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Research paper

Changes in epidemiological features of vaccine preventable infectious diseases among three eras of national vaccination strategies from 1953 to 2018 in Shanghai, China

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ABSTRACT

Background: Recurring outbreaks of infectious diseases highlight the importance of population vaccination strategies. We aimed to assess the impact of national vaccination strategies on vaccine-preventable infectious diseases (VPDs) in Shanghai, China and to identify vulnerable groups that may benefit from future vaccination policies.

Methods: Infectious disease data from 1953 to 2018 was obtained from Xuhui District Center for Disease Control and Prevention, Shanghai China. We used joinpoint regression to show incidence, mortality and fatality trends and to determine annual percent change in incidence of 12 VPDs among three eras of national immunization strategies: (1)1953–1977, (2)1978–2007, and(3)2008–2018.

Findings: Incidence, mortality, and fatality from VPDs have decreased drastically over the three eras, despite the inclusion of more diseases over time. Strikingly, the overall yearly incidence of VPDs shows an increasing trend from 2000 to 2018 in Shanghai (annual percentage changes, APC:7.7, $p = 0.025$). In the third era (2008–2018), the three VPDs with the highest incidence were varicella (80.2 cases/100,000), hand, foot, and mouth disease (HFMD) (73.6 cases/100,000), and hepatitis (43.5 cases/100,000). A significant upward trend was also observed in hepatitis (APC:24.9, $p < 0.001$), varicella (APC:5.9, $p = 0.006$), and HFMD (APC:11.8, $p = 0.003$) from 2008–2018. Hepatitis and tuberculosis are the only VPDs with fatality cases in this period.

Interpretation: Focus is needed in controlling adult hepatitis and tuberculosis, either by introducing adult booster vaccines or by research into more effective vaccines. Varicella and HFMD are on the rise, but vaccines for these are not included in national programs. Strategies funded by government agencies or encouraged by research incentives are needed for varicella and HFMD, such as two-dose and novel multi-valent vaccines, respectively.

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Research in context

Evidence before this study

National immunization programs worldwide have shown to be effective in preventing many infectious diseases or vaccine preventable diseases (VPDs). However, recurring outbreaks of infectious diseases highlight the importance of population vaccination strategies and their upkeep. Papers published within the last 10 years illustrate that hepatitis A and tuberculosis remain the most commonly reported VPDs in many parts of the world. Increasing trends were seen in measles in USA (2001–2011). Meanwhile, indigenous children and those under 2 years old were most affected by pneumococcal meningitis and invasive pneumococcal disease and remain primary vaccination targets in western Australia. Studies based on most of VPDs from national surveillance data are limited. We searched PubMed and web of knowledge up until December 1st 2020, using keywords (“vaccine preventable diseases”) AND (“incidence” or “morbidity”) AND (“national immunization” or “national vaccine recommendations”) AND (“population based” or “surveillance”).

Added value of this study

We have identified six reports separately from the United States, Singapore, Italy, Vietnam, Australia and China. These studies, primarily describe changes in vaccination procedures and comparisons of morbidity and mortality in their respective countries. Our study builds on these previous evidences, utilizing data from the well-organized population-based registry system on infectious diseases in Shanghai (1953–2018). Our study adds important information to VPD epidemiology since the setting is China, a country with a large proportion of infectious diseases globally and different vaccines included in the national immunization program than in other countries. Through trend analysis, we have identified changes in high-burden VPDs over time and different age groups with higher disease burden. This is in contrast to a majority of the previous studies having only reported overall disease occurrence, which does not help to identify vulnerable populations for further intervention.

Implications of all the available evidence

Despite most VPDs having been eliminated after a long-term and progressive scale-up of the national immunization program in China, adult hepatitis and tuberculosis still pose as burdens to the Chinese population. This highlights the necessity of introducing adult booster vaccines or research into more effective vaccines. Meanwhile, varicella and hand, foot, mouth disease appear on the rise among the young generation. Our results provide much needed reference data from which policymakers in China can better identify vulnerable populations that can benefit with further expanded immunization and public health programs or with further research into new vaccines.

1. Introduction

In the past, infectious diseases were a major threat to human health and had been critical factors in reduced life expectancy. Improvements in nutrition, sanitation and public health policies have led to the decrease in incidence of infectious diseases and correspondingly, to increases in average life expectancy [1]. However, these factors alone may not be enough to ensure population health in the emergence of novel infectious diseases, such as the 2019 coronavirus (COVID-19). In light of this recent epidemic, it is clear

that infectious diseases still play an important role in global health policy, transportation safety and economy [2].

