The impact of immunization programs on 10 vaccine preventable diseases in Italy: 1900–2015

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ABSTRACT

Background: Vaccination has determined a dramatic decline in morbidity and mortality from infectious diseases over the last century. However, low perceived risk of the infectious threat and increased concern about vaccines' safety led to a reduction in vaccine coverage, with increased risk of disease outbreaks.
Methods: Annual surveillance data of nationally communicable infectious diseases in Italy between 1900 and 2015 were used to derive trends in morbidity and mortality rates before and after vaccine introduction, focusing particularly on the effect of vaccination programs. Autoregressive integrated moving average models were applied to ten vaccine-preventable diseases: diphtheria, tetanus, poliomyelitis, hepatitis B, pertussis, measles, mumps, rubella, chickenpox, and invasive meningococcal disease. Results of these models referring to data before the immunization programs were projected on the vaccination period to estimate expected cases. The difference between observed and projected cases provided estimates of cases avoided by vaccination.
Results: The temporal trend for each disease started with high incidence rates, followed by a period of persisting reduction. After vaccine introduction, and particularly after the recommendation for universal use among children, the current rates were much lower than those forecasted without vaccination, both in the whole population and among the 0-to-4 year olds, which is, generally, the most susceptible age class. Assuming that the difference between incidence rates before and after vaccination programs was attributable only to vaccine, more than 4 million cases were prevented, and nearly 35% of them among children in the early years of life. Diphtheria was the disease with the highest number of prevented cases, followed by mumps, chickenpox and measles.
Conclusions: Universal vaccination programs represent the most effective prevention tool against infectious diseases, having a major impact on human health. Health authorities should make any effort to strengthen public confidence in vaccines, highlighting scientific evidence of vaccination benefits.

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1. Introduction

Vaccination programs, along with sanitation measures, are considered the most important public health tools, having a considerable impact on morbidity and mortality at the global level [1,2]. However, vaccines are often victims of their own success, and low risk perception due to the dramatic decline of vaccine preventable diseases (VPDs) may lead to complacency, which is an important component of vaccine hesitance or even refusal [3]. As a consequence, a decline in vaccination coverage may occur, even in contexts where access to high quality vaccination services is ensured. In order to increase confidence on the positive effects of vaccines, it is extremely important to provide information on their impact on the health of both individuals and communities. Up to now, only a few long term series of cases of vaccine preventable diseases were available in a limited number of countries [4–7].

In Italy, a country with universal access to care and treatment, an increasing number of vaccines has been actively offered

free-of-charge to all the individuals belonging to age groups or risk categories included in the vaccination schedules approved at the national level, even though the implementation may have varied across the country (administratively divided in 19 Regions and two autonomous Provinces), causing a certain degree of heterogeneity for some vaccines through the national territory. Up to the end of 2016, four vaccines were mandatory by law for all newborns (anti-polio, tetanus, diphtheria, and hepatitis B), whereas other vaccines (against measles-mumps-rubella, pertussis, *Haemophilus influenzae* type b, pneumococcus, and meningococcus C) were only recommended [8].

In order to quantify the impact of vaccination programs on morbidity and mortality in Italy, we reconstructed and evaluated the temporal trends of 10 VPDs. We estimated also the number of cases and deaths prevented by vaccination in the last 115 years. The present study is focused on early childhood vaccines.

2. Methods

2.1. Data sources

Yearly surveillance data on morbidity and mortality of vaccine preventable infectious diseases occurred between 1900 (or the first year of reporting) and 2015 (2012 for mortality) in Italy were obtained from the National Institute of Statistics (ISTAT) and the Ministry of Health (MoH). Specifically, mortality data by gender and class of age were retrieved from the annuaries and, since 1980, from the mortality database of ISTAT; morbidity data were retrieved from the annuaries of ISTAT for the period 1900–1997, and from the Infectious disease information system of MoH for the period 1998–2015. Population data were obtained from the Human Mortality Database (http://www.mortality.org/cgi-bin/hmd/country.php?cntr-ITA&level=1) for the period 1900–1951, and from ISTAT database for the period 1952–2015 (www.demo.istat.it).

2.2. Statistical analysis

Ten vaccine-preventable infectious diseases were selected to calculate annual mortality and morbidity rates: diphtheria, tetanus, poliomyelitis, hepatitis B, pertussis, measles, mumps, rubella, chickenpox, and meningococcus. Currently, the number of deaths due to hepatitis B are partially available and morbidity data before 1987 were recorded in an aggregate way for all types of hepatitis, therefore these data were not considered. In addition, the impact of vaccination against *Haemophilus influenzae* type b and pneumococcus was not included, since data on invasive bacterial diseases caused by these pathogens were reported grouped with other pathogens before vaccine introduction. Finally, data on meningococcal meningitis by serogroup were not available.

Annual mortality rates were calculated by standardizing the reported counts of deaths by gender and age class, considering the 2016 Italian population as reference, to take into account changes over time in the age structure of the population. With regard to morbidity, incidence rates were calculated as crude rate, since the reported counts of cases classified by gender and age class were available only after 1954. Mortality and morbidity rates for children aged 0–4 years were also computed.

Autoregressive integrated moving average (ARIMA) models were applied to log-transformed annual mortality and morbidity rates before vaccination started, both for all ages and for 0–4 years old children. Dickey–Fuller test was used to assess the non-stationarity (trend or difference stationarity) of the time series. Autocorrelation and partial autocorrelation plots were used for identifying the order of the autoregressive model, while the

Akaike's and Schwarz's Bayesian information criteria were considered for assessing model fit. Results of these ARIMA models referring to data before the immunization programs were projected on the vaccination period to show the impact of immunization and to estimate the expected number of cases in absence of vaccination. Expected deaths after vaccine introduction were estimated only for diphtheria, tetanus and poliomyelitis, which presented the highest mortality rates before the implementation of universal immunization. The difference between observed and projected cases provided estimates of cases avoided by vaccination.

Statistical analyses were performed using the Stata software, version 13 (Stata Cooperation, College Station, Texas, USA).

