Article

Impact of immunization programs on 11 childhood vaccine-preventable diseases in China: 1950–2018
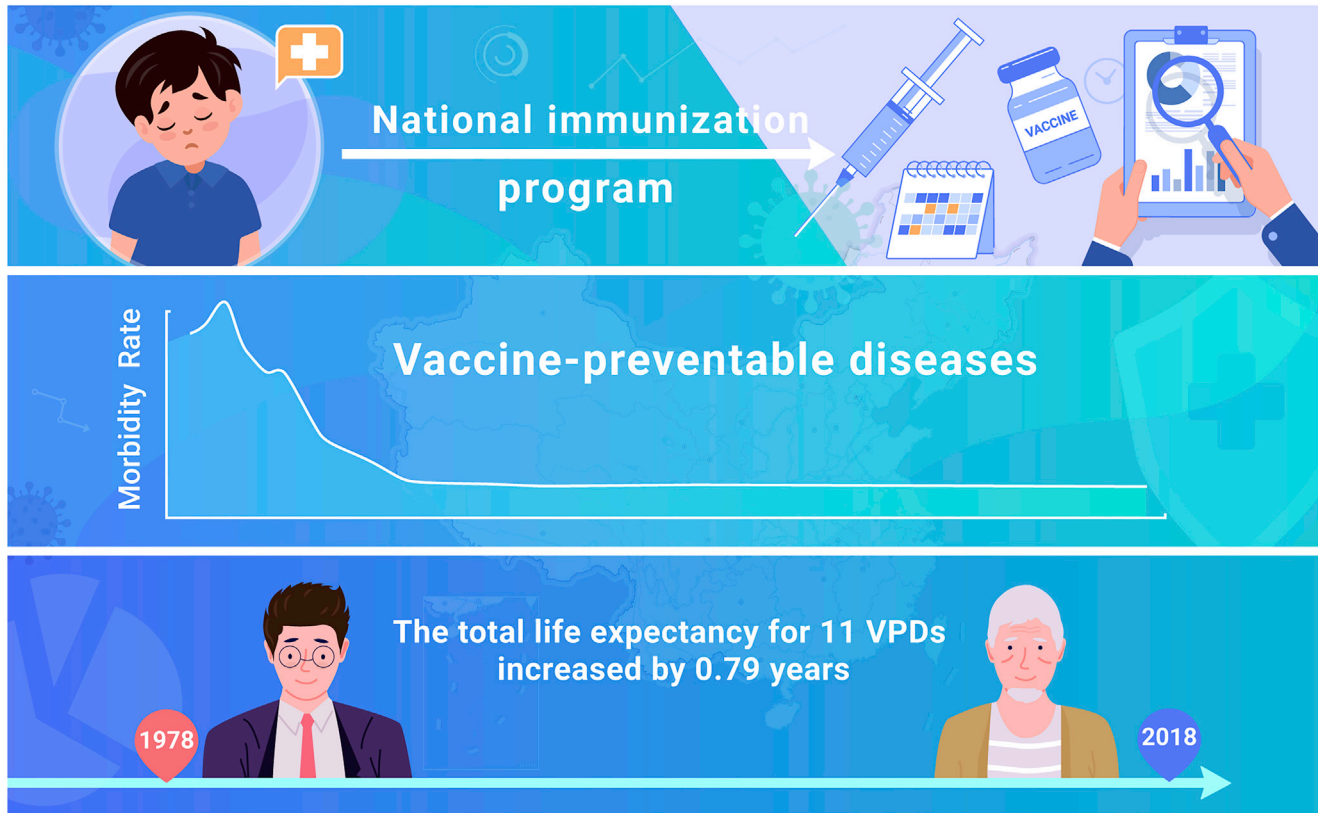
Jinhua Pan,[1,7] Yesheng Wang,[1,7] Lingsheng Cao,[3] Ying Wang,[4] Qi Zhao,[1,2] Shenglan Tang,[5] Wenfeng Gong,[6] Lei Guo,[5] Zhixi Liu,[1] Zexuan Wen,[1] Bo Zheng,[1] and Weibing Wang[1,2,*]

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Graphical abstract

Public summary

- 11 vaccine-preventable diseases (VPDs) were examined to measure the impact of the national immunization program

- Most of the 11 VPDs exhibited dramatic declines in morbidity rate after their integration into the Expanded Program on Immunization (EPI)

- From 1978 to 2018, the total life expectancy for the 11 VPDs increased by 0.79 years, and similar results were obtained for different age groups

- Improving vaccination coverage is a key aspect of controlling VPDs in China

Impact of immunization programs on 11 childhood vaccine-preventable diseases in China: 1950–2018

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To evaluate the achievements of China's immunization program between 1950 and 2018, we chose 11 vaccine-preventable diseases (VPDs) as representative notifiable diseases and used annual surveillance data obtained between 1950 and 2018 to derive disease incidence and mortality trends. Quasi-Poisson and polynomial regression models were used to estimate the impacts of specific vaccine programs, and life-table methods were used to calculate the loss of life expectancy, years of life lost, and loss of working years. The total notification number for the 11 VPDs was 211,866,000 from 1950 to 2018. The greatest number occurred in 1959, with a total incidence of 1,723 per million persons. From 1978 to 2018, a substantial decline was observed in the incidence of major infectious diseases. The incidence of pertussis fell 98% from 126.35 to 1.58 per million, and the incidences of measles, meningococcal meningitis, and Japanese encephalitis fell 99%, 99%, and 98%, respectively. The regression models showed that most of the 11 diseases exhibited dramatic declines in morbidity after their integration into the Expanded Program on Immunization (EPI), while varicella and paratyphoid fever, which were not integrated into the EPI, showed increased morbidity. From 1978 to 2018, the total life expectancy for the 11 VPDs increased by 0.79 years, and similar results were obtained for different age groups. China has had great success in controlling VPDs in recent decades, and improving vaccination coverage is a key aspect of controlling VPDs in China.

Keywords: China; vaccine-preventable diseases; morbidity; mortality; immunization

INTRODUCTION

Vaccination has been one of the most successful and cost-effective public health interventions in the last century and has saved millions of people from various diseases.[1–3] The benefits of vaccination include the eradication of one deadly disease, smallpox,[4] and the near eradication of another, poliomyelitis.[5,6] In 1974, the World Health Organization (WHO) established the Expanded Program on Immunization (EPI) with the goal of increasing immunization coverage among children throughout the world.[7,8] The EPI has contributed significantly to reducing the global burden of VPDs over the past decades.[9,10]

China has one of the largest and oldest immunization programs in the world, with over 16 million infants vaccinated each year.[11,12] Work on immunization began in earnest as soon as the People's Republic of China was founded in 1949.[13] Based on immunization strategies, policy requirements, and implementation progress, China's immunization plan can be divided into four stages from 1950 to 2018. The first stage was the pre-planned immunization program (1950–1977), during which the main strategy was to imple-

ment seasonal assault vaccinations with diphtheria vaccine,[14] pertussis vaccine,[15] Japanese encephalitis vaccine,[16] and bacillus Calmette-Guerin (BCG) vaccine for tuberculosis.[17] In 1978, in response to a call from the WHO, the Ministry of Health proposed the concept of a Planned Immunization Program suitable for China's national conditions,[18] thereby moving China's vaccination work into the planned immunization stage (1978–2000).[19]

Rapid progress was made during the immunization program stage (2001–2007). During this period, the cold chain system for immunization was established and improved, and the incidence of VPDs was controlled to a low level. In 2001, the Planned Immunization Program was reorganized and renamed the China National Immunization Program (NIP) to reflect the expansion of its remit to include a growing range of programmatic issues and the introduction of new vaccines.[20] While the Planned Immunization Program used five vaccines to prevent seven diseases, the NIP used 14 vaccines to prevent 15 diseases, including the routine vaccination of children with 11 vaccines to prevent 12 diseases.[21]

The fourth stage began early in 2008 with the introduction of the "Implementation Plan for Expanding the National Immunization Plan" (hereafter referred to as "the Plan").[22] The overall goal of the Plan was to comprehensively implement an expanded NIP, continue to maintain a polio-free state, eliminate measles, control hepatitis B, and further reduce the incidence of VPDs. According to the Plan, the vaccines against hepatitis B, tuberculosis, polio, diphtheria/pertussis/tetanus (DPT), measles/DPT, hepatitis A, meningitis, encephalitis B, and mumps are included in the NIP, and school-age children undergo regular vaccination.[23]

In the past 70 years, China's immunization program has been developed rapidly and comprehensively, making significant contributions in protecting the health of the population, reducing the morbidity and mortality of VPDs, and improving the per capita life expectancy. Recently, although some studies have reported on overall notification rates of VPDs, there has been no publication of systematic data on disease burdens associated with VPDs in China. Here, to quantify the impact of the NIP on the prevention and control of infectious diseases, we evaluated patterns in morbidity and mortality of 11 VPDs in China based on national surveillance data. We also estimated the decrease in life expectancy caused by these infectious diseases since the introduction of their vaccines.