It is estimated that around 2–3 million deaths annually throughout the world are averted due to vaccinations [3]. China has one of the largest and oldest immunization programs in the world, producing approximately 700 million doses of vaccines each year [4]. As vaccination coverage for basic vaccines increased significantly since the 1980s [5], the number of cases of vaccine-preventable diseases (VPDs) have decreased significantly in China [6].

Shanghai is one of China's largest cities with higher standards for healthcare and with more regulated public health policy. Since the introduction of the first vaccination plan in 1978, incidence of most VPDs has remained under control. However, several outbreaks have occurred in recent decades and have affected Shanghai, including a hepatitis A epidemic in 1987 (a result of ingestion of infected blood clams) [7], rubella in 1993 [8], and additionally, persistent outbreaks of varicella, hand, foot, and mouth disease (HFMD) and influenza in the last two decades [9,10]. As one of the leading cities in public health quality, other Chinese cities look to Shanghai for adoption of health policies. Thus, recurrent VPDs outbreaks within Shanghai indicate the need for a detailed assessment of infectious disease trends in order to plan future public health intervention programs. We aimed to illustrate VPDs epidemiology in terms of incidence and mortality among the three stages of nationwide vaccinations, in order to identify vulnerable populations that can benefit with further public health programs.

2. Methods*2.1. Data collection*

Infectious disease data from 1953 to 2003 was obtained from the infectious diseases statistical report of the Xuhui District Center for Disease Control and Prevention (CDC) in Shanghai, China. In that period, medical institutions in Xuhui District reported infectious disease cases to the Xuhui District CDC. Data from 2004 to 2018 was obtained from the National Infectious Disease Reporting System (NIDRS). During this period, clinicians have been required to register patient information in the NIDRS within 24 h of an infectious disease diagnosis. Demographic data was obtained from the Vital Statistics Department of the Xuhui District CDC. Due to the lack of demographic data on the migrant population, this study only includes data of Shanghai residents with household registration. For population trends of different age groups in the studied areas of Shanghai from 1953 to 2018, please see Supplementary Figure 1. Data of vaccine coverage was obtained from Shanghai Immunization Information System.

2.2. China's immunization strategy in different eras

According to China's vaccination strategy, the 66-year period between 1953 and 2018 is divided into three stages: (1) Pre-planned Immunization era (1953–1977); (2) Planned Immunization era (1978–2007), and (3) The Expanded Program on Immunization (EPI, 2008–2018). (1) During the Pre-planned Immunization era, vaccination strategy was to focus vaccinations during the winter and spring seasons of each year. During this period, China introduced diphtheria vaccine in 1953, pertussis vaccine in 1953, Japanese encephalitis vaccine (JEV) in 1953, Bacille Calmette-Guérin vaccine (BCG) in 1954 for tuberculosis, polio vaccine in 1960, measles vaccine (MV) in 1965, diphtheria, tetanus and pertussis combined vaccine (DTP) in 1973, and mumps vaccine in 1976 [11] (Table 1). (2) Under the Planned Immunization era, China began to implement population vaccination strategies for children. Since 1978, China has incorporated four vaccines into its

Table 1
Information on vaccine-preventable diseases and corresponding vaccines in Shanghai, China*.

VPD	Monitoring start (year)	Vaccine availability (year)	Target age group	Inclusion in National Immunization Program	Vaccine coverage in 2018 [‡]
Measles	1953	1965	Susceptible individuals over 8 months	National in 1978	99.4% for 2-dose MMR
Pertussis	1953	1953	Children aged 3 months to 18 months	National in 1978	99.6% for 4-dose DTP
ECM	1953	1980	Children aged 6 months to 6 years	National in 2008	99.6% for 4-dose
JE	1953	1953	Children aged 8 months to 6 years	National in 2008	99.7 for 2-dose
Diphtheria	1953	1953	Children aged 3 months to 6 years	National in 1978	99.6% for 4-dose DTP
Polio	1956	1960	Children aged 2 months to 4 years and susceptible individuals	National in 1978	99.4% for 3-dose
Hepatitis [†]	1956	HepB in 1992 HepA in 1995 HepE in 2012	HepB: Infants 0–6 months of age and susceptible individuals HepA: Children aged over 18 months and susceptible individuals HepE: Susceptible individuals over 16 years	Shanghai in 1996 for HepB National in 2002 for HepB National in 2008 for HepA	99.4% for 3-dose HepB 99.5% for 2-dose HepA 0.0% for HepE
Tuberculosis	1990	1954	Newborn	National in 1978	99.4% for 1-dose BCG
Mumps	1990	1976	Susceptible individuals over 8 months	National in 2008	99.4% for 2-dose MMR
Rubella	1990	1998	Susceptible individuals over 8 months	National in 2008	99.4% for 2-dose MMR
Varicella	2005	1998	Susceptible individuals over 12 months	Shanghai in August 2018	99.6% for 2-dose
HFMD	2007	2016	Susceptible individuals over 6 months	Not included	40.7% for 2-dose among children aged ≤5 years

