The public health impact of vaccination programmes in the Netherlands

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Chapter 2

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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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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Abstract

Background

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

Methods

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

Findings

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

Interpretation

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

Introduction

The 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 (Armstrong et al., 1999; Tuljapurkar et al., 2000; Breiman et al., 2004). One of the foremost preventive measures has been the introduction of mass vaccination programmes (Breiman et al., 2004; Roush and Murphy, 2007; Centers for Disease Control and Prevention (CDC), 2011; Hinman et al., 2011; Van Panhuis et al., 2013; Greenwood, 2014). However, a precise quantification of the contribution of vaccinations to the fall in childhood mortality burden is not available. Such a quantitative assessment of the effect of vaccination programmes would help parents to reach an informed decision about vaccinating their children, and would inform the debate about the effectiveness of such programmes (Kata, 2010).

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

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

Materials and methods

Mortality data

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

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

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

Data for population sizes and vaccination coverage

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

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

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

Outcomes

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

Statistics

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

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

Role of the funding source

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

Results

Mortality rates

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

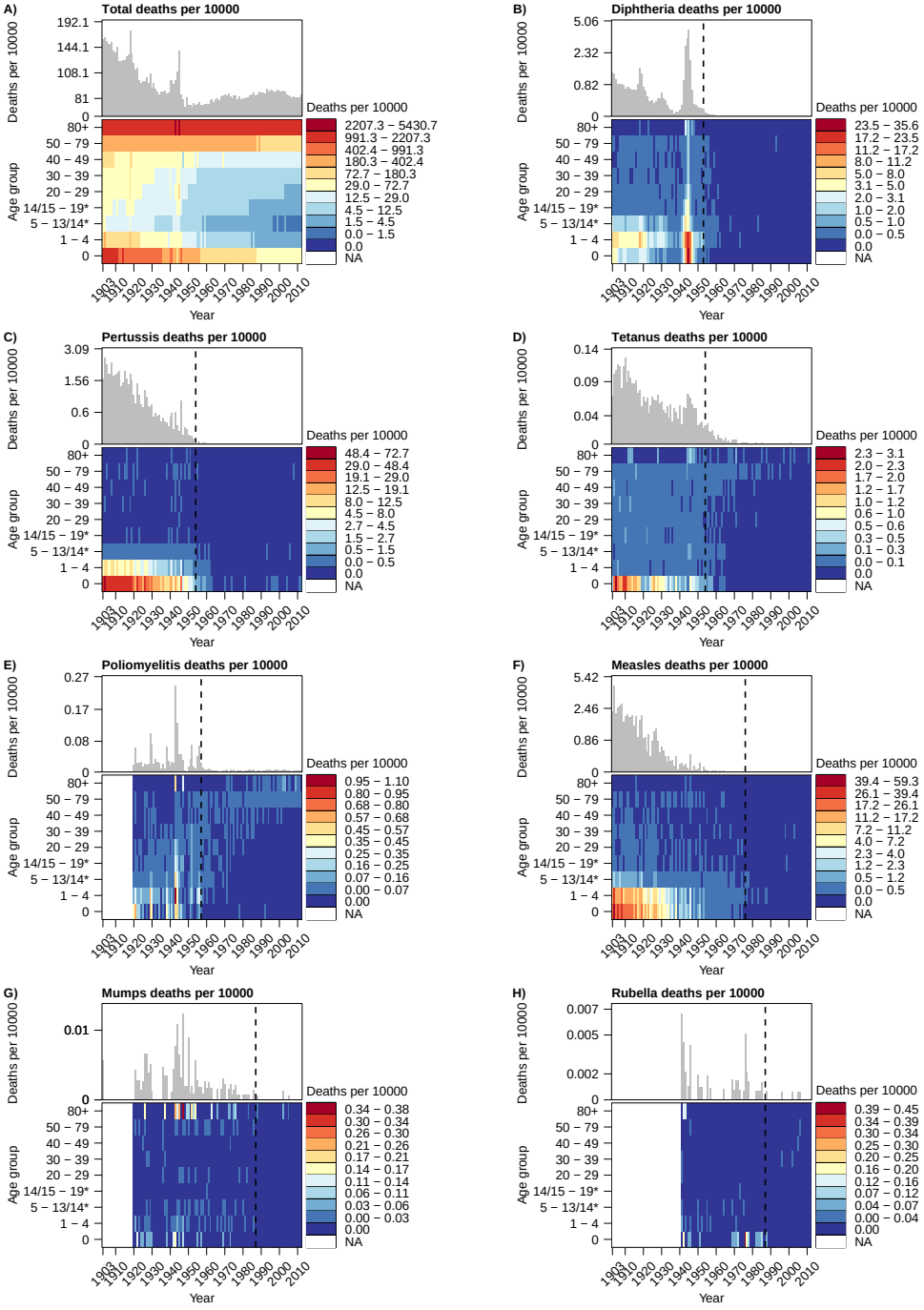

Figure 2.1: All-cause and cause-specific mortality rates, the Netherlands 1903–2012. Figure shows mortality rates for all causes, diphtheria, pertussis, tetanus, poliomyelitis, measles, mumps, and rubella. Top panels show the total number of deaths per 10 000 individuals per year, and bottom panels show age-specific mortality rates. Dashed line in B-H shows the start of mass vaccination. *In 1920 these age-groups changed from 5–13 to 5–14 and from 14–19 changed to 15–19.

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

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

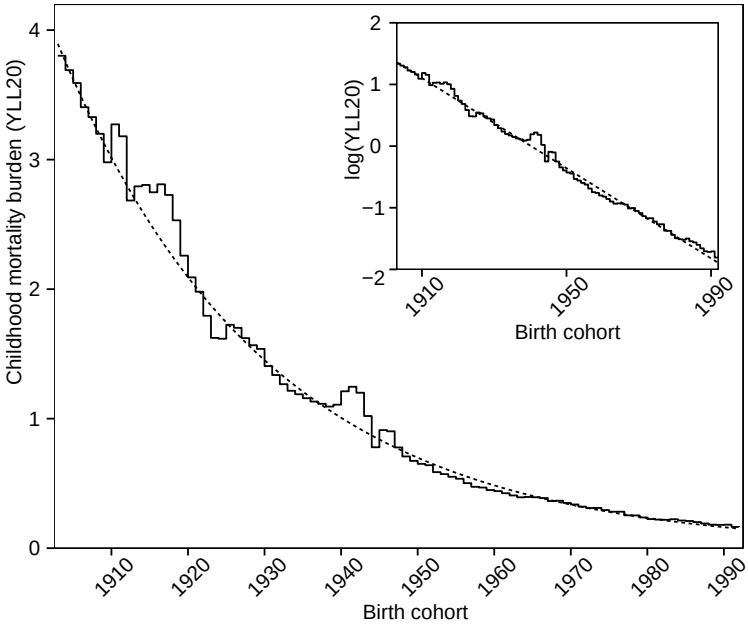

Figure 2.2: All-cause childhood mortality burden in years of life lost up to age 20 years per live birth, the Netherlands 1903–1992. Data are years of life lost up to age 20 years (YLL20) per live birth in Netherlands for birth cohorts from 1903 to 1992 (solid line) with best-fit exponential reduction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