3. Results

3.1. Temporal trend of mortality and morbidity rates for ten vaccine-preventable diseases

3.1.1. Diphtheria

Immunization with the inactivated diphtheria toxoid was compulsory introduced in 1939 for children aged 2–10 years; in 1968, it was indicated for children in the second year of life, in combination with the inactivated tetanus toxoid. Until 1939, diphtheria was a common disease, causing thousands of deaths every year (Fig. 1A and Supplementary Fig. S1A). From the beginning of the twentieth century to the forties, between 15,000 and 30,000 cases were annually reported (incidence rate was 30–75 per 100,000) (Fig. 1B and Supplementary Fig. S1B). After World War II, large-scale immunization programs allowed a rapid decrease of morbidity and mortality rates, although the latter had already begun to decline. Until the late thirties, mean mortality rates were 4.20 and 66.30 in the whole population and in the 0-to-4 years old class, respectively, falling to 0.52 and 8.08 after vaccine introduction (Supplementary Table S1). Similarly, morbidity rates sharply declined during the vaccination period (Table 1). The last case of diphtheria in Italy was notified in 1996.

3.1.2. Tetanus

The number of tetanus cases has dramatically dropped since the introduction of tetanus toxoid vaccine for at risk professional categories in 1963, while mortality rates have begun to decrease in the fifties (Fig. 2C–D and Supplementary Fig. S1C–D). This vaccination became mandatory for children in the second year of life in 1968. Over 13,000 cases were annually reported until the mid-sixties, with a morbidity rate of 1.3–1.5 per 100,000; then, the number dropped to less than 1000 at the beginning of the seventies (morbidity rate 0.5–0.7 per 100,000). In the same period, the annual number of deaths decreased from 500-to-1000 to less than 200 (mortality rate 0.4–0.5 per 100,000). The temporal trend of mortality rates for children aged 0–4 years showed an irregular pattern, with peaks at the beginning of the twentieth century, in 1920s and 1950s (Supplementary Fig. S1C). Morbidity rates declined under 0.5 per 100,000 since the early seventies; however, a peak of cases (53) occurred in 1989 (Supplementary Fig. S1D).

3.1.3. Poliomyelitis

Following the epidemic peak in 1958, the inactivated Salk polio vaccine (IPV) was recommended for the population aged 0–20 years in 1959. In 1964 the Sabin live attenuated oral polio (OPV) vaccine was used in the vaccination campaign against poliomyelitis, and became compulsory in 1966 for children within the first year of age. Before the universal vaccination thousands of cases of acute flaccid paralysis were reported every year (morbidity rate 17.2 per 100,000), and mortality rates ranged from 4 to 7 per 100,000 among 0-to-4 years old children (Fig. 2A–B and
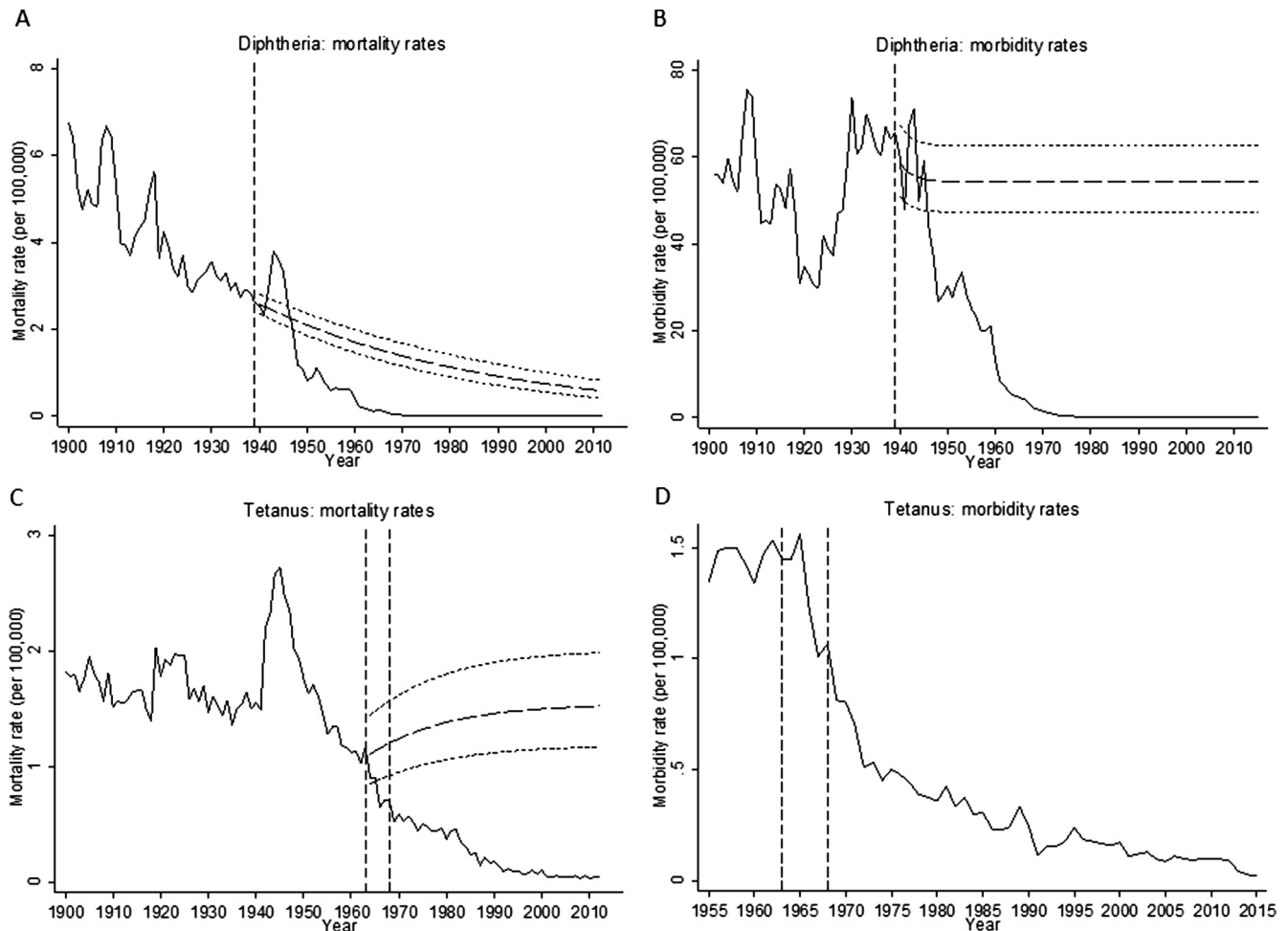
Fig. 1. Temporal trend for diphtheria and tetanus. Diphtheria yearly mortality rates 1900–2012 (A) and morbidity rates 1900–2015 (B). Tetanus yearly mortality rates 1900–2012 (C) and morbidity rates 1955–2015 (D). Vertical lines indicate the year of vaccine introduction or the year in which vaccination became mandatory. Dotted lines represent the projected estimates (with 95% confidence interval) after vaccination. Immunization with the inactivated diphtheria toxoid was introduced in 1939 for children aged 2–10 years. Tetanus toxoid vaccine was introduced for professional categories at risk in 1963 and became mandatory for children in the second year of life in 1968, when it was combined in the diphtheria-tetanus vaccine. Diphtheria mortality rates (A): trend-stationary series with world war I period effect included in the model. Diphtheria morbidity rates (B): first-order autoregressive model with post-world war I period effect. Tetanus mortality rates (C): second-order autoregressive model with post-world war I and II period effects. Tetanus morbidity rates (D): white noise model.