VPD: vaccine-preventable disease; ECM: Epidemic cerebrospinal meningitis; JE: Japanese encephalitis; HFMD: hand, foot, and mouth disease; HepB: hepatitis B vaccine; HepA: hepatitis A vaccine; HepE: hepatitis E vaccine; MMR: measles, mumps and rubella combined vaccine; DTP: diphtheria, tetanus and pertussis combined vaccine; BCG: Bacille Calmette-Guérin vaccine.

* Surveillance for neonatal tetanus began in 1953 and the vaccine was introduced in 1957 for children aged 3–6 years, high-risk population and post-traumatic immunization. The DTP vaccine was included in national immunization in 1978. No cases of neonatal tetanus were reported during the period 1953–2018.

[†] Cases of hepatitis can be classified as hepatitis A, B, C and E. Currently, HepE is not included in China's or Shanghai's immunization program. As of 2018, we have not found any records of Shanghai residents getting hepatitis E vaccine in the Shanghai Immunization Information System.

[‡] The vaccine coverage here is not for the whole population, but for the children of the respective vaccination procedures.

national immunization program, including BCG, DTP, polio vaccine and MV. From 1978–2007, eight additional vaccines were introduced for children and susceptible individuals on a voluntary basis in China, including Group A meningococcal polysaccharide vaccine (MPV-A) in 1982, hepatitis B vaccine (HepB) in 1992, hepatitis A vaccine (HepA) in 1995, rubella vaccine in 1998, Group A and C meningococcal polysaccharide vaccine (MPV-AC) in 2002, measles and rubella combined vaccine (MR) in 2002, measles, mumps and rubella combined vaccine (MMR) in 2002, and measles and mumps combined vaccine (MM) in 2003 [11–13]. HepB was included in the national immunization program for free in 2002 [12]. (3) In EPI era, based on the five vaccines in the national immunization program, China incorporated HepA, MPV-A, MPV-AC JEV, and MMR vaccines into the national immunization program. Hepatitis E vaccine (HepE) has been used for susceptible individuals aged over 16 years on a voluntary basis since 2012 [14].

2.3. Vaccine-preventable diseases (VPDs)

The national immunization program covers vaccines for: measles, pertussis, epidemic cerebrospinal meningitis (ECM), JE, diphtheria, tetanus, polio, hepatitis B, tuberculosis, mumps, rubella, hepatitis A (Table 1). Hepatitis cases in China have been typed since 1990, first into hepatitis A and hepatitis B, and then into hepatitis C and hepatitis E in 1997, but there are still some cases of hepatitis that have not been classified. Therefore, we combined all hepatitis cases together as one VPD for analysis in this study. We

also analyzed hepatitis into five subgroups: hepatitis A, hepatitis B, hepatitis C, hepatitis E, and unclassified. Furthermore, varicella and HFMD began to be monitored in 2005 and 2007, respectively, in Shanghai, China. Although vaccines against these two diseases have been licensed for children in 1998 and 2016, respectively, they are not included in the national immunization program. Since no cases of tetanus were reported in Xuhui District from 1953 to 2018, a total of 12 VPDs were included in this present study: ten VPDs prevented by national immunization planning vaccines and two VPDs prevented by non-national immunization planning vaccines.