RESULTS

Overall patterns of the 11 VPDs

The greatest number of VPDs since 1950 was reported in 1959, when there were more than 11.5 million reported cases and a total incidence rate of 1,723 per 100,000 persons (Figure 1); about 95.25% of these cases were made up of measles and pertussis, accounting for the large number
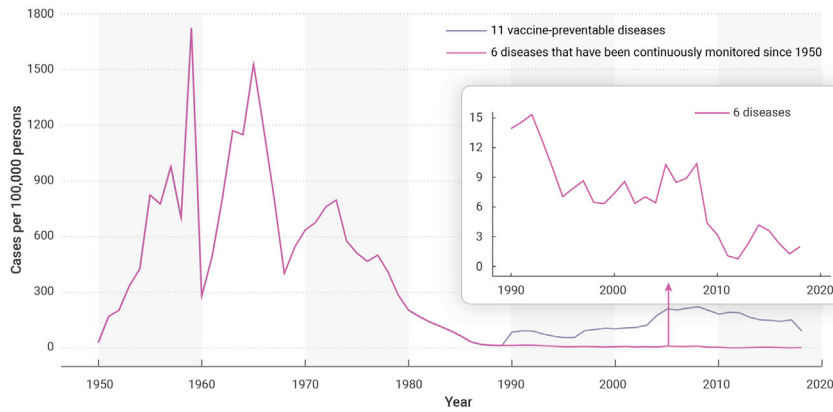
Figure 1. Annual incidence rate of the 11 selected vaccine-preventable diseases and six long-studied diseases in China from 1950 to 2018 The blue line in the large chart shows the incidence rate of the 11 vaccine-preventable diseases (VPDs), and the pink line represents the six diseases that have been continually monitored since 1950 in China (here called long-studied diseases: Japanese encephalitis, diphtheria, meningococcal meningitis, measles, poliomyelitis, pertussis). Since the incidence rates of the remaining five diseases were only available after 1990, the two lines overlap before that year. The small chart shows the incidence of the six long-studied diseases from 1990 to 2015.

of infected measles patients in China in the 1960s. As immunization gradually progressed, the incidence rate of VPDs declined throughout the 1980s until it reached a nadir of 13 per 100,000 persons in 1989. The establishment of the National Notifiable Diseases Network Direct Reporting System (NNDNDRS) in 2004 led to the discovery of more cases. In general, the annual incidence of the 11 diseases showed a significant downward trend during the first three periods, especially during the EPI and NIP periods (Figure 1). In the fourth period, the incidence of the 11 diseases was basically stable at a relatively low level. In addition to our analysis of the 11 VPDs, we separately examined the long-term trends in a subset of six VPDs that had been continuously monitored throughout the study period (Japanese encephalitis, diphtheria, meningococcal meningitis, measles, poliomyelitis, and pertussis; here called the "long-studied" diseases or VPDs). The incidence of the six long-studied diseases was the same as that of the 11 diseases before 1990, because the data for the other five diseases were collected after 1990. Unlike the incidence of the 11 diseases, that of the six long-studied diseases was low in 1990 and has remained relatively stable since then.

Similar to the incidence data, the highest annual mortality rate of the 11 diseases was observed in 1959 (during the pre-planned immunization period), when the number of total deaths exceeded 335,700 cases. The highest annual mortality rate was 49.96/100,000 in 1959; the lowest annual mortality rate was 0.038/100,000 in 2017, which represented a decline of 99.92% compared with 1959. The annual mortality rate of the 11 diseases showed significant declines in different periods, with the most significant declines (nearly 100%) seen during the periods associated with the relevant immunization programs (Figure 2). Similarly, our separate analysis of the mortality trends for the six long-studied diseases revealed that prior to 1990 the mortality rates for these six diseases were the same as those for the 11 VPDs. After 1990, the mortality rates for the six diseases declined slowly and eventually approached zero.

The results (Figure 3) showed that the incidences of most of the VPDs (9 of 11) peaked before 2000, the exceptions being hepatitis B and tuberculosis, for which the highest notification rates were observed in the most recent year. Moreover, the incidence of hepatitis B and tuberculosis has remained consistently high in many areas.

Top diseases causing major health consequences

In 1977, of the 11 studied diseases, the three highest numbers of cases were seen for measles, pertussis, and meningococcal meningitis (Figure 4), which was consistent with the highest incidence of measles and pertussis (95.25%). During this period, the top three diseases that caused the most deaths were meningococcal meningitis, measles, and Japanese encephalitis.

In 2001, of the 11 studied diseases the three highest numbers of cases came from hepatitis B, tuberculosis, and hepatitis A, while the three highest numbers of deaths came from tuberculosis, hepatitis B, and Japanese encephalitis. During the relevant period, China included the group A meningitis vaccine and the Japanese encephalitis vaccine into the planned immunization vaccination program. With the realization of the targeted 85% vaccine

coverage for children in provinces, counties, and townships in 1990, the types of diseases causing major health hazards have also changed.

During the immunization program period, the hepatitis B (in 2002) and hepatitis A (in 2008) vaccines were included in the NIP. Thus, it is unsurprising that hepatitis A had fallen out of the top three in 2018. During the EPI period, the Chinese government carried out a series of immunization-strengthening activities; these included nationwide measles immunization-strengthening activities, which were put into place in 2010 and made significant progress toward eliminating measles. As a result, the incidence of measles ranked fourth among 11 VPDs in 2008 and sixth in 2018. Figure·S1 shows the vaccine coverage rates and incidence rates of the 11 VPDs whereby overall, the incidence rates of the VPDs decrease as the coverage of the respective vaccinations increases.

Total incidence of the six long-studied diseases by province

We collected data on the incidence of the six long-studied diseases in various provincial administrative districts from 1950 to 2016 and calculated the total incidence for each disease in each province for each of the four stages. As shown in Figure 5, the incidence of all six diseases was highest during the first stage, when China's newly initiated immunization planning was mainly based on the implementation of assault vaccinations. Thereafter, the immunization program gradually took shape, as did the child immunization planning framework. Since 1978, children's program immunization work has been implemented nationwide, with timely and effective vaccinations administered to school-age children in accordance with the prescribed immunization procedures. The vaccines against tuberculosis, polio, DTP, and measles were included in the early immunization program for children in China. It is therefore unsurprising that the incidence of all six diseases was much lower during the second stage. Interestingly, the incidence of these six diseases remained relatively high in many midwestern provinces compared with the eastern provinces. In the third and fourth stages, the morbidity by province of the six long-studied diseases continued to decline; this was particularly notable in some provinces in the eastern and central regions, where the overall incidence of these diseases had dropped to less than 5/100,000 by 2016.