Supplementary Fig. S2A–B). After the vaccine introduction disease morbidity and mortality dramatically declined, particularly among children under five years of age (Table 1 and Supplementary Tables S1–S2). The last death was recorded in 1978, while the last case occurred in 1988. In 1999, the IPV vaccine replaced the OPV due to safety concerns and risk-benefit considerations.

3.1.4. Hepatitis B

The first anti-hepatitis B vaccine, licensed in 1982, contained purified hepatitis B surface antigen (HBsAg) obtained from the plasma of people with chronic hepatitis B virus (HBV) infection. In the eighties, the vaccine was considered for use only in high risk individuals. In 1986, a recombinant DNA HBV vaccine was introduced, which became mandatory in 1991 for children in the first year of life and twelve years old adolescents. In the year 2000, a hexavalent formulation containing the HBV vaccine in combination with diphtheria, polio, tetanus, pertussis, and *Haemophilus influenzae* type b was licensed. A dramatic decrease of HBV acute disease occurred since 1991 following the introduction of mandatory vaccination, except for a peak of cases (3 3 7) occurred in 1995 among children aged 0–4 years (Fig. 2C and Supplementary Fig. S2C). Morbidity rates decreased from 5.52 to 2.53 per

100,000 in the whole population in the vaccination period (Table 1), and from 2.33 to 1.40 per 100,000 among children under five years (Supplementary Table S2).

3.1.5. Pertussis

Recommendations for pertussis immunization were released in 1961, when the whole cell vaccine became available; however, vaccination coverage substantially increased (from less than 30% to greater than 90%) only after the introduction of a better tolerated acellular vaccine, which was offered free of charge in all Italian regions since 1995. The death rate was about 150 per 100,000 among 0-to-4 years old children at the beginning of the twentieth century (Fig. 3A and Supplementary Fig. S3A). Pertussis mortality started to decline progressively over time, even before the introduction of immunization, and no disease-related death was reported after 2006. In particular, death rates declined from 46.50 to 0.01 per 100,000 among children under five years in the vaccination period, and morbidity rates decreased from 289.42 to 37.65 per 100,000 (Supplementary Tables S1–S2). Epidemic cycles occurred regularly every three-to-five years, until large-scale vaccination allowed a rapid reduction in disease occurrence (Fig. 3B and Supplementary Fig. S3B). In the last decade, few hundred cases

Table 1
Morbidity rates and prevented cases due to ten infectious diseases by the national vaccination programs.

Vaccine-preventable diseases	Pre-vaccination period	Post-vaccination period	Pre-vaccination morbidity rates (per 100,000)	Post-vaccination morbidity rates (per 100,000)	Reported cases	Prevented cases (95% C.I.)	Vaccine coverage 2015 (24 months) (%)
Diphtheria	1901–1938	1939–2015	53.03	11.42	403,712	1,832,142 (1,540,355–2,167,723)	93.3
Tetanus	1955–1962	1963–2015	1.45	0.39	10,673	30,818 (29,905–32,824)	93.6
Poliomyelitis	1925–1963	1964–2015	5.23	0.06	1,651	198,279 (162,693–241,572)	93.4
Hepatitis B	1987–1990	1991–2015	5.52	2.53	34,880	41,675 (39,092–51,341)	93.2
Pertussis	1925–1994	1995–2015	42.79	3.97	47,751	234,958 (82,466–566,026)	93.3
Measles	1901–1998	1999–2015	183.16	5.93	58,376	277,417 (187,579–400,312)	85.3
Mumps	1936–1998	1999–2015	60.45	13.11	127,357	1,026,714 (634,083–1,624,411)	85.2
Rubella	1970–1998	1999–2015	35.94	2.61	25,529	226,478 (158,679–319,240)	85.2
Chickenpox	1925–2002	2003–2015	86.91	124.65	949,504	679,512 (617,171–744,353)	30.7
Meningococcus	1976–2004	2005–2015	0.84	0.27	1,734	1,563 (1,235–1,936)	76.6

C.I., confidence interval.
Recommendations for pertussis immunization were released in 1961 but vaccination coverage remained low until 1995, when acellular pertussis vaccine was introduced and was included in the national vaccination program.
Measles vaccine was introduced in 1976, mumps in 1982 and rubella in 1972. Vaccination coverage remained low until 1999, when combined measles-mumps-rubella immunization was included in the national recommended vaccination schedule.
Vaccine coverages 2015 were extracted from The Ministry of Health data (http://www.salute.gov.it/imgs/C_17_tavole_20_allegati_iitemAllegati_0_fileAllegati_itemFile_3_file.pdf).

were reported every year. Since the nineties, the *Bordetella pertussis* vaccine is administered in combination with diphtheria and tetanus vaccines or, more often, contained in the hexavalent formulation.