2.4. Statistical analysis

Incidence was defined as the number of incident disease cases divided by the total population size. Average yearly incidence was the average of incidence of all years in each of the three vaccination periods. Mortality was defined as the number of deaths divided by the total population size. Fatality was defined as the number of deaths divided by the total number of incident cases. Chi-square tests were used to compare incidence, mortality and fatality from different years or immunization periods. Joinpoint regression modelling was used to determine incidence, mortality and fatality trends. Annual percentage changes (APC) of all 12 VPDs separately and combined, from 1953 to 2018, were calculated. APC is estimated by the joinpoint regression program of the American Cancer Research Center. APC represents the slope of a given trend, where $APC < 0$ indicates a downward trend year by year and $APC > 0$ in-

dicates an upward trend year by year. The significance test for a change in trend is the *t*-test of interval slope, and a *p* value of <0.05 was considered significant. An APC with *p* value ≥ 0.05 (non-significant) indicates a stable trend of disease.

Incidence or mortality within five-year intervals were compared, in which the highest rate was used as the denominator. Values for this proportion ranged from 0 (lowest) to 1 (highest) and colored according to the gradient of a heat map. Trends in incidence, mortality and fatality for VPDs by age were also analyzed. These were limited to two vaccination periods (1990–2007 and 2008–2018) as earlier years records had no age-related information. Changes in incidence and mortality of VPDs among 5-year age groups between 1990–2007 and 2008–2018 were depicted in a heat map, in which the highest rate among all age groups was used as the denominator for each period separately. Data were analyzed by SPSS 18.0 and Joinpoint (version 4.3.1). Excel software was used to make bubble diagrams, curve charts and heat maps.

2.5. Role of funding source

The funders of this study had no role in the study design, data collection, data analysis, interpretation or the writing of this report. The corresponding authors had full access to all the data and had final responsibility for the decision to submit for publication.

3. Results

3.1. VPDs in three immunization eras

During the period 1953–2018, a total of 276,576 cases of VPDs were reported in Xuhui District of Shanghai, China. Of these cases, 175,543 were reported during Pre-planned Immunization (1953–1977), 78,198 were reported during Planned Immunization (1978–2007), and 22,835 were reported during EPI (2008–2018) (Table 2).

From 1953–1977, seven VPDs were managed: measles, pertussis, ECM, JE, diphtheria, polio and hepatitis. Of these VPDs, the top three in incidence were measles (1014.6 cases/100,000), hepatitis (352.7 cases/100,000), and pertussis (279.8 cases/100,000), which accounted for 96.8% of reported cases during that period. Among the cases in this period, a total of 1362 deaths were recorded, resulting in a fatality of 7.8 deaths per 1000 VPDs cases. The top three VPDs in fatality were JE (150.3 deaths/1000 cases), polio (61.6 deaths/1000 cases), and ECM (33.1 deaths/1000 cases).

From 1978–2007 another five VPDs were managed: tuberculosis, mumps, rubella, varicella, and HFMD. During this period, the three VPDs with the highest incidence were hepatitis (221.3 cases/100,000), mumps (106.3 cases/100,000), and varicella (74.5 cases/100,000). Among all cases in this period, a total of 218 deaths were recorded, resulting in a case fatality rate of 2.8 deaths per 1000 VPD cases. The top three VPDs in fatality were JE (101.7 deaths/1000 cases), tuberculosis (21.4 deaths/1000 cases), and ECM (9.9 deaths/1000 cases).

During the EPI era (2008–2018), the incidence of all 12 VPDs together was 227.2 cases /100,000. The majority of new cases were of varicella (80.2 cases/100,000) and HFMD (73.6 cases /100,000), accounting for over 67.7% of new VPD cases. The third highest incidence was hepatitis (43.5 cases /100,000), of which more than two-thirds was hepatitis B (68.8%, 3009/4376), followed by hepatitis C (17.7%, 773/4376) and hepatitis E (10.2%, 445/4376). During this period, three VPDs (JE, diphtheria, and polio) had no reported cases and the incidence of four VPDs (measles, pertussis, ECM, and, rubella) was no higher than 0.5 cases per 100,000 individuals. Only two VPDs incurred fatalities in this period: tuberculosis (12.1 deaths/1000 cases) and hepatitis (2.5 deaths/1000 cases), resulting in a total number of 34 deaths and a fatality rate of 1.5 per 1000 VPD cases (Table 2).

3.2. Trends in incidence, mortality, and fatality

The total average annual incidence of VPDs had significantly decreased over the periods of immunization, despite the inclusion of more diseases over time. Compared to the first period (Pre-planned Immunization), the second period (Planned Immunization) had significantly lower incidence of VPD (1663.2 vs 361.4 cases/100,000; chi square value = 15,375.2, $p < 0.001$), even though 5 additional VPDs were included in the second period. The third period (EPI) had significant reductions in incidence of overall VPDs compared to the second period (227.2 vs. 361.4 cases/100,000; chi square value = 3876.6, $p < 0.001$).