Impact of EPI evaluated by the quasi-Poisson regression model

As shown in Table 1, with the exceptions of tuberculosis (for which we lacked epidemic data before 1997), hepatitis B (the incidence increased), mumps, and rubella (the confidence interval included zero), there have been considerable reductions in the incidence rates of many VPDs since the EPI was first introduced into the NIP. Notably, varicella and paratyphoid fever, which are category-2 vaccines, showed increased incidence rates after their cutoff years. The number of rubella cases was relatively small, such that the confidence interval of the regression model was large; therefore, we did not compare other diseases with rubella. On the other hand, despite the subsequent introduction of effective vaccines through the EPI in the 2000s, the incidence of mumps and hepatitis B were still on the rise; we speculated
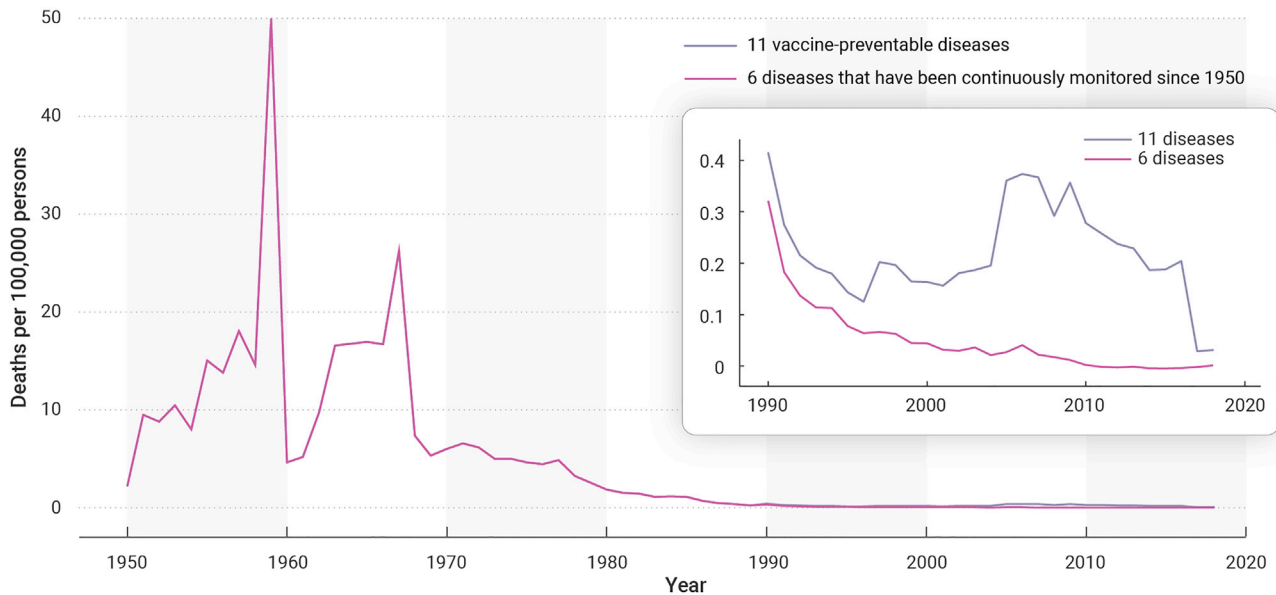
Figure 2. Annual mortality rate of 11 selected VPDs and six long-studied diseases in China from 1950 to 2018 The blue line represents the mortality rate of the 11 VPDs, and the pink line represents the six long-studied diseases. Since the mortality rates of the remaining five diseases were only available after 1990, the two lines overlap before that year.

that this may be due to under-reporting during the early stages. To verify this, we used polynomial regression model combined with Global Burden of Diseases (GBD) data to adjust the seven possibly under-reported and under-ascertained diseases included in GBD data (Figure S2), and used the adjusted data to re-establish the quasi-Poisson regression model. This model generated the same conclusions, which support our conjecture. Given that hepatitis B vaccination in China has made great strides in preventing infections among newborns, changes in the incidence of neonatal hepatitis B were calculated separately. Although the analysis performed using national surveillance data yielded the same result as hepatitis B of all ages, the GBD data showed that the incidence of neonatal hepatitis B has dropped significantly (−90.11; 95% confidence interval −94.79 to −82.95).

Loss of life expectancy because of the 11 VPDs

From 1978 to 2018, the total increase in life expectancy at death due to the 11 VPDs was 0.79 years (about 9.25 months) (Figure 6). The increases by disease included the following: meningococcal meningitis, 2.86 months; Japanese encephalitis, 1.95 months; measles, 1.83 months; hepatitis A, 0.09 months; and hepatitis B, 0.50 months. The effects of different diseases on life expectancy from 1978 to 2018 can be seen in Table S1. For all 11 VPDs, the value of this indicator was 0.01 months in 2018 and 1.30 months in 1978. By 2018, the vaccines had increased the life expectancy for these 11 diseases by 1.29 months compared with the data from 1978. As shown in Figure 6, since the implementation of the Planned Immunization Program the increase in life expectancy after excluding death due to any of the 11 VPDs has decreased rapidly over the years. Compared with the 1978 value of 0.11, the increased life expectancy without the cause of death for the 11 VPDs had decreased by 99.1% in 2018.

The impacts of these infectious diseases on life expectancy were also examined for different age groups. Our results revealed that the impacts of the 11 VPDs gradually decreased over time in people older than 15 years of age (Figure S3) as well as in younger age groups. Similar results were obtained for the loss of healthy life years and loss of work years due to early deaths from these infectious diseases (Table S2). From 2004 to 2016, the total loss of healthy life years due to early death caused by the 11 VPDs was 1,182,322 person-years; with the exception of 2012, the loss of healthy life years showed a downward trend over time. In 2016, the loss of healthy life years due to early death from the infectious diseases was 53,137 person-

years, significantly lower than the 81,593 person-years in 2004 (a decrease of 37.5%).

DISCUSSION

Disease control has always been the main goal of China's immunization efforts, and disease incidence has always been the main metric used to guide the development of immunization strategies and assess immunization program performance.[13] Here, we explored patterns in the morbidity and mortality of 11 VPDs in China to evaluate the effect of China's immunization programs on the prevention and control of infectious diseases. The total incidence rate of the 11 VPDs dropped significantly from 1950 to 2018, with a particularly notable decrease seen after the 1970s. However, the changes in the total incidence of the 11 VPDs differed among the four stages of China's immunization program. The total incidence increased between 1950 and 1965 but has largely declined since 1966. After 1990, the total incidence increased slightly, perhaps in response to the establishment and improvement of the NNDNDRS. The top five VPDs in terms of annual morbidity and mortality were identified, and this analysis showed that the proportions of deaths caused by meningococcal meningitis, Japanese encephalitis, and pertussis had substantially declined by 2018.

Successful implementation of routine immunization programs against VPDs has contributed to a steep decrease in the incidence of these diseases in China. The national smallpox vaccination campaign in 1949–1952 using more than 500 million doses of vaccine led to a vaccination coverage of >90% in the country and finally to elimination of the disease in the 1960s. Routine vaccination for prevention of polio, diphtheria, pertussis, tetanus, measles, and tuberculosis was initiated in the 1960s in the larger cities and later expanded to rural areas in the country, leading to substantial declines in the incidence and mortality of these diseases. The largest drops in the absolute VPD burden occurred since the 1970s, with the establishment of the EPI. From 1978 to 2018, the incidence of diseases that caused major health hazards have declined substantially: the incidence of pertussis fell 98% from 126.35 to 1.58 per million; that of measles fell 99% from 249.76 to 0.28; that of meningococcal meningitis fell 99% from 32.23 to 0.01; and that of Japanese encephalitis fell 98% from 5.39 to 0.13. A study conducted by Yu et al. reviewed national and provincial health department archives and performed a combined analysis of disease surveillance and serosurvey data from 1950 through 2016 in China.[13] They found that after the introduction
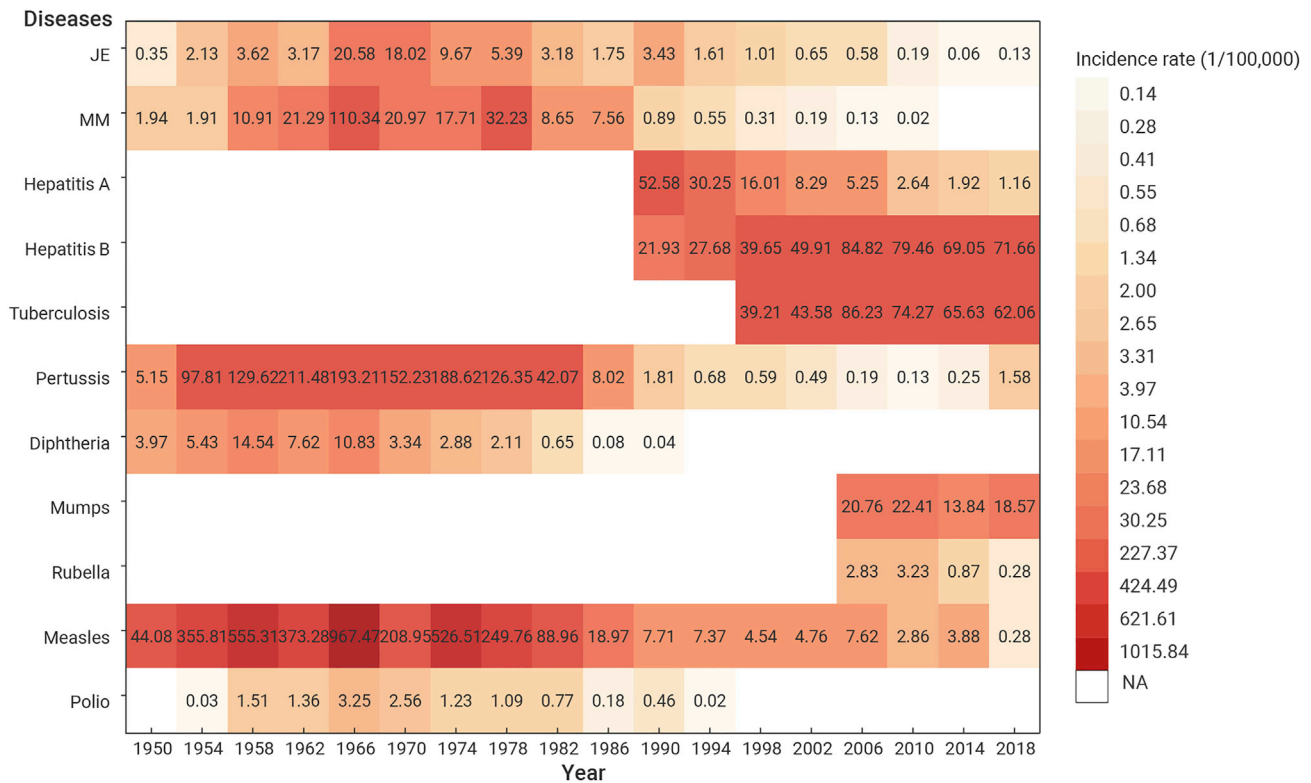
Figure 3. Detailed annual incidence rates of the 11 VPDs in China, 1950−2018