3.1.6. Measles

In 1976, a single-antigen live attenuated measles vaccine was recommended by the Ministry of Health, but vaccine coverage remained under 20% until the early nineties, reaching 50% only in the late nineties. In 1999, a combined measles-mumps-rubella (MMR) vaccine was included in the national immunization schedule, and vaccine coverage rapidly increased to nearly 90%. Mortality rates had progressively decreased even before the vaccine was licensed, becoming less than 1 per 100,000 in the whole population in the early fifties (Fig. 3C) and among children only after 1976 (Supplementary Fig. S3C). The cyclic epidemic peaks decreased after the vaccine was introduced and were further reduced as soon as a higher coverage was achieved (Fig. 3D and Supplementary Fig. S3D). A measles elimination plan was launched in 2003 with the aim of interrupting endemic transmission, but the incidence decreased below one confirmed case per 100,000 people only in 2015. However, vaccine coverage never reached levels as high as needed to stop the transmission (i.e., ≥95%), and epidemics continue to occur, as demonstrated by the recent outbreak occurred in 2017 (more than 4500 cases) (Ministry of Health data: http://www.salute.gov.it/portale/temi/documenti/morbillo/Bollettino_morbillo_26-2017).

3.1.7. Mumps

Anti-mumps immunization was introduced in 1982 and recommended for males in pre- and post-puberty. Vaccine coverage remained below 50% until the early nineties, sharply increasing only after 1999 when the MMR national vaccination program was launched. Mortality rates were low since the mid-eighties, between 0 and 3 deaths occurring each year (Fig. 4A and Supplementary Fig. S4A). Until the eighties, disease incidence progressively increased, remaining substantially stable but with periodic peaks between 1982 and 1999, then it declined rapidly to less than 2 per 100,000 people in the years 2000 s (Fig. 4B). As a result of a low vaccination coverage, incidence rates between 1982 and 1999 were greater than those recorded in the pre-vaccination period among 0-to-4 years old children (Supplementary Fig. S4B).

3.1.8. Rubella

The anti-rubella live attenuated vaccine became available since 1972. Initially, the vaccine was recommended only for girls in pre-puberty, but in 1999, with the introduction of the MMR national immunization program, it was recommended to all children in the second year of life (Fig. 4C–D and Supplementary Fig. S4C–D). Consequently, morbidity rates declined rapidly from 35.94 to 2.61 per 100,000 in the whole population, and from 148.28 to 8.20 among children under five year olds (Table 1 and Supplementary Table S2). Mortality rates remained fairly low over time, being less than 0.05 cases per 100,000 among under five years old children since the mid-seventies (Supplementary Table S1).

