis), the contribution decreased rapidly in the first half of the 20th century, and remained around 1.2% in the second half. Since 1950, there have been no



**Figure 3: Vaccination coverage in the Netherlands and disease-specific contribution to childhood mortality burden**

Data are for birth cohorts from 1903 to 1992, vaccination coverage (red) and the contribution (as a percentage) to childhood mortality burden before the age of 20 (blue) for diphtheria, pertussis, tetanus, poliomyelitis, measles, mumps, and rubella.

rapid decreases of the contribution to life-years lost before age 20 for either of these negative controls (appendix).

We estimated that mass vaccination programmes averted 148 000 (95% prediction interval 110 000–201 000) years of life lost before age 20 among children born before 1992. This finding corresponds to 9000 deaths (6000–12 000) averted. During the vaccination period, the population of the Netherlands grew from about 10 million in 1950 to 16 million in 1992 (appendix). Most of the averted mortality burden was attributable to vaccination against pertussis; vaccination against diphtheria was the second biggest contributor (table).

|               | Year of introduction of vaccination | Average contribution to all-cause mortality burden |                    | Reduction in mortality burden due to mass vaccinations (95% prediction interval) |                     |
|---------------|-------------------------------------|--|--------------------|--|---------------------|
|               |                                     | Before introduction                                | After introduction | YLL20 in thousands   | Deaths in thousands |
| Diphtheria    | 1953                                | 1.36%  | 0.004%             | 38 (28–52)   | 3 (2–4)             |
| Pertussis     | 1954                                | 3.75%  | 0.024%             | 103 (79–134)   | 6 (4–7)             |
| Tetanus       | 1954                                | 0.13%  | 0.003%             | 3 (1–6)  | 0.2 (0.1–0.4)       |
| Poliomyelitis | 1957                                | 0.15%  | 0.005%             | 3 (1–8)  | 0.3 (0.1–0.6)       |
| Measles*      | 1976                                | ..   | ..                 | 0.3 (0.2–0.5)  | 0.02 (0.01–0.03)    |
| Mumps†        | 1987                                | 0.01%  | ..                 | ..   | ..                  |
| Rubella†      | 1987                                | 0.02%  | ..                 | ..   | ..                  |

The contributions over the vaccination period were taken as an average over the period, starting five cohorts after the start of mass vaccination up to cohort 1992. The contributions to the all-cause mortality burden over the prevaccination period were taken as an average over the period 1903–30 for diphtheria, 1903–46 for pertussis, 1903–53 for tetanus, 1920–56 for poliomyelitis, 1920–84 for mumps, and 1941–84 for rubella. Reductions in mortality burden were estimated as the difference between the actual burden after introduction of vaccination, and the burden that would have resulted had the contribution to mortality due to that disease remained constant. YLL20= years of life lost up to age 20 years. \*The contribution of measles to all-cause mortality burden decreased in the prevaccination period, and no value is provided. †For mumps and rubella, too few results were available after introduction of vaccinations to calculate an average.

**Table: Effect of mass vaccination programmes against childhood infectious diseases in the Netherlands, birth cohorts 1903–92**

## Discussion

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

The overall exponential reduction in all-cause mortality burden during the 20th century is striking and in line with reports for other countries.<sup>1,2,15</sup> A range of factors contributed to this decrease for a wide range of causes of death, such as better nutritional status and increased standard of living, improved hygiene, increased access to clean water, improved sewage collection and disposal, better housing, improvements in medical treatment (such as availability of antibiotics), and lower birth rates.<sup>15–20</sup> However, none of these factors changed suddenly and drastically during the period after World War 2, such that they could provide a plausible explanation for the rapid decrease in contribution to mortality burden for any specific vaccine-preventable disease that we noted in our analysis. This idea is lent support by the absence of sudden decreases in the contribution to mortality burden in the negative controls, although a gradually decreasing trend was noted for diarrhoea.

For some infections, we recorded a fall in the contribution to the childhood mortality burden in birth cohorts born a few years before mass vaccination started (figure 3). Because we assessed mortality burden by birth cohort, such a decrease is to be expected: older birth cohorts might have been partly protected from infection by vaccinated individuals in adjacent birth cohorts.<sup>21</sup> Additionally, some children in these birth cohorts might have been protected because of individual, often unregistered, administration of vaccines (in particular, this might have played a part for diphtheria and pertussis).

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

Changes in the registration of causes of death did not affect cause-specific contributions to the childhood mortality burden. Mortality records rely on the validity and reliability of the cause of death registered on death certificates and the subsequent coding according to the current ICD coding lists. The validity might change over time depending on the advancement of medical knowledge, the sensitivity and specificity of clinical diagnoses, new regulations, ICD revisions, coding practices, and the skills of certifiers.<sup>22</sup> The codes used in our analysis changed little over time. Where they changed, we visually inspected the mortality trends for any discontinuities due to changes in registration. We did not record any substantial anomalies for the diseases presented in this report. Therefore, we believe it unlikely that changes in death registration caused the sudden and striking reductions in childhood mortality burden.

To the best of our knowledge, our study is the first to compare accurate vaccination coverage data with mortality rates for many birth cohorts born before and after introduction of mass vaccination, while correcting for long-term trends in mortality. Our findings are in line with those of earlier studies<sup>2,4,5,23</sup> in the Netherlands and other countries, suggesting that findings might be similar in other populations as well. Further investigation of data for other populations with similar methods would provide an opportunity to validate our results. Another possibility for further investigation involves analysing older time series to capture the epidemiological transition that started in Netherlands during the 19th century.<sup>14</sup> For a complete picture of the benefit of vaccination

programmes, it is essential to account for the incidence of disease in addition to mortality.<sup>5</sup>

In many countries around the world, including the Netherlands, vaccine-preventable diseases continue to cause outbreaks, mainly in communities with low vaccination coverage, and are a major cause of considerable disease burden.<sup>24–28</sup> In the continuing debate about the effectiveness of vaccinations, people who are sceptical about vaccines often use the decrease in the number of deaths due to vaccine-preventable infections before mass vaccination to cast doubt on the effectiveness of vaccination programmes. We show that, indeed, mortality burden did decrease before mass vaccination, but that after correcting for this long-term trend, the effectiveness of most vaccination programmes on mortality can be clearly detected. Our findings, when taken together, suggest that if a vaccine-preventable disease were to resurge, it would be unlikely to lead to prevaccination levels of mortality because of the overall decrease in childhood mortality burden. Additionally, our results suggest that the rapid reductions in the contribution of vaccine-preventable diseases to the childhood mortality burden were caused by the introduction of mass vaccination, and that vaccination programmes have been effective in further reducing the mortality burden. We believe these results will be useful to emphasise the effectiveness of vaccination programmes to both public health experts and the general population, and to help parents to make an informed decision about vaccinating their children.

#### Contributors

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

#### Declaration of interests

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

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