of a vaccine, and particularly after its recommendation for universal use among children, the incidence rates were much lower than those for diseases without vaccination. This is completely in line with our present findings. In other countries, various studies have highlighted the benefits of vaccination policies. Analysis of the incidence and mortality of five VPDs captured by Vietnam's national surveillance suggested that between 1980 and 2010, up to 5.7 million disease cases and 26,000 deaths may have been prevented by the extended program of immunization.[24] In addition, a study conducted in Iran demonstrated that vaccination has had a positive impact on the control of four communicable diseases.[25]

Our quasi-Poisson regression model showed that there have been considerable declines in the morbidities of many VPDs since the EPI was first introduced into the NIP. In contrast, varicella and paratyphoid fever, which are targeted by category-2 vaccines, showed increased incidence rates after their cutoff years. Also, despite the introduction of effective vaccines through the EPI in the 2000s, the incidence of mumps and hepatitis B has remained on the rise. We speculated that these increases may have reflected under-reporting during the earlier stages.[26] To verify this, we used a polynomial regression model to adjust for under-reporting and under-ascertainment of the surveillance and GBD data, and re-established the quasi-Poisson regression model. This analysis supported the same conclusions as the original model for all of the VPDs except hepatitis B. The change in the incidence of hepatitis B between the pre- and post-vaccination period was lower for the adjusted data than for the original data, which supports the idea that the under-reporting and under-ascertainment of hepatitis B were more serious in the early stage and have been alleviated in recent years in China.

A study on neonatal hepatitis B vaccination found that such vaccination contributed only 0.28 months to life expectancy, and that even the better effects of vaccines against measles, rubella, mumps, and whooping cough did not improve life expectancy by more than 0.11 months.[27] Here we report that, compared with the 1990 data, the contribution of hepatitis B vaccine to the life expectancy of newborns in 2018 was 0.16 months. Compared with the 1978 data, the contribution of the measles vaccine to the life

span of newborns in 2018 was nearly 0.40 months. Similarly, compared with the period before the introduction of hepatitis A vaccine in 1990, the life expectancy of newborns increased by 0.02 months in 2018, while for those who joined EPI in 2007, compared with 1978 the life expectancy of newborns increased by 0.53 months and 0.23 months in 2018 (Table S2). Thus, vaccination against the 11 VPDs studied herein had significant positive effects on life expectancy in China.

A few limitations of our study should be noted. First, the increasing incidence of notifiable diseases during the first few years following the implementation of national surveillance, particularly before 1960, may not necessarily represent a rise in the occurrence of infections but rather a gradual improvement in the notification system (e.g., with more provinces reporting cases in the later years).[28] Second, the passive nature of the surveillance system could have resulted in under-reporting and/or under-ascertainment of the true disease burden.[29,30] This is particularly true during periods when there was massive political, social, and/or economic chaos nationwide, such as during the Cultural Revolution (1966−1976). Indeed, this could explain the sudden drop in incidence rates seen in the late 1960s. Aside from such societal changes, individual behavioral factors also need to be taken into consideration when we examine the under-reporting of diseases.

In conclusion, the burden of VPDs has been declining in China in the past decades. Fluctuations in disease notifications reflect not only changes in disease transmission but also improvement in disease surveillance, prevention, and treatment. China continues to report a relatively large number of infectious diseases each year, but the current disease spectrum differs from that seen in earlier years. Strengthening of the NIP, together with enhancement of informatization and improvement of vaccine coverage, will facilitate better control of VPDs in China in the future.

MATERIALS AND METHODS
Data sources
We constructed a standardized vaccine-preventable infectious disease dataset by extracting information from the National Disease Reporting System and the GBD.[31] Data on the total population and natural deaths of the population were obtained
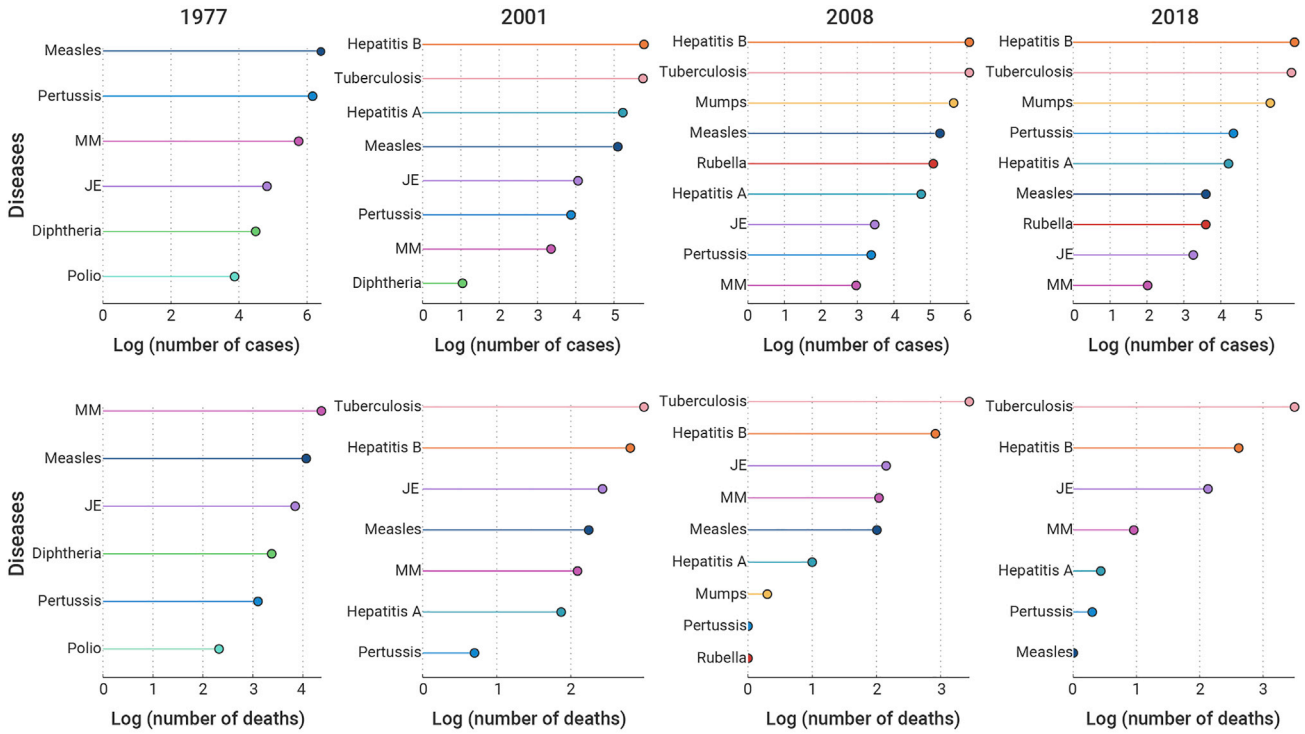
Figure 4. Annual number of cases (top) and deaths (bottom) for the 11 selected VPDs in 1977, 2001, 2008, and 2018

from the China Statistical Yearbook.[32] The compiled dataset included the number of reported cases and deaths and the computed incidence and mortality rates associated with the 11 VPDs for the period spanning 1950 to 2018.