3.1.9. Chickenpox

Anti-chickenpox vaccination is the only one for which there was no universal vaccine recommendation throughout the country during the considered period. Starting from 2003, 8 Regions (which represent nearly 40% of the Italian population) included varicella in their immunization programs with different schedules in children aged 13–15 months and 5–6 years. The National Immunization Prevention Plan 2005–2007 recommended anti-chickenpox vaccine only in high-risk subjects and susceptible adolescents, leaving the adoption of specific vaccination programs to the Regions. Consequently, at a national level vaccine coverage has been always very low, reaching 30.7% in 2015. Although death rates decreased among 0–4 years old children since the mid-seventies (Fig. 5A and Supplementary Fig. S5A), morbidity rates in the last decade resulted still around 70–100 and 800–1000 per 100,000 in all age classes and among children, respectively (Fig. 5B and Supplementary Fig. S5B). Morbidity rates after vaccine introduction were greater than those observed in the pre-vaccination period (Table 1 and Supplementary Table S2), showing an increase after the mid-eighties both in the whole population and among 0-to-4 years old children (Fig. 5B and Supplementary Fig. S5B).

3.1.10. Meningococcus

Meningococcal serogroup C conjugate vaccine was introduced in Italy in 2005, but it was included in the national immunization plan only in the year 2012. During this period, the vaccination coverage progressively increased, from nearly 55% to about 75%. Since the nineties, mortality and incidence rates due to invasive
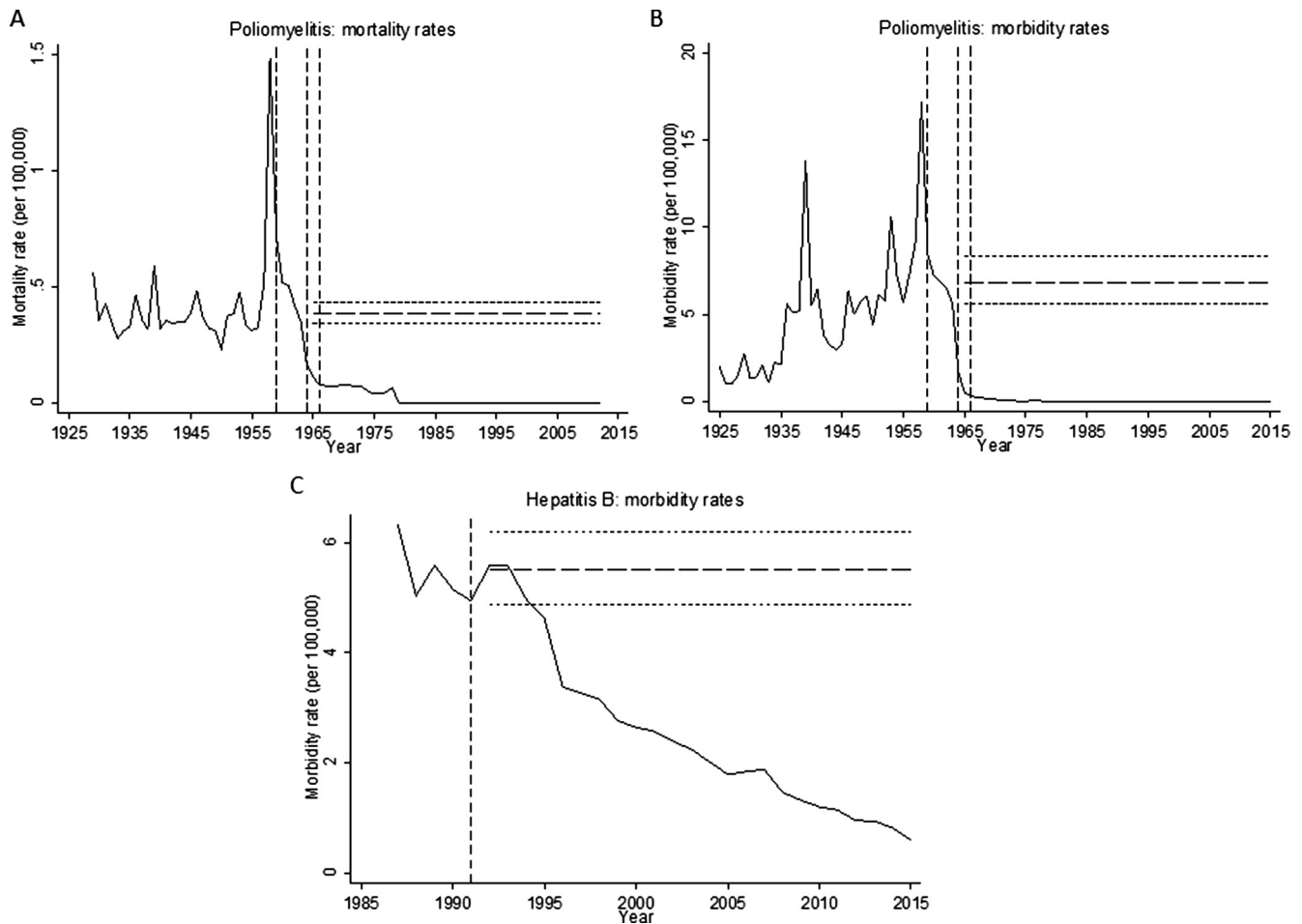
Fig. 2. Temporal trend for poliomyelitis and hepatitis B. Polio yearly mortality rates 1929–2012 (A) and morbidity rates 1925–2015 (B). Hepatitis B yearly morbidity rates 1987–2015 (C). Vertical lines indicate the year of vaccine introduction or national vaccination plan or the year in which vaccination became mandatory. Dotted lines represent the projected estimates (with 95% confidence interval) after vaccination. The anti-polio vaccine was introduced in 1959. In 1964 was conducted a vaccination campaign against poliomyelitis in the population aged 0–20 years which became compulsory in 1966 for children within the first year of age. In 1991 the recombinant DNA HBV vaccine became mandatory for children in the first year of life and adolescents twelve years old. Polio mortality rates (A): first-order autoregressive model with the epidemic peak (occurred in 1958) effect. Polio morbidity rates (B): white noise model with first period (1925–1935) and world war II and post-war period effects. Hepatitis B morbidity rates (C): white noise model.