A depiction of annual number of new VPD cases are shown in Fig. 1, and their respective year of monitoring start and vaccines availability are shown in Table 1. City- and nation-wide outbreaks of hepatitis A in 1987 and rubella in 1993, respectively, show a sudden increase in the number of cases in Shanghai. Although measles did not have a significant downward trend in the Pre-planned Immunization era (APC = -5.2 [95%CI: -11.9 to 2.0], $p = 0.148$), a significant downward trend was observed in the second period (Planned Immunization era) (APC = -5.9 [95%CI: -9.0 to -2.7], $p < 0.001$), followed by stabilization in the third period (EPI era) (Table 3). Pertussis showed a significant downward trend before stabilizing in the third period. Diphtheria and polio showed significant downward trends in the first period and stabilized since the second period. Hepatitis did not show an upward or downward trend in the first two periods, but showed an upward trend in the third period (APC = 24.9 [95%CI: 16.8 to 33.7], $p < 0.001$), as did varicella (APC = 5.9 [95%CI: 2.1 to 9.8], $p = 0.006$), and HFMD (APC = 11.8 [95%CI: 4.9 to 19.0], $p = 0.003$). As for hepatitis, in the last two eras, hepatitis C increased continuously, hepatitis B decreased and then increased, hepatitis A decreased and then stabilized, and hepatitis E remained stable (Table 3). ECM showed a significant upward trend in the first period, followed by a downward trend in the second period. JE and rubella showed a stable and then downward trend in the two monitored periods. Incidence of tuberculosis stabilized after having a downward trend in the second period (Table 3).

With the overall incidence trend, two rising periods were observed, mainly in the years 1953–1958 (APC: 29.8, $p = 0.015$), and 2000–2018 (APC: 7.7, $p = 0.025$). Two decline periods were also identified: 1958–1985 (APC: -12.5, $p < 0.001$) and 1988–2000 (APC: -25.2, $p < 0.001$). With regards to mortality, two significant periods of downward trend were observed: 1953–1969 (APC: -13.4, $p < 0.001$) and 1969–2018 (APC: -5.4, $p < 0.001$). Overall downward trends for fatality were observed, although two period of non-significant increase trends were observed in 1964–1968 (APC: 42.6, $p = 0.099$), and 1992–2002 (APC: 20.1, $p = 0.067$) (Fig. 2A to C). Incidence and mortality within 5-year intervals of the different VPDs have been compared. The VPDs with the highest incidence changed from measles in the early of Pre-planned Immunization era, to hepatitis in the Planned Immunization era, to HFMD and varicella in the EPI era (Fig. 2D). A general shift from measles, to hepatitis, and to tuberculosis as the diseases with highest mortality was observed over time (Fig. 2E).

3.3. Incidence, mortality, and fatality in different age groups

In the period of available age data, 1990–2018, the highest incidence of 8 VPDs (excluding diphtheria and polio due to no reported cases, and varicella and HFMD due to no data from 1990–2004) was found in children under 10 years old. In the period of EPI (2008–2018), incidence was significantly lower than the period of 1990–2007 of Planned Immunization in each age group except for ≥ 85 years of age, Fig. 3A. The overall incidence was also significantly lower than the period of Planned Immuniza-

Table 2
Incidence and case-fatality for 12 vaccine-preventable infectious diseases among different immunization eras in Shanghai, China, from 1953 to 2018.