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

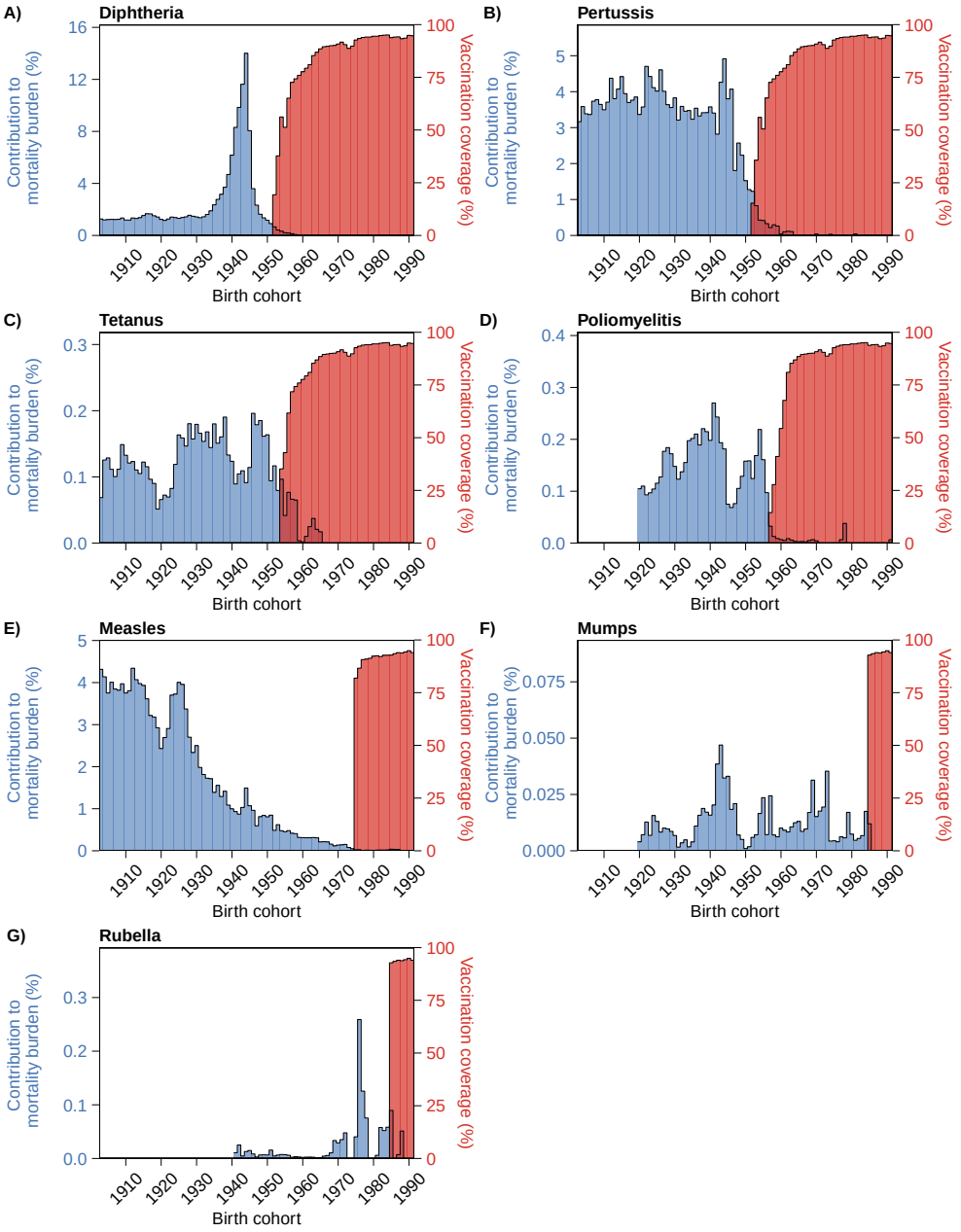

Figure 2.3: Vaccination coverage and disease-specific contribution to childhood mortality burden, the Netherlands 1903–1992. Data are for birth cohorts from 1903 to 1992 (red) and the contribution (as percentage) to childhood mortality burden before the age of 20 (blue) for diphtheria, pertussis, tetanus,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

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

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

		Average contribution to all-cause mortality burden		Reduction in mortality burden due to mass vaccinations [95% prediction interval]	
Disease	**Year mass vaccination started**	**Before vaccination**	**After vaccination**	**Yll20 in thousands**	**Deaths in thousands**
Diphtheria	1953	1.36%	0.004%	38 [28, 52]	3 [2, 4]
Pertussis	1954	3.75%	0.024%	103 [79, 134]	6 [4, 7]
Tetanus	1954	0.13%	0.003%	3[1, 6]	0.2 [0.1, 0.4]
Poliomyelitis	1957	0.15%	0.005%	3 [1, 8]	0.3 [0.1, 0.6]
Measles[1]	1976			0.3 [0.2, 0.5]	0.02 [0.01, 0.03]
Mumps[2]	1987	0.01%			
Rubella[2]	1987	0.02%			

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

[2] For mumps and rubella, too few results were available after introduction of vaccinations to calculate an average.