meningococcal disease remained rather stable, but a major decrease in disease cases was observed after meningococcal C vaccine introduction (Fig. 5C–D and Supplementary Fig. S5C–D). In 2010 tetravalent meningococcal vaccines against serogroups A, C, W135 and Y became available for children; in addition, a recombinant vaccine against serogroup B, which is currently the most common in Italy, was licensed in 2013 and has been recommended since 2014.

3.2. Prevented deaths and cases due to infectious diseases since the vaccine introduction

Numbers of prevented deaths and cases since the introduction of specific immunization programs were computed after estimating the expected number of cases and death in absence of vaccination. In particular, it was estimated that more than 70,000 deaths were prevented by vaccination against diphtheria, tetanus, and poliomyelitis, the three infectious diseases with the highest mortality rates during the last century (Supplementary Table S3).

Assuming that the difference between morbidity rates before and after vaccines' introduction was attributable only to immunization programs, more than 4 million of cases were prevented by vaccination, nearly 35% of them among children in the early

years of life (Table 1 and Supplementary Table S4). The number of cases prevented per disease depended on incidence rates before vaccination and the duration of the vaccination period. Diphtheria was the disease with the highest number of cases prevented, followed by mumps, chickenpox and measles.

4. Discussion

Routinely used vaccines are effective and safe public health tools which protect human communities against infectious diseases. Thanks to vaccination, the morbidity and mortality of many severe diseases has drastically decreased at the global level, and billions of complications and deaths have been avoided [1,9,10]. Such positive effects of vaccination become stronger with increasing vaccine coverage, as a consequence of herd immunity, which confers indirect protection also to unvaccinated people [10,11]. However, if an optimal level of vaccine coverage is not maintained, diseases which have been temporarily eliminated in a country, such as polio or diphtheria, may reappear because infectious agents continue to circulate worldwide. In this context, it is important to quantify vaccines' beneficial effects in order to inform people about the advantages of immunization. Therefore, we reconstructed the long-term trend of 10 VPDs in Italy,
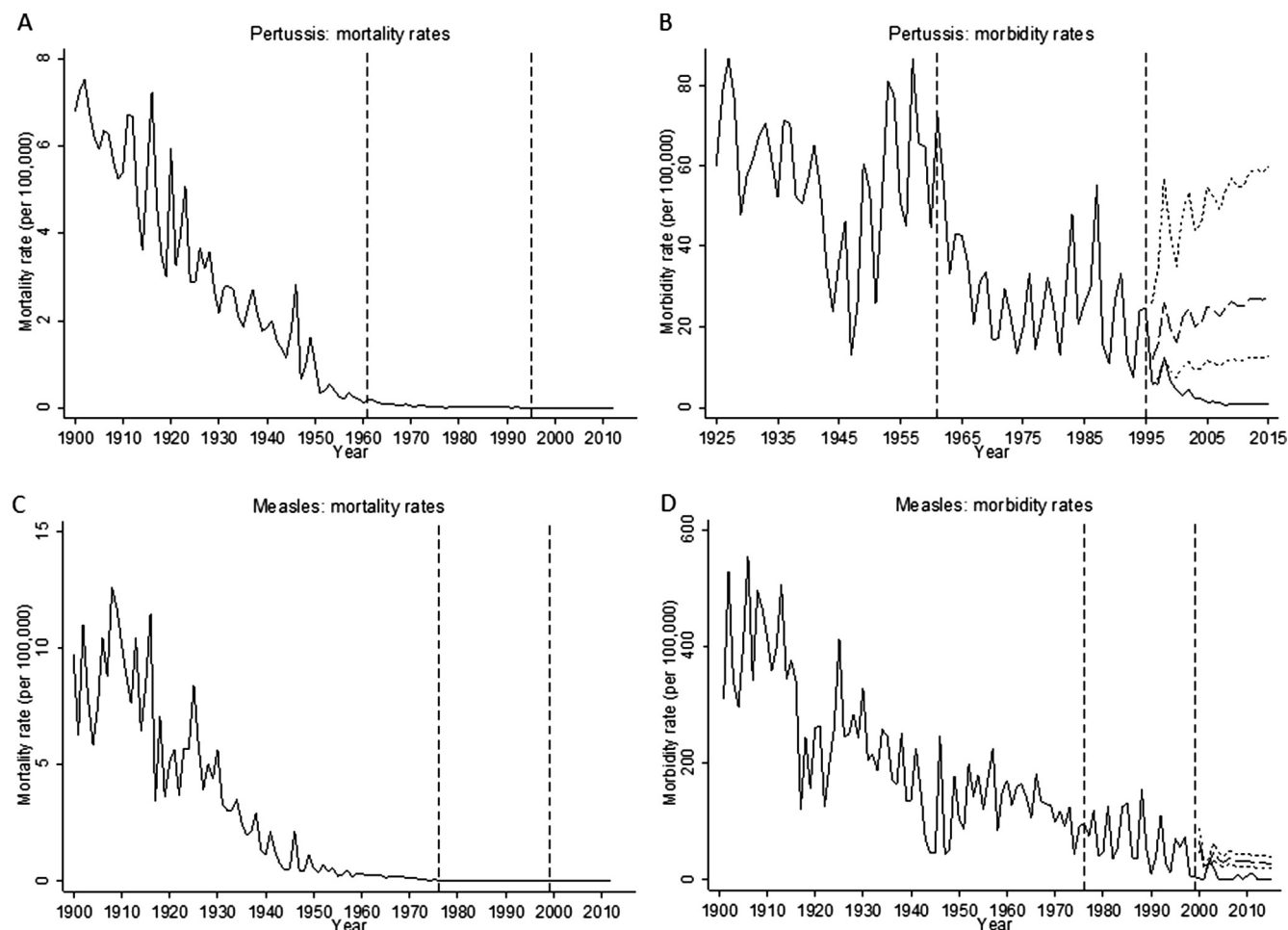
Fig. 3. Temporal trend for pertussis and measles. Pertussis yearly mortality rates 1900–2012 (A) and morbidity rates 1925–2015 (B). Measles yearly mortality rates 1900–2012 (C) and morbidity rates 1901–2015 (D). Vertical lines indicate the year of vaccine introduction or national vaccination program. Dotted lines represent the projected estimates (with 95% confidence interval) after vaccination. Recommendation for pertussis immunization was released in 1961, when the whole cell vaccine became available, however vaccination coverage substantially increased only after the introduction in 1995 of a better tolerated acellular vaccine. In 1976, a live attenuated measles vaccine was recommended, but the vaccine coverage sharply increased only after 1999, when the combined MMR vaccination was included in the national immunization plan. Pertussis morbidity rates (B): third-order autoregressive model. Measles morbidity rates (D): third-order autoregressive model with deterministic trend.

estimating the impact of vaccination programs on morbidity and mortality. Overall, more than 4 million cases of VPDs and 70,000 deaths due to diphtheria, tetanus, and polio only were prevented during the years considered in the study. Details on the type of vaccines available in Italy are included in Supplementary Table S5.

Vaccination coverage is a key measure of immunization system performance. In Italy, coverage rates showed an increasing trend until 2010 but then these have been decreasing [12,13]. Particularly, coverage rates for mandatory vaccines were maintained above the 95% target from 2002 to 2013 and then decreased to nearly 93%. MMR vaccine coverage has been increasing from 2000 to 2010, it was highest in 2010 (91%) and has drastically decreased since then to nearly 85%. Chickenpox vaccine coverage in eight pilot regions ranged from 51% to 84% in 2014 [13]. Meningococcal C conjugate vaccine has been well introduced in infants immunization schedules in all regions, reaching over 76% coverage at the national level. It has been observed in some cases that suboptimal levels of no vaccination could cause worse health outcomes than non vaccination [14]. Although the current vaccination coverage is close but not at the optimal level for many diseases it is of note that our analyses highlighted a reduction in morbidity and mortality for all of them. We also estimated a positive impact on morbidity also for varicella for which there was not a universal recommendation until 2017.