VPDs	Year of start monitoring	Pre-planned immunization era* (1953–1977)				Planned immunization era (1978–2007)				EPI era (2008–2018)				Total (1953–2018)			
		Cases (n)	Incidence [†]	Deaths (n)	Average fatality [‡]	Cases (n)	Incidence [†]	Deaths (n)	Average fatality [‡]	Cases (n)	Incidence [†]	Deaths (n)	Average fatality [‡]	Cases (n)	Incidence [†]	Deaths (n)	Average fatality [‡]
Measles	1953	107,088	1014.6	766	7.2	286	1.3	0	0.0	54	0.5	0	0.0	107,428	254.3	766	7.1
Pertussis	1953	29,536	279.8	38	1.3	435	2.0	0	0.0	3	0.0	0	0.0	29,974	71.0	38	1.3
ECM	1953	3080	29.2	102	33.1	101	0.5	1	9.9	1	0.0	0	0.0	3182	7.5	103	32.4
JE	1953	985	9.3	148	150.3	118	0.5	12	101.7	0	0.0	0	/	1103	2.6	160	145.1
Diphtheria	1953	844	8.0	26	30.8	0	0.0	0	/	0	0.0	0	/	844	2.0	26	30.8
Polio	1956	633	6.7	39	61.6	0	0.0	0	/	0	0.0	0	/	633	1.5	39	61.6
Hepatitis [§]	1956	33,377	352.7	243	7.3	47,879	221.3	100	2.1	4376	43.5	11	2.5	85,632	208.1	354	4.1
Hepatitis A	1990	–	–	–	–	1313	8.8	5	3.8	111	1.1	0	0.0	1424	5.7	5	3.5
Hepatitis B	1990	–	–	–	–	1737	11.6	15	8.6	3009	29.9	8	2.7	4746	19.0	23	4.8
Hepatitis C	1997	–	–	–	–	76	0.8	0	0.0	773	7.7	0	0.0	849	4.3	0	0.0
Hepatitis E	1997	–	–	–	–	519	5.4	3	5.8	445	4.4	2	4.5	964	4.9	5	5.2
Unclassified	1956	33,377	352.7	243	7.3	44,234	204.4	77	1.7	38	0.4	1	26.3	77,649	188.7	321	4.1
Tuberculosis	1990	–	–	–	–	4903	32.8	105	21.4	1903	18.9	23	12.1	6806	27.2	128	18.8
Mumps	1990	–	–	–	–	15,868	106.3	0	0.0	1016	10.1	0	0.0	16,884	67.6	0	0.0
Rubella	1990	–	–	–	–	6004	40.2	0	0.0	18	0.2	0	0.0	6022	24.1	0	0.0
Varicella	2005	–	–	–	–	1987	74.5	0	0.0	8066	80.2	0	0.0	10,053	79.0	0	0.0
HFMD	2007	–	–	–	–	617	69.4	0	0.0	7398	73.6	0	0.0	8015	73.2	0	0.0
Total		175,543	1663.2	1362	7.8	78,198	361.4	218	2.8	22,835	227.2	34	1.5	276,576	654.7	1614	5.8

VPDs: vaccine-preventable diseases; EPI: The Expanded Program on Immunization; ECM: Epidemic cerebrospinal meningitis; JE: Japanese encephalitis; HFMD: hand, foot, and mouth disease.

Values that consist of a single hyphen (-) indicate that no data were collected.

Values that consist of a forward slash (/) indicate that case-fatality ratios could not be calculated due to 0 yearly incidence of the disease.

* Information on select infectious diseases in the Pre-planned immunization era was available: measles, pertussis, ECM, JE, diphtheria, hepatitis, and polio.

[†] per 100,000.

[‡] per 1000.

[§] Hepatitis cases in China have been typed since 1990, first into hepatitis A and hepatitis B, and then into hepatitis C and hepatitis E in 1997, but there are still some cases of hepatitis that have not been classified. Therefore, we combined all hepatitis cases together as one VPD and further divided hepatitis into five subgroups for analysis.