Data on vaccination coverage of Japanese encephalitis, meningococcal meningitis, and hepatitis A were collected from national vaccination coverage surveys

that were conducted in selected provinces during 1998–2018 in China. All surveys utilized multi-stage probability of selection proportional to population size sampling based on WHO guidelines.[33] Data on vaccination rates for other diseases were obtained from the WHO website (http://apps.who.int/gho/data/node.main.A824?lang=en).
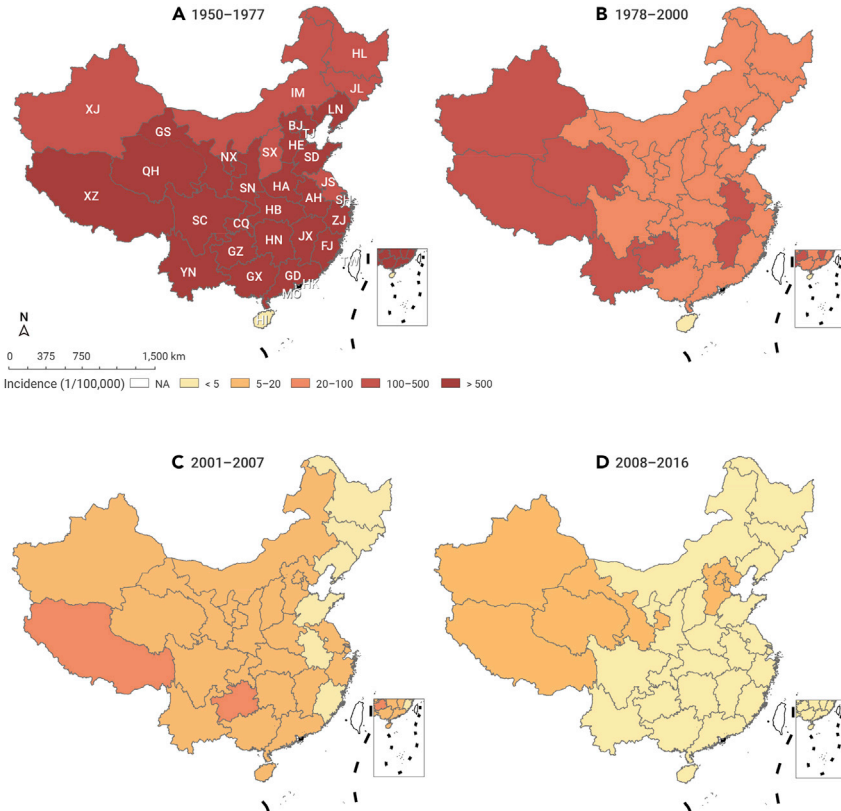

Figure 5. Total incidence of the six long-studied diseases in different provinces in China since 1950 The national distribution of the incidence rates of the six long-studied diseases: the darker the color, the higher the incidence rate. Chongqing became a municipality directly under the central government in 1997; prior to 1997 it belonged to Sichuan Province, so disease epidemic data were not listed separately until 1997. When calculating the incidence before 1997, we used the incidence rate of Sichuan Province. In addition, subregional information for the 11 diseases was only collected in 2016.

Table 1. Impact of routine vaccination on the incidence rates of the selected vaccine-preventable diseases

Disease	Year of integration into EPI	Time period[a] (years)	Change in incidence (%) (95% confidence interval)[d]	Change in incidence (%) (95% confidence interval)[e]
Measles	1978	20 (1969−1988)	−79.66 (−87.97, −67.43)	−80.74 (−88.43, −69.60)
Pertussis	1978	20 (1969−1988)	−82.6 (−89.26, −73.15)	−80.80 (−87.61, −71.41)
Diphtheria	1978	20 (1969−1988)	−81.39 (−89.42, −69.3)	−81.29 (−89.39, −69.09)
Polio	1978	20 (1969−1988)	−74.50 (−87.10, −53.53)	NA
Tuberculosis[b]	1978	NA	NA	NA
Hepatitis B	2002	20 (1993−2012)	109.30 (78.33, 146.39)	1.72 (−73.75, 296.22)
Hepatitis B in newborns	2002	20 (1993−2012)	108.59 (55.75, 182.26)	−90.11 (−94.79, −82.95)
Mumps[c]	2007	8 (2004−2011)	28.21 (0.19, 64.48)	NA
Rubella[c]	2007	8 (2004−2011)	82.49 (−9.50, 287.29)	NA
Hepatitis A	2007	10 (2003−2012)	−54.21 (−66.18, −38.68)	−66.47 (−96.16, 68.24)
Meningococcal meningitis	2007	10 (2003−2012)	−78.21 (−89.11, −60.13)	−76.25 (−98.12, 29.49)
Japanese encephalitis	2007	10 (2003−2012)	−58.27 (−72.30, −38.50)	−65.26 (−95.86, 72.19)
Varicella	2002	20 (1993−2012)	NA	0.27 (−0.24, 0.79)
Varicella	2004	20 (1995−2014)	NA	0.74 (0.24, 1.25)
Varicella	2007	20 (1998−2017)	NA	1.4 (1.16, 1.64)
Paratyphoid fever	2002	20 (1993−2012)	NA	1.17 (0.53, 1.83)
Paratyphoid fever	2004	20 (1995−2014)	NA	2.14 (1.17, 3.12)
Paratyphoid fever	2007	20 (1998−2017)	NA	4.36 (2.29, 6.47)

NA, no data available.
[a]The number of years included in the regression is different for each disease and is based on the data availability and the year of integration into the EPI.
[b]Tuberculosis: data available from 1997 onward.
[c]Mumps and rubella: data available from 2004 onward.
[d]Data from our reported system.
[e]Data from GBD and estimate.

Descriptive and statistical analyses

Eleven VPDs targeted by category-1 vaccines were selected: meningococcal meningitis, measles, polio, diphtheria, pertussis, tuberculosis, hepatitis B, hepatitis A, Japanese encephalitis, mumps, and rubella. Two diseases targeted by category-2 vaccines were selected as a control (varicella and paratyphoid fever). To assess the historical incidence pattern of the 11 VPDs we calculated the annual total incidence and mortality rates for each disease, with the total population of the country in that year taken as the denominator.

Information related to China's NIP was obtained from various sources, including reports from the WHO Western Pacific Region Office and other published papers.[34−37]

We used the year of the introduction of each vaccine into the EPI as a cutoff year to define the pre-vaccination period (i.e., the 10 years prior to and including the cutoff year) and post-vaccination period (i.e., the 10 years after the cutoff year). Therefore, the total number of years included in the analysis for each disease ranged from 8 to 20 years, depending on the data availability and the cutoff year. Under an assumption that any changes to incidence rates of the analyzed VPDs were entirely attributable to immunization, the effectiveness of the EPI was estimated by using quasi-Poisson regression models to estimate the change in incidence rates for each disease from the pre- to post-vaccination period, following previous published studies.[38−40] In addition, we selected varicella and paratyphoid as controls, which were not integrated into
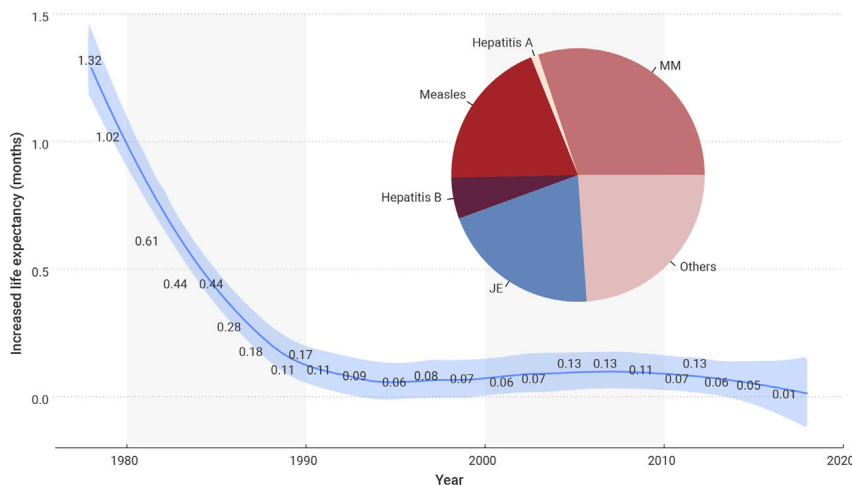