A study conducted in the US comparing trends of 13 VPDs showed a decline greater than 92% in cases and 99% in deaths due to VPDs such as diphtheria, mumps, pertussis, and tetanus [6], completely in line with our data. Furthermore, endemic transmission of polioviruses, measles, and rubella was even eliminated in the country. In another study in US, vaccination with 7 recommended childhood vaccines was estimated to prevent 33,000 deaths and 14 million cases of disease in every birth cohort, saving $10 billion in direct costs and $33 billion in costs including disability and lost productivity [15]. Another study conducted in US analyzed the long-term trend of weekly surveillance reports for 8 VPDs [7]. Overall, it was estimated that about 103 million cases were prevented by vaccination. Also in other countries, several studies highlighted the benefits of vaccination policies. Data on 5 VPDs incidence and mortality, from Vietnam's national surveillance, suggested that in 1980–2010 period up to 5.7 million diseases and 26,000 deaths may have been prevented by the extended program of immunization [16]. Data on 10 VPDs in Croatia over 1945–2011 period showed a steadily reduction of disease burden with the improvement of vaccination coverage [17]. A study conducted in Iran demonstrated that vaccination has had a positive impact on the control of 4 communicable diseases [18]. Diphtheria and tetanus death rates showed a reduction by nearly 85% from 1990 to 2010, whereas fatality rates for measles and whooping cough declined by 94% and 96%, respectively.
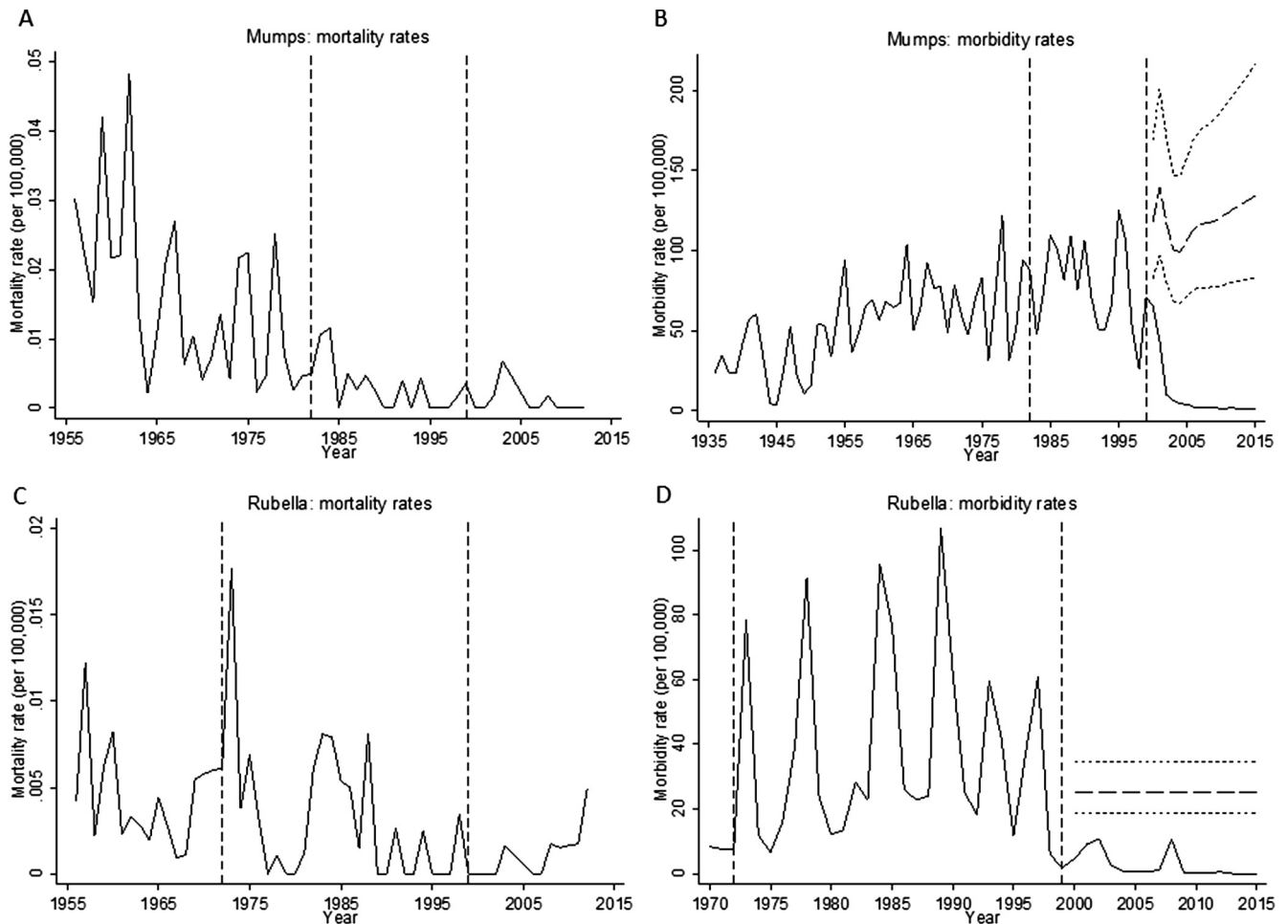
Fig. 4. Temporal trend for mumps and rubella. Mumps yearly mortality rates 1956–2012 (A) and morbidity rates 1936–2015 (B). Rubella yearly mortality rates 1956–2012 (C) and morbidity rates 1970–2015 (D). Vertical lines indicate the year of vaccine introduction or national vaccination plan. Dotted lines represent the projected estimates (with 95% confidence interval) after vaccination. Live attenuated anti-mumps vaccine was introduced in 1982 but vaccine coverage remained low until 1999 with the MMR national vaccination program. The anti-rubella live attenuated vaccine was available since 1972. Initially, the vaccination was recommended only for girls in pre-puberty, but in 1999, with the introduction of the MMR national immunization program, it was recommended for all children in the second year of life. Mumps morbidity rates (B): second-order autoregressive model with deterministic trend. Rubella morbidity rates (D): white noise model.

Before drawing conclusions, some limits of the study should be mentioned. In particular, in accordance with studies conducted in the US, we assumed that the entire difference between incidence and mortality rates during the pre-vaccination period and those during the vaccination period was attributable to immunization programs. However, other factors, such as sanitation, might have played a role in the declining trend. Specifically, the increasing use of antibiotics may have altered the mortality rate for vaccine preventable bacterial diseases independently on vaccination. Although these factors could not be accounted for in the data analysis, the persistent decline in disease incidence rates after vaccine introduction supports the conclusion that vaccination programs were a leading cause of the reduction of the burden of VPDs in our country. Underreporting, under diagnosis and limited access to care could have also influenced the observed trends, but it is likely that these issues were even higher in the pre-vaccination era than in recent times, thus being likely to results in conservative estimates of the effect of vaccination programs. Efficient and reliable surveillance and notification systems are essential for monitoring public health and disease outbreaks. However, most systems are affected by a degree of under diagnosis and underreporting that influence morbidity and mortality rates. Increased

incidence rates around vaccine introduction are very likely due to a surveillance artefact with a reduction of underreporting and this could have biased our projections. This effect seems to be particularly important for chickenpox for which incidence rates until the late seventies were artificially low. In fact, a study conducted in Italy showed that in the years 1976–1996 only 1 case of varicella out of 8 was reported [19]. Due to this artefact, also the projected incidence could appear too high (see Fig. 5B). It is of note that performing another analysis restricting the data before vaccination to the period 1985–2002 (mean morbidity rates 175.40) we still found a reduction in morbidity (data not shown). Overall, quantification of underreporting can contribute to better understanding the communicable disease burden and to evaluate the impact of universal vaccination.