Discussion

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

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

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

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

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

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

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

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

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

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

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Research in context

Evidence before this study

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

Added value of this study

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

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

Implications of all the available evidence

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

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Supplementary information to Chapter 2

Mortality data

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

Population size

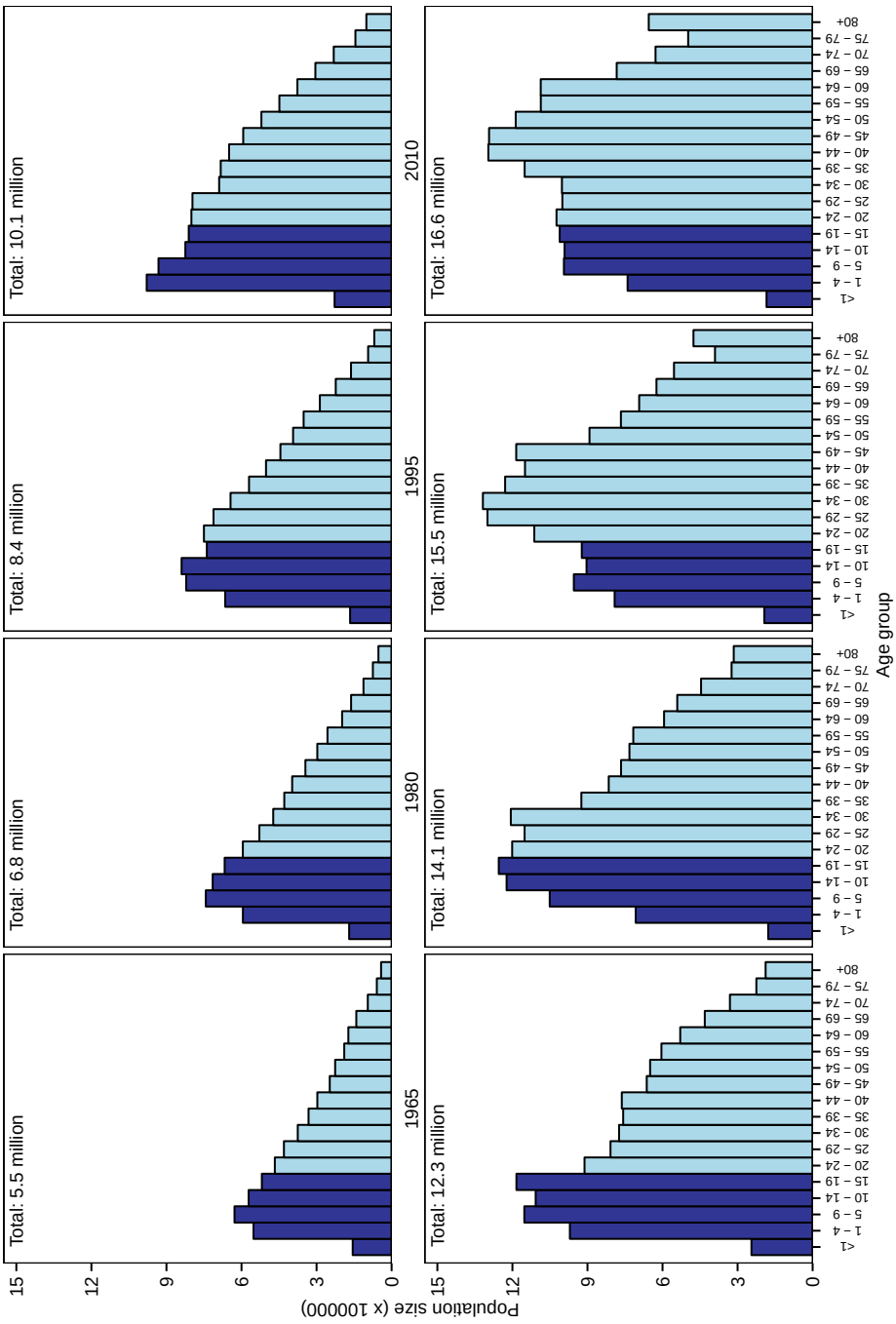
For the period 1903–1949 we transcribed and digitised the estimated population size of the Netherlands stratified by 5-year age-groups from a compilation of periodic reports by Statistics Netherlands. These population estimates were derived from periodic national census performed by Statistics Netherlands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