Figure 6. Decrease in life expectancy caused by infectious diseases from 1978 to 2018 Impact of the 11 studied VPDs on life expectancy from 1978 to 2018 (the lines were smoothed by using locally estimated scatterplot smoothing regression). The life expectancy from 2004 to 2018 was calculated from the census data of China in 2010. Since we did not have data for the third and fourth censuses, which were conducted in 1982 and 1990, the life expectancy from 1978 to 2003 was calculated according to the census data of China in 2000. We were unable to obtain the incidence data of each age group for measles, meningococcal meningitis, and Japanese encephalitis from 1978 to 2003 and for hepatitis A and hepatitis B from 1990 to 2003. We used the incidence ratios of each age group in 2004 for our calculation. The incidence ratio of each age group in 2017−2018 was calculated according to the incidence ratio in 2016. For better comparison, the age-specific proportion of each disease was calculated as the proportion of the 11 studied diseases.

the EPI (2002, 2004, and 2007 were chosen as a cutoff year). GBD data were corrected for disease under-reporting and under-ascertainment by using Dismod.MR.[41] To further verify the efficacy of vaccines pre- and post-vaccination, we implemented quasi-Poisson regression using adjusted GBD data. Since the data of GBD only covered the period from 1990 to 2017, we built a polynomial regression model based on the incidence data of GBD, the data reported in China, and the year to predict the possible data were adjusted for under-reporting and under-ascertainment of these infectious diseases from 1950 to 1989 and 2018.

The abbreviated life-table method was used to calculate the decrease in life expectancy caused by infectious diseases from 1978 to 2018 and the distribution of these reductions in different age groups in 2010 and 2016. Details on the life-table method and the calculation of the potential years of life lost and potential working years lost caused by premature death from infectious diseases from 2004 to 2016 are presented in supplemental information.

Statistical software

We used R 3.5.1 (https://cran.r-project.org/bin/windows/base/old/3.5.1/) to construct quasi-Poisson regression models and polynomial regression models, and we used ArcGIS version 10.2 (ESRI, Redlands, CA, USA) to draw the thematic map of the disease incidence in different provinces.

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AUTHOR CONTRIBUTIONS

J.P., Y.W., and W.W. designed and implemented the study. J.P., Y.W., Z.L., Z.W., B.Z., and L.C. collected the relevant data. J.P. and Y.W. analyzed and processed the results and drafted the manuscript. Y.W., Q.Z., S.T., W.G., L.G., and W.W. revised the structure of the paper and polished the language. All authors critically reviewed and approved the final version of the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

LEAD CONTACT WEBSITE

http://sph.fudan.edu.cn/t/14.

SUPPLEMENTAL INFORMATION

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Supplemental Information

Impact of immunization programs on 11 childhood

vaccine-preventable diseases in China: 1950–2018

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Impact of immunization programs on 11 childhood vaccine-preventable diseases in China:

1950-2018

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Supplemental Materials and Methods

Quasi-Poisson

We used the year during which each vaccine was introduced into the EPI as a cutoff year to define the pre-vaccination period (ten years prior to and including the cutoff year) and post-vaccination period (ten years after the cutoff year). The total number of years included in the analysis for each disease ranged from eight to twenty years, depending on the data availability and cutoff year. By assuming that any changes to the incidence rates of the examined VPDs were entirely attributable to immunization, we estimated the effectiveness of the EPI by using quasi-Poisson regression models to estimate the change in the incidence rate for each disease from the pre- to post-vaccination period. Diseases without available data prior to integration of the vaccine in the EPI (i.e., the pre-vaccination period) could not be included in these analyses.

Life table

The abbreviated life table method was used to calculate the decrease of life expectancy caused by infectious diseases from 1978 to 2018, and the distribution of these reductions in different age groups in 2010 and 2016. We were unable to obtain the incidence data for each age group from 1978 to 2003, and thus used the incidence ratio of each age group in 2004 for our calculation. The incidence ratio of each age group in 2017-2018 was calculated according to the incidence ratio in 2016. The potential years of life lost (PYLL) and potential working years lost caused by premature death from infectious diseases from 2004 to 2016 were estimated. Premature death was defined as death caused by not living to the expected lifespan, and was calculated based on the natural mortality rate of the Chinese census.

Supplemental Results

Impact of vaccination coverage on morbidity rates of VPDs

Figure S1. shows the relationship between the vaccination coverages and incidence rates of the VPDs. Focusing on diphtheria and pertussis, we see that after the combined DTP vaccine became available free for all children across the country in 1978, the transmission of the two diseases declined significantly. Similarly, the incidence of measles rapidly declined shortly after the measles-rubella vaccine and the measles-mumps-rubella vaccine were integrated into the EPI program in 1978 and 2007, respectively, and also following the initiation of supplementary immunization activity in 2008. Conversely, even though effective vaccines against tuberculosis and hepatitis B were integrated into the EPI in the 2000s, the incidences of these diseases have continued to rise. The incidence trends of the other nine diseases were basically consistent with those of the corresponding vaccination coverages. In 1982, the Ministry of Health set EPI targets (to be reached by 1990) of 80%-90% coverage for DPT and 90%-95% coverage for OPV and measles by the time a child reached school age. Therefore, the coverage of these vaccines increased during the 1980s. By 2003, however, central government funds accounted for only 1% of total immunization expenditures and more than 50% of expenditures were being made at the village and township levels, with the result that the coverage of vaccines was on the decline. In 2004, the central government for the first time allocated funds for vaccine delivery and administration at the village and township levels. In 2004–2005, the State Council passed the Law on the Prevention and Treatment of Infectious Diseases, reaffirming the requirements for all children to be fully vaccinated. Together, these measures strengthened the financing for vaccines and vaccination services, resulting in increased and more equitable coverage and a historically low VPD burden. From 1978 to 2018, the incidence of pertussis fell 98% from 126·35 to 1·58 per million; measles fell 99% from 249·76 to 0·28 per 100,000; meningococcal meningitis fell 99% from 32·23 to 0·01 per million; and JE fell 98% from

5·39 to 0·13 per million. The last case of diphtheria was reported in 2006.
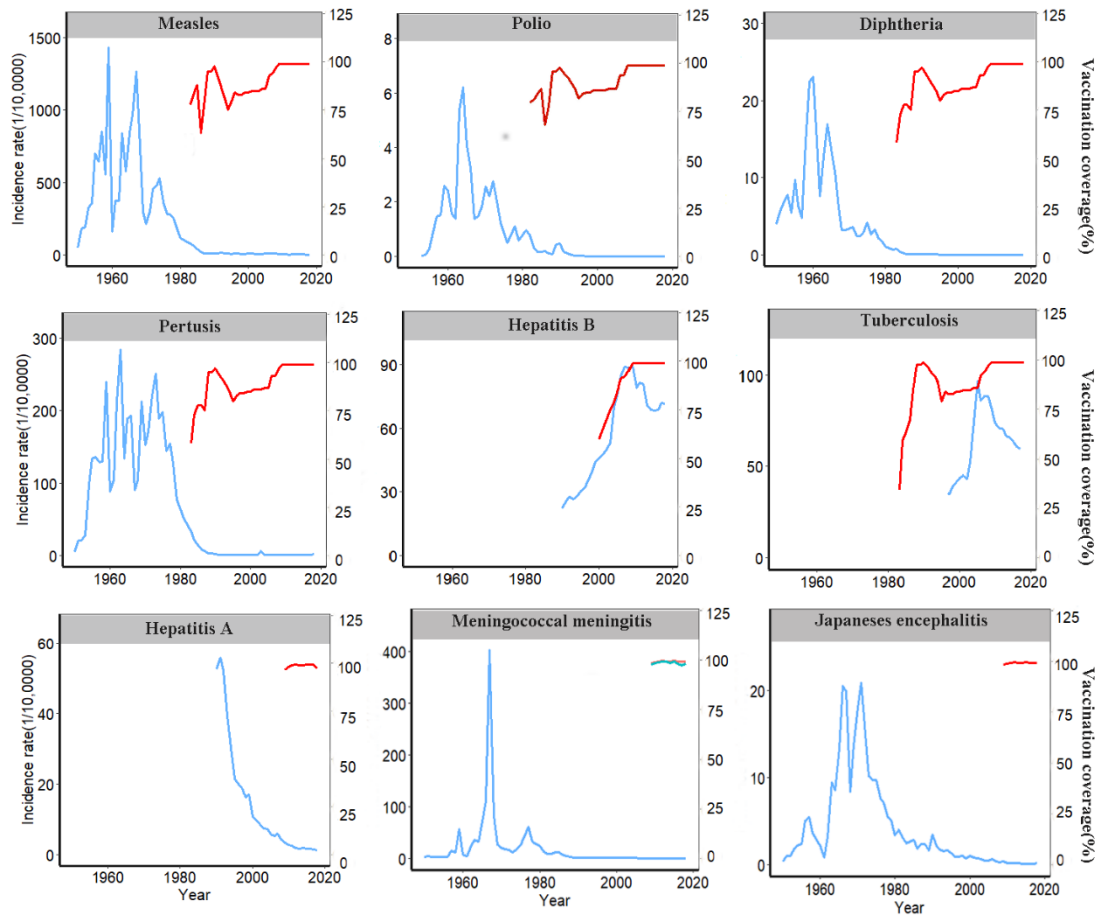