In some cases, such as tetanus and hepatitis B morbidity, the limited availability of historical data before the vaccine introduction may have affected the real time trend estimate before vaccine introduction and, consequently, the incidence rates prediction. In particular, we considered for hepatitis B morbidity data from 1987 to 1990 as pre-vaccination period. However, since 1983 a selective vaccination program targeted to people at increased risk of infection because of their style life was introduced on regional
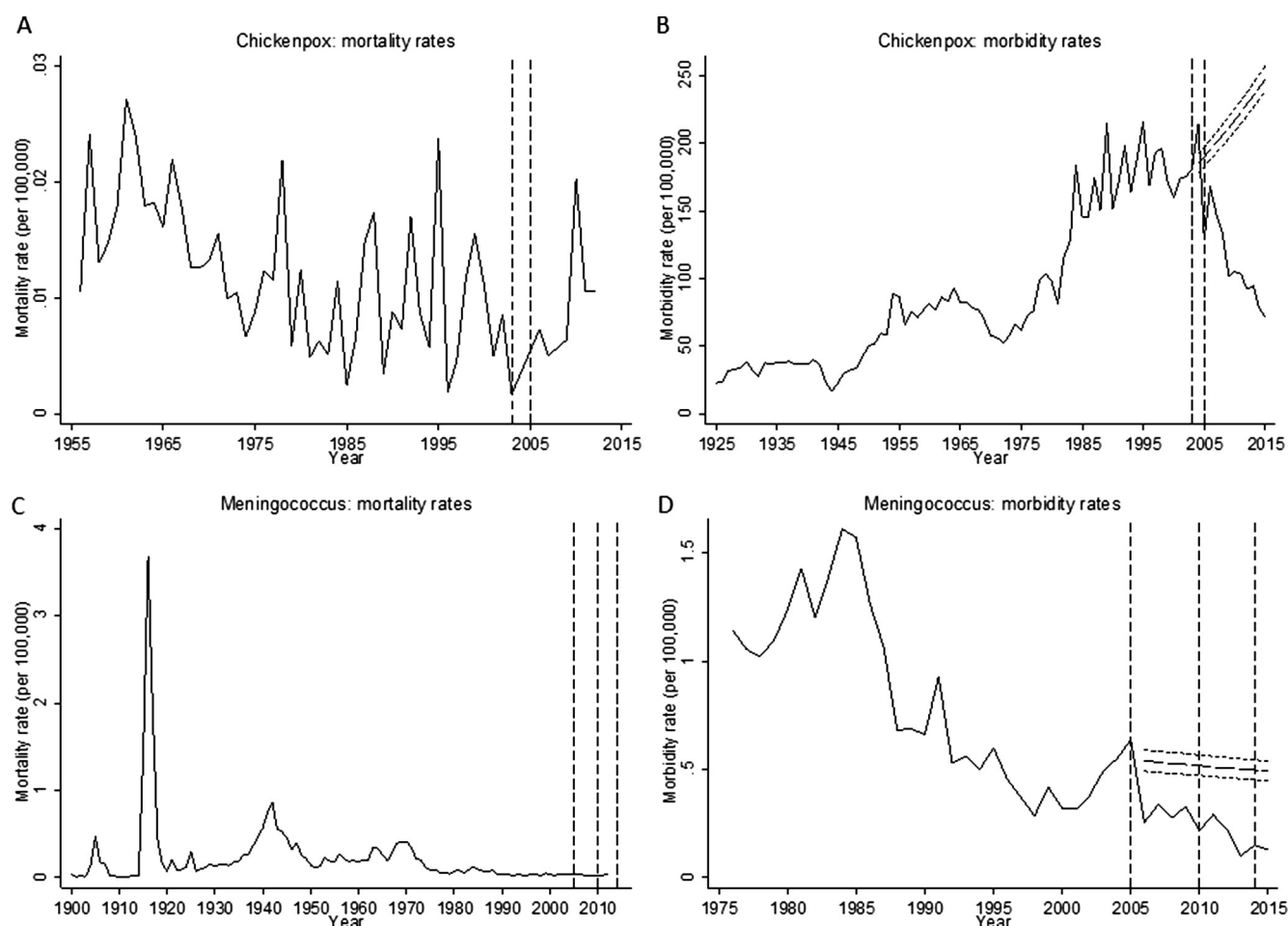
Fig. 5. Temporal trend for chickenpox and meningococcus. Chickenpox yearly mortality rates 1956–2012 (A) and morbidity rates 1925–2015 (B). Meningococcus yearly mortality rates 1900–2012 (C) and morbidity rates 1976–2015 (D). Vertical lines indicate the year of vaccine introduction or recommendation. Dotted lines represent the projected estimates (with 95% confidence interval) after vaccination. Starting from 2003, eight Regions (which represent nearly 40% of the Italian population) included live attenuated anti-chickenpox vaccination in their immunization programs with different schedules in children aged 13–15 months and 5–6 years. The National Immunization Prevention Plan 2005–2007 recommended anti-chickenpox vaccine only in high-risk subjects and susceptible adolescents, leaving the adoption of specific vaccination programs to the Regions. Consequently, at a national level vaccine coverage has been always very low (around 30%). Meningococcal serogroup C conjugate vaccine was introduced in 2005, but it was included in the Italian national immunization plan only in 2012. Tetravalent meningococcal vaccines against serogroups A, C, W135 and Y became available in 2010; in addition, a recombinant vaccine against serogroup B was licensed in 2013 and has been recommended since 2014. Chickenpox morbidity rates (B): random walk model. Meningococcus morbidity rates (D): random walk model.

basis. It is likely that the impact of this vaccine was underestimated.

5. Conclusions

In recent years, vaccines are losing public confidence with consequent decreasing coverage trends [13]. In this context, Italian National Health Authorities have been addressed by the Council of the European Union to promote and support vaccination policies, conveying the importance of vaccination to the patients as well as to scientific and professional associations [20]. Our analysis strongly supports the value of vaccination quantifying its impact on 10 VPDs. Thanks to the use of vaccines, millions of cases and thousands of deaths due to infectious diseases were averted in Italy. The results of this study will be very useful for future vaccination strategies and information prevention policies for the population and for other stakeholders.

Authors' contributions

PP conceived the study, coordinated the study's activities, contributed to the data analysis and manuscript preparation. SB per-

formed the statistical analyses and contributed to the manuscript preparation. FP collected the data, revised literature for vaccine offer and for the safety of the commercial vaccines. SI collected the data and revised literature for the efficacy of vaccines. FL and LC contributed to revise literature for the efficacy and safety of the commercial vaccines. MMB supervised the data analysis. WR contributed to critical review. PS conceived the study and revised the article. GR conceived the study and contributed to the manuscript preparation. All authors approved the final article.

Competing interests

The authors declare that they have no competing interests.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.vaccine.2018.01.065.

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