Vaccination coverage

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

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

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



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

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

Determining and interpreting national vaccination coverage

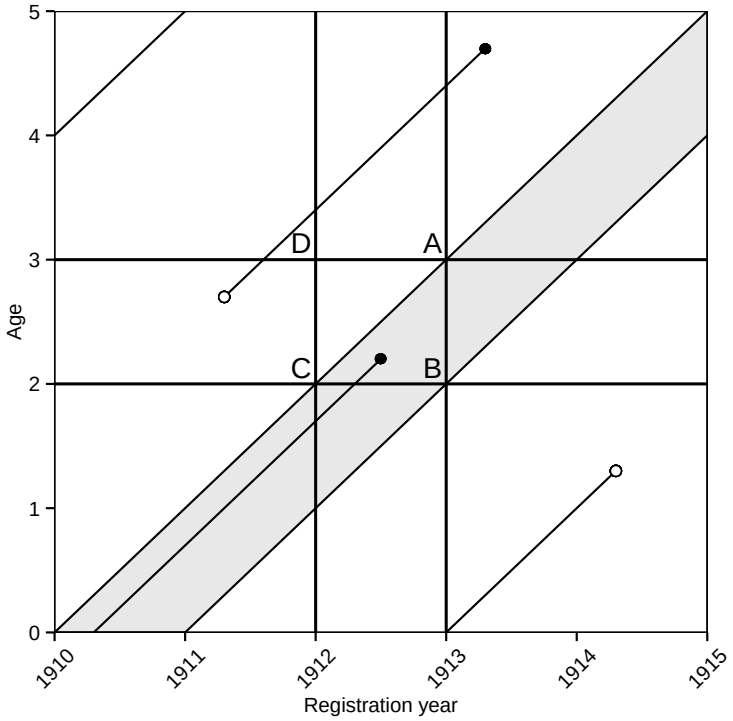
The method to calculate the national vaccination coverage changed several times over the years. These changes in the calculation have little impact on the resulting estimates. Until 1962, the number of vaccines distributed was divided by the number of registered children of a certain age. From 1962 to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