Figure S1. Annual incidence rates of selected VPDs and vaccination coverage

The gray background indicates the period in which the vaccination for a given disease was integrated into the national Expanded Program on Immunizations (EPI). The blue line indicates the morbidity rate of the disease; the red line represents the vaccination rate of the disease; and the green line represents the vaccination rate for the group A + C vaccine. Data on vaccination coverage of Japanese encephalitis, meningococcal meningitis and hepatitis A were collected from national vaccination coverage surveys. Data on vaccination rates for other diseases were obtained from the WHO website (http://apps.who.int/gho/data/node.main.A824?lang=en
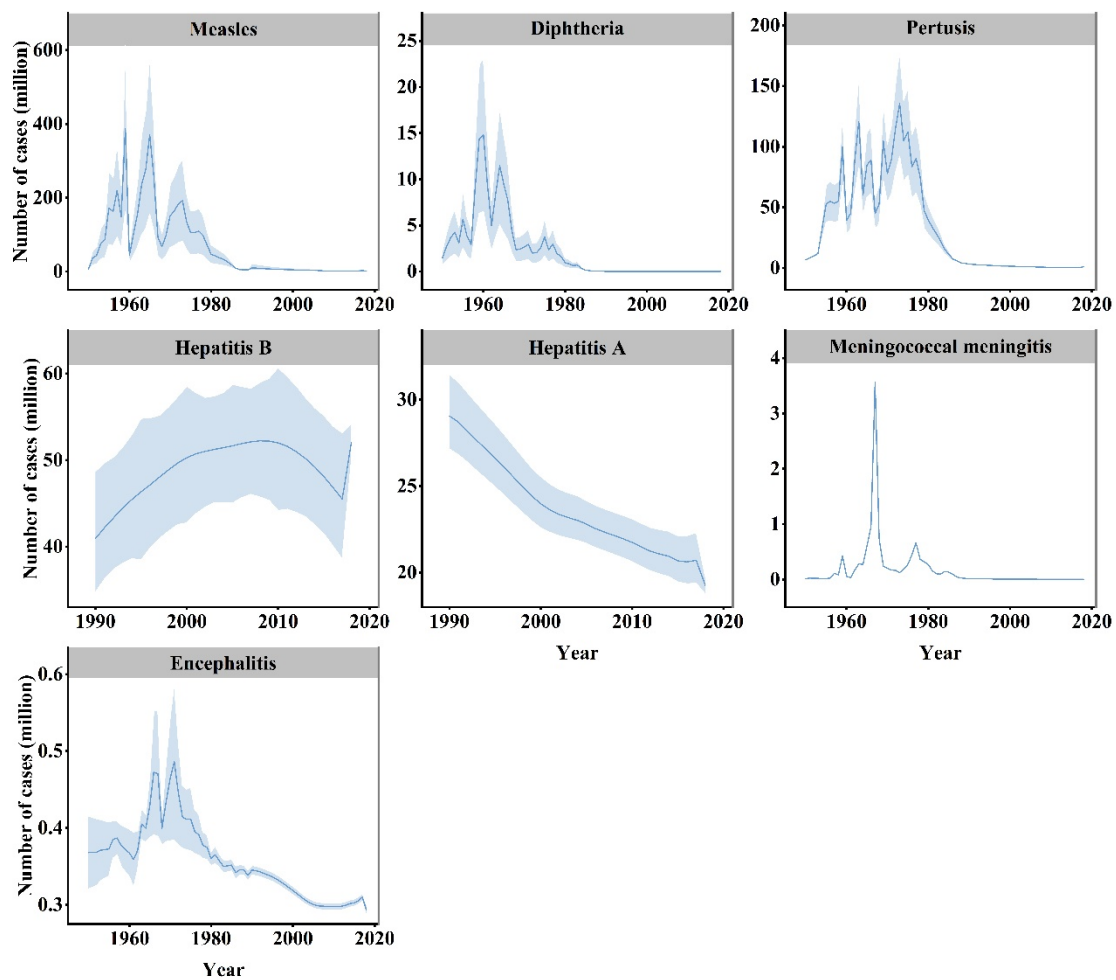
Figure S2. Number of infectious cases adjusted for underreported and under-ascertainment. The solid line represents the number of infectious cases and the dash area are 95% confidence interval. Cases between 1990 and 2017 were from GBD websites, cases between 1950 and 1989 and the year of 2018 were estimate from polynomial regression model

The burden of the 11 VPDs

For hepatitis A and hepatitis B, which were not included in the EPI in 1978, the impact on life expectancy has been calculated since 1990, when these vaccines were introduced. When the hepatitis B vaccine was first introduced in 1990, the impact of hepatitis B-related death on the life expectancy of newborns was 0·023 months; in 2018, when the hepatitis B vaccination rate reached more than 95%, the impact of hepatitis B-related death on the life expectancy of newborns dropped to 0·007 months. Compared with the value in 1990, the contribution of the hepatitis B vaccine to the life expectancy of

newborns in 2018 was 0·16 months. Similarly, the 1990 introduction of the hepatitis A vaccine increased the life expectancy of newborns in 2018 by 0·015 months. By 2018, the life expectancy of neonates for meningococcal and Japanese encephalitis increased by 0·53 months and 0·23 months, respectively, relative to the 1978 levels (Table S1).

When the measles vaccine was first added to the EPI in 1978, the impact of measles death on the life expectancy of newborns was 0·40 months. In 2018, when the measles vaccine vaccination rate was above 95%, the death rate impact was 0·00002 months. The impact of several other VPDS on life expectancy in 1978-2018 is presented in the supplementary information. Overall, the impact of these 11 diseases on life expectancy decreased during the study period.

Similar results were obtained for the loss of healthy life years and loss of work years due to early deaths from these infectious diseases. Table S2 show the loss of healthy life years and loss of work years due to 11 VPDs. From 2004 to 2016, the total loss of healthy life years due to early death caused by the 11 VPDs was 1,182,322 person-years, except for an increase seen in 2012, the loss of healthy life showed a downward trend over time. In 2016, the loss of healthy life years due to early death from the infectious diseases was 53,136·77 person-years, which was significantly lower than the 81,592·79 person-years in 2004 (a decrease of 37·5%).
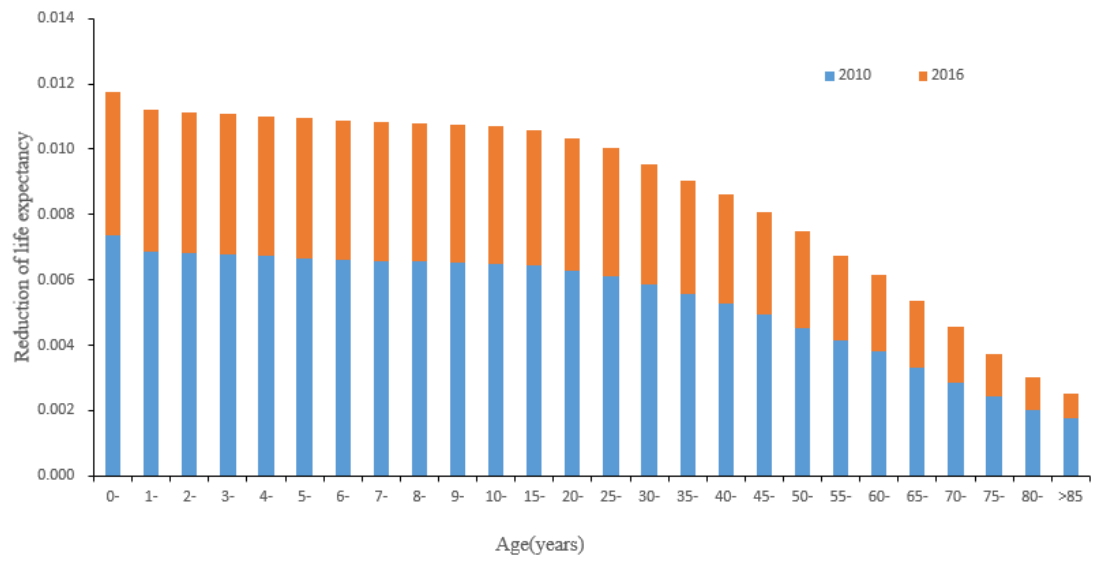
Figure S3. The impacts of the 11 diseases on life expectancy for different age groups

Table S1. The effect of vaccine-preventable diseases on life expectancy in 1978-2018

Year	Hepatitis A		Meningococcal Meningitis		Measles		Hepatitis B		Japanese encephalitis		Total of eleven diseases	
	years	months	years	months	years	months	years	months	years	months	years	months
1978			0·044470	0·533636	0·033021	0·396253			0·019287	0·231439	0·108308	1·299693
1979			0·035311	0·423727	0·025826	0·309916			0·016017	0·192205	0·084726	1·016715
1980			0·029751	0·357007	0·016344	0·196129			0·010460	0·125514	0·130526	1·566311
1981			0·017652	0·211822	0·013729	0·164743			0·013729	0·164743	0·050359	0·604304
1982			0·014056	0·168666	0·016671	0·200052			0·012748	0·152974	0·048068	0·576821
1983			0·012748	0·152974	0·013075	0·156897			0·007844	0·094133	0·037273	0·447277
1984			0·018917	0·227006	0·009260	0·111118			0·007537	0·090446	0·038133	0·457600
1985			0·019300	0·231596	0·008374	0·100487			0·019300	0·231596	0·036982	0·443784
1986			0·014513	0·174159	0·002615	0·031376			0·004935	0·059223	0·023341	0·280093
1987			0·006962	0·083542	0·000654	0·007844			0·007027	0·084327	0·015331	0·183967
1988			0·005001	0·060008	0·001601	0·019217			0·006373	0·076482	0·013313	0·159753
1989			0·003105	0·037259	0·001046	0·012550			0·004020	0·048241	0·008825	0·105901
1990	0·001209	0·014511	0·002222	0·026669	0·000556	0·006667	0·001928	0·023139	0·007714	0·092564	0·014219	0·170628
1991	0·001079	0·012942	0·001536	0·018433	0·001003	0·012040	0·001928	0·023139	0·003432	0·041181	0·009351	0·112216
1992	0·000882	0·010589	0·001405	0·016864	0·001128	0·013531	0·001732	0·020786	0·002092	0·025101	0·007439	0·089269
1993	0·000686	0·008236	0·000915	0·010981	0·001049	0·012589	0·001896	0·022747	0·001961	0·023532	0·006677	0·080130
1994	0·000546	0·006550	0·001039	0·012472	0·000690	0·008275	0·001696	0·020355	0·002186	0·026238	0·006338	0·076050
1995	0·000428	0·005138	0·001023	0·012276	0·000297	0·003569	0·001758	0·021100	0·001526	0·018315	0·005105	0·061263
1996	0·000363	0·004353	0·000945	0·011334	0·000428	0·005138	0·001700	0·020394	0·001039	0·012472	0·004523	0·054281
1997	0·000458	0·005491	0·000788	0·009452	0·000677	0·008118	0·001889	0·022669	0·001003	0·01204	0·007086	0·085033
1998	0·000353	0·004236	0·000641	0·007687	0·000346	0·004157	0·001575	0·018904	0·001330	0·015962	0·006697	0·080365
1999	0·000291	0·003490	0·000448	0·005373	0·000402	0·004824	0·001291	0·015492	0·000915	0·010981	0·005749	0·068990
2000	0·000196	0·002353	0·000350	0·004196	0·000431	0·005177	0·001530	0·018355	0·000431	0·005177	0·005766	0·069186

2001	0·000190	0·002275	0·000291	0·003490	0·000412	0·004942	0·001405	0·016864	0·000634	0·007608	0·005439	0·065264
2002	0·000206	0·002471	0·000314	0·003765	0·000337	0·004040	0·001902	0·022826	0·000559	0·006706	0·005952	0·071422
2003	0·000170	0·002039	0·000337	0·004040	0·000193	0·002314	0·001863	0·022355	0·000886	0·010628	0·006324	0·075893
2004	0·000099	0·001186	0·000701	0·008415	0·000128	0·001533	0·001568	0·018819	0·000828	0·009932	0·006357	0·076283
2005	0·000093	0·001120	0·000792	0·009506	0·000220	0·002645	0·001678	0·020142	0·000942	0·011306	0·010257	0·123090
2006	0·000092	0·001101	0·000604	0·007253	0·000155	0·001860	0·001824	0·021885	0·001805	0·021664	0·010719	0·128623
2007	0·000073	0·000876	0·000502	0·006029	0·000301	0·003613	0·00152	0·018245	0·000929	0·011151	0·010082	0·120985
2008	0·000021	0·000251	0·000444	0·005328	0·000459	0·005505	0·001471	0·017648	0·000576	0·006911	0·008077	0·096924
2009	0·000043	0·000512	0·000270	0·003246	0·000170	0·002034	0·001362	0·016349	0·000645	0·007735	0·009238	0·110856
2010	0·000012	0·000146	0·000123	0·001474	0·000111	0·001335	0·001158	0·013900	0·000343	0·004113	0·007376	0·088513
2011	0·000027	0·000321	0·000199	0·002393	0·000043	0·000514	0·001042	0·012505	0·000273	0·003280	0·006255	0·075056
2012	0·000019	0·000224	0·000199	0·002393	0·000085	0·001020	0·001829	0·021944	0·000446	0·005355	0·010952	0·131424
2013	0·000003	0·000040	0·000091	0·001093	0·000126	0·001511	0·000863	0·010350	0·000201	0·002415	0·005293	0·063516
2014	0·000011	0·000133	0·000052	0·000623	0·000131	0·001575	0·000562	0·006748	0·000102	0·001224	0·00426	0·051121
2015	0·000021	0·00025	0·000060	0·000722	0·000154	0·001846	0·000542	0·006505	0·000074	0·000888	0·004274	0·051293
2016	0·000006	0·000075	0·000042	0·000507	0·000076	0·000912	0·000600	0·007204	0·000128	0·001533	0·004394	0·052732
2017	0·000006	0·000070	0·000028	0·000335	0·000007	0·000088	0·000624	0·007488	0·000116	0·001392	0·000781	0·009373
2018	0·000004	0·000053	0·000015	0·000176	0·000001	0·000018	0·000604	0·007249	0·000197	0·002369	0·000825	0·009899

Table S2. Loss of healthy life and work years due to early death from the 11 vaccine-preventable diseases

Year	Loss of healthy life years (person years)	Total population	Early mortality rate	Loss of work years (person years)
2004	81592·79	1299880000	0·00006277	47410
2005	126949·6	1307560000	0·00009709	71137·5
2006	136593·4	1314480000	0·00010391	76960
2007	120585·1	1321290000	0·00009126	66375
2008	97181·57	1328020000	0·00007318	53487·5
2009	104323·7	1334500000	0·00007817	55740
2010	81033·93	1340910000	0·00006043	42905
2011	76899·41	1347350000	0·00005707	41262·5
2012	133739·4	1354040000	0·00009877	70355
2013	66203·94	1360720000	0·00004865	35052·5
2014	52293·87	1367820000	0·00003823	27477·5
2015	51788·21	1274620000	0·00004063	26907·5
2016	53136·77	1382710000	0·00003843	26955
Total	1182322	17333900000	0·00006821	642025