Reconstruction of cohort-specific mortality

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

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

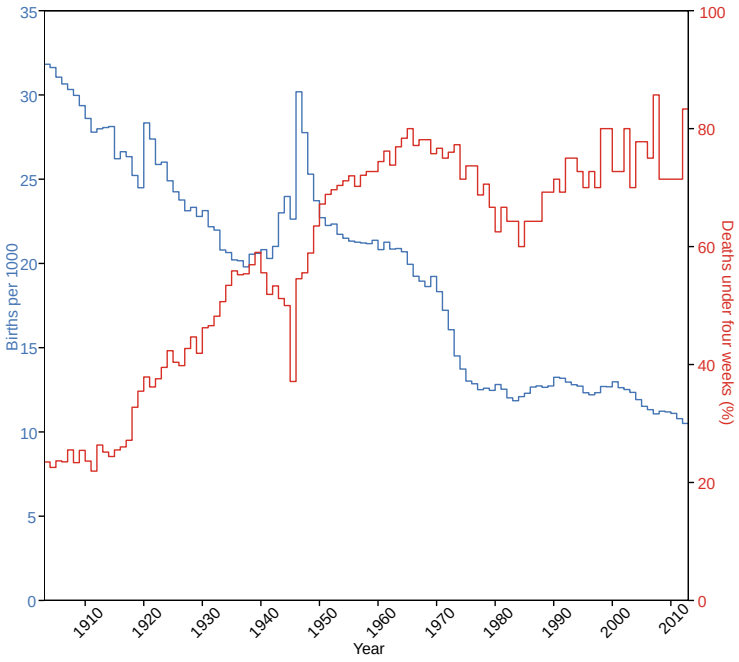
We have information on the number of deaths by registration year and by age-group (Lexis-squares), and we need to obtain the corresponding number of deaths by birth cohort (Lexis-triangles). To achieve this, we first assigned each reported death a specific age. For the age-groups 5–13, 14–19, 20–29,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



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

Birth rates and neonatal mortality

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



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

Years of Life Lost (YLL) estimation

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

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

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

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

$$E_\tau = \int_0^\tau \hat{S}(t)\mathrm{d}t \tag{2.2}$$

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

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

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

$$L_j(0,\tau) = \int_0^\tau \hat{F}_j(t)\mathrm{d}t \tag{2.4}$$

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

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

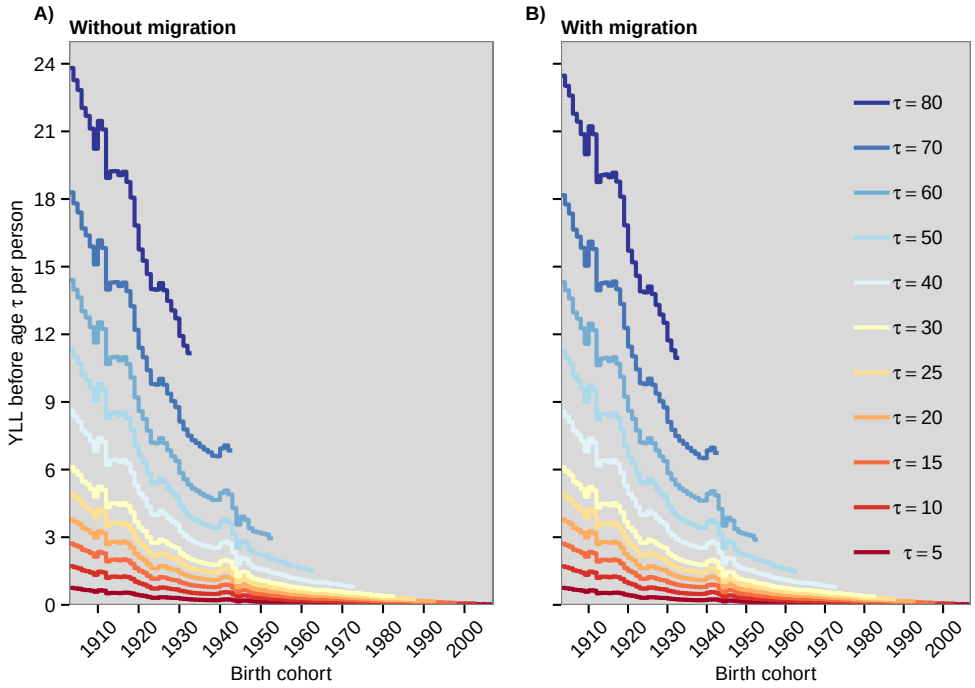
When we integrate the balance equation from age 0 to age τ we obtain:

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

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

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

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



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

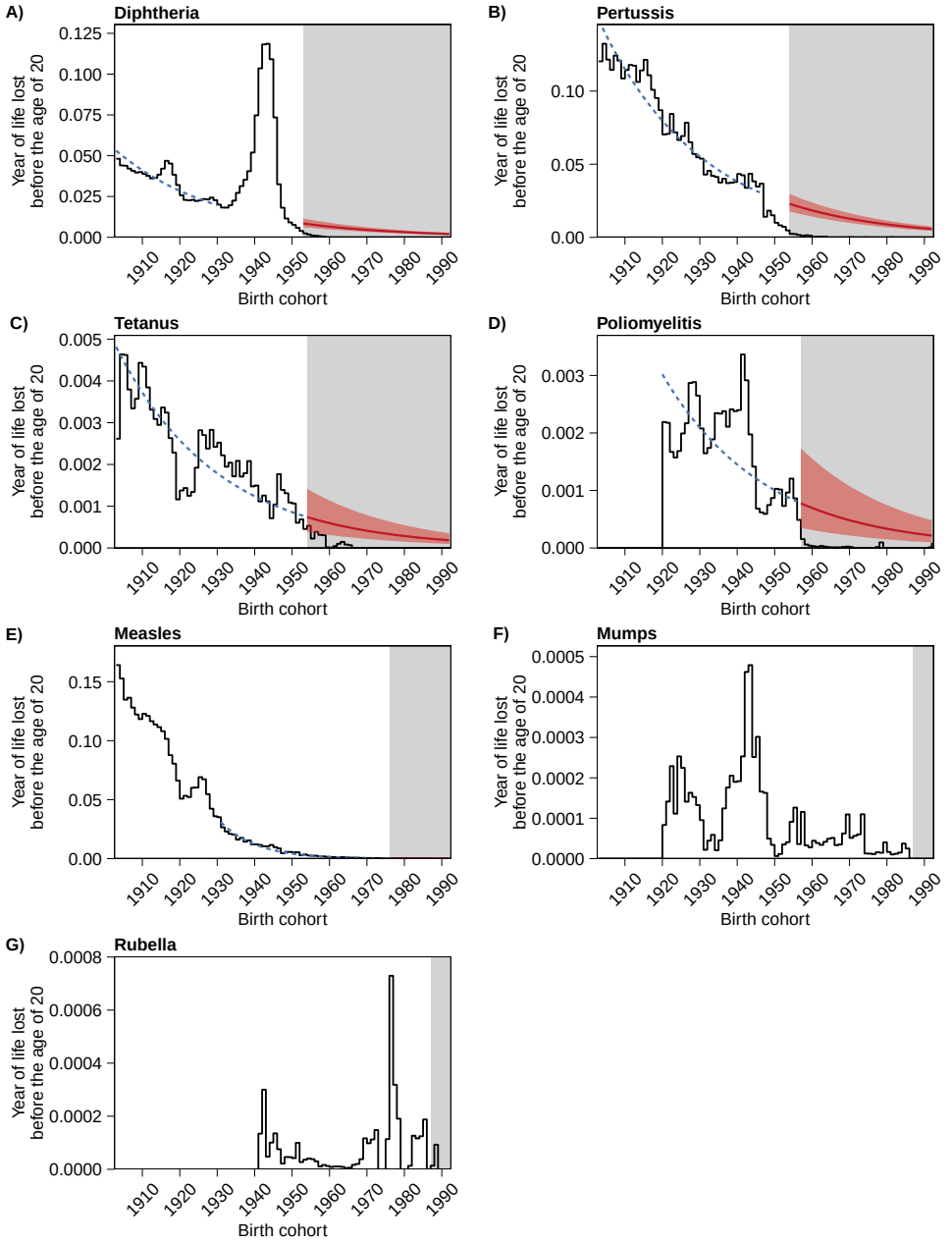
Since the cause-specific life-years lost add up to the total life-years before age τ, we can define the contribution of each cause of death to the total years of life lost before age τ:

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

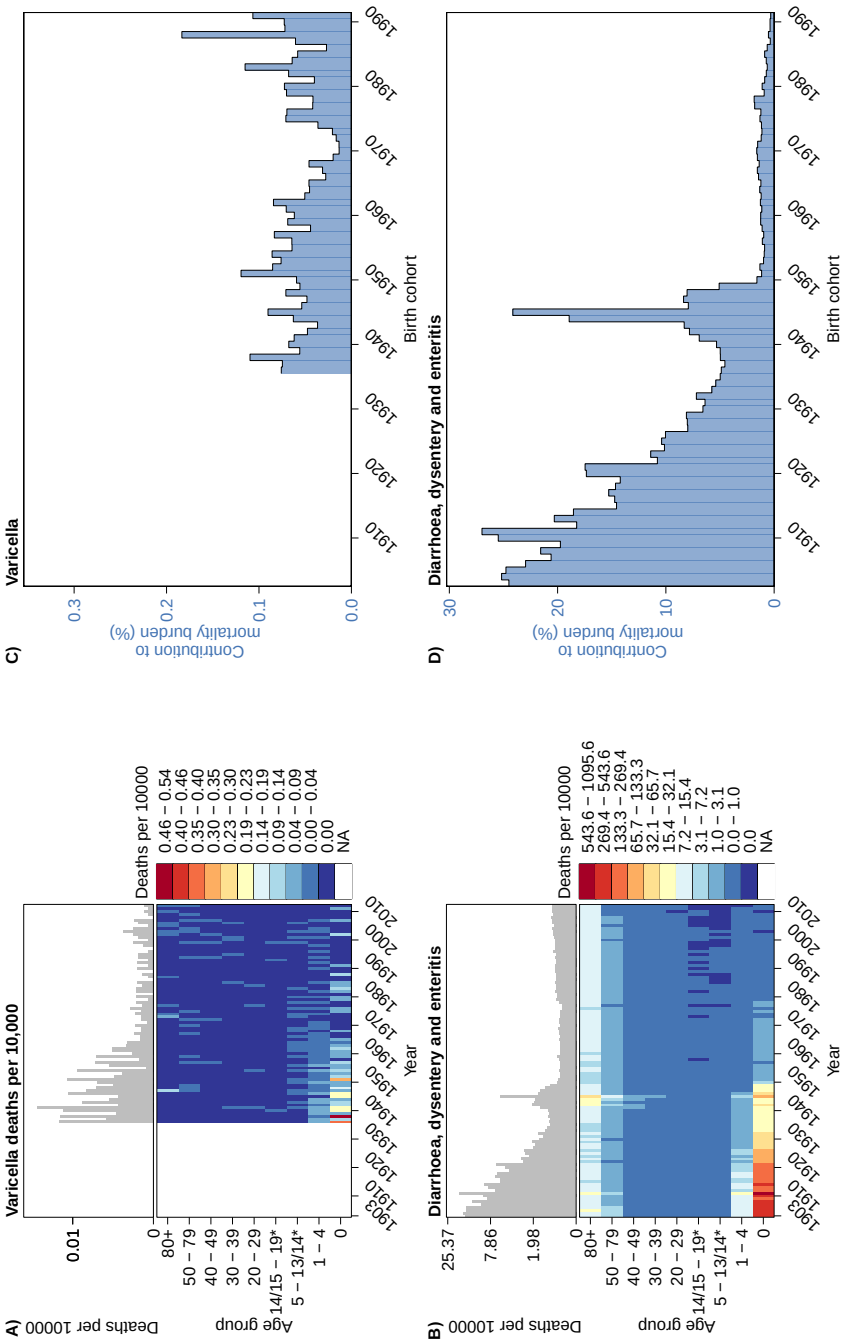
For each birth cohort we estimated the number of life-years lost before age τ due to cause j, $L_j(0,\tau)$, using a cut-off age $\tau = 20$. The results are shown in Supplementary Figure 2.5. For each birth cohort we also estimated the cause-specific contribution to this mortality burden, $C_j(0,\tau)$.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

Reduction in mortality burden due to mass vaccination programmes

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



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



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

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

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

Migration

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

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