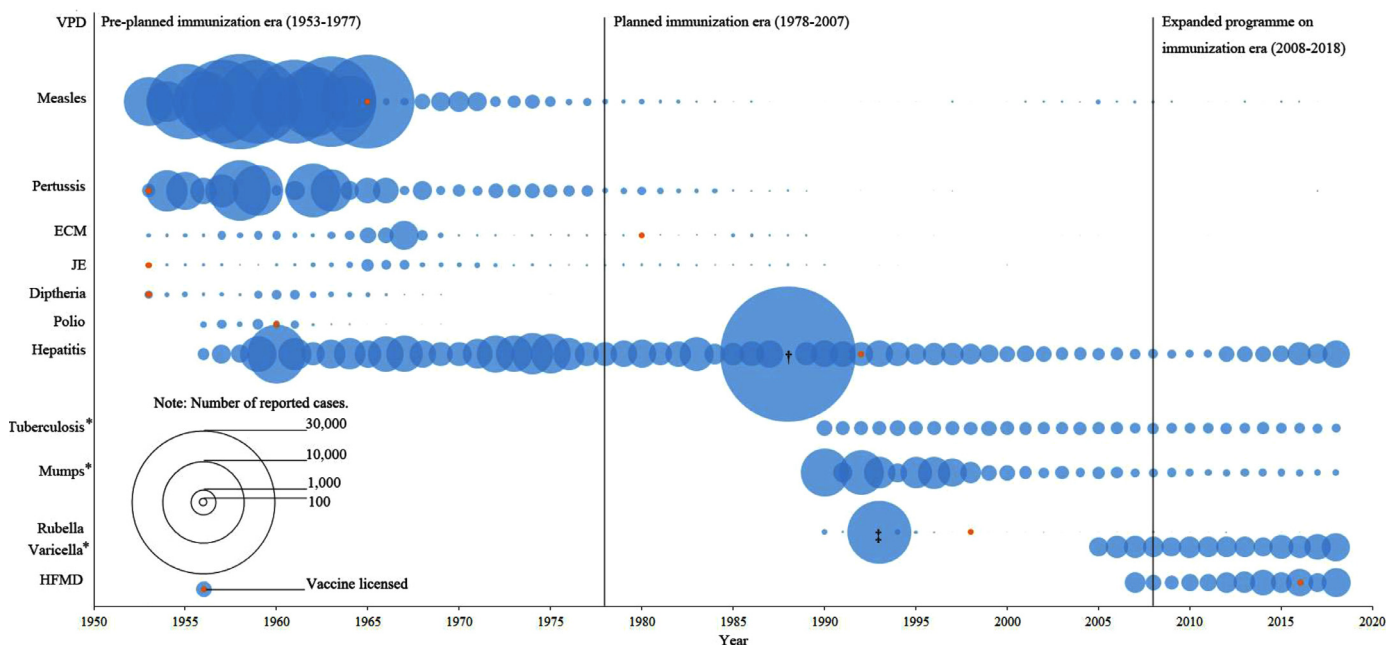


Fig. 1. Number of reported cases of 12 vaccine-preventable infectious diseases within three different immunization eras, represented as bubble diagrams. VPD: vaccine-preventable disease; ECM: Epidemic cerebrospinal meningitis; JE: Japanese encephalitis; HFMD: hand, foot, and mouth disease. Vertical lines indicate the start of a new immunization era: 1978 and 2008. Sphere (or “bubble”) size indicates the annual number of cases, which is proportional to the size indicated by the legend key. A red sphere indicates the year of vaccine licensing. Asterisks (*) indicate that the vaccine used to prevent the infectious disease was available earlier than the time of disease surveillance and is not identified in the figure. Dagger (†) indicates outbreak of hepatitis A in 1987 in Shanghai, China. Double dagger (‡) indicates outbreak of rubella in 1993 in China.

Table 3
Annual percentage change in incidence of 12 vaccine-preventable infectious diseases among different immunization eras in Shanghai, China, from 1953 to 2018.

VPDs	Pre-planned immunization era (1953–1977)			Planned immunization era (1978–2007)			EPI era (2008–2018)		
	APC*	(95% CI)*	P value	APC*	(95% CI)*	P value	APC*	(95% CI)*	P value
Measles	-5.2	(-11.9 to 2.0)	0.148	-5.9	(-9.0 to -2.7)	<0.001	-9.7	(-20.4 to 2.5)	0.102
Pertussis	-11.1	(-16.6 to -5.1)	0.001	-24.2	(-29.4 to -18.6)	<0.001	/	/	/
ECM	18.2	(4.0 to 34.4)	0.013	-11.8	(-16.3 to -7.1)	<0.001	/	/	/
JE	2.4	(-7.0 to 12.9)	0.611	-12.3	(-16.9 to -7.4)	<0.001	/	/	/
Diphtheria	-8.3	(-15.7 to -0.3)	0.043	/	/	/	/	/	/
Polio	-19.4	(-34.3 to -1.2)	0.040	/	/	/	/	/	/
Hepatitis†	-0.7	(-5.0 to 3.8)	0.752	-10.9	(-21.5 to 1.1)	0.073	24.9	(16.8 to 33.7)	<0.001
Hepatitis A	-	-	-	-7.8	(-11.9 to -3.5)	0.002	3.1	(-4.2 to 11.0)	0.367
Hepatitis B	-	-	-	-4.0	(-6.7 to -1.1)	0.001	32.0	(19.1 to 46.4)	<0.001
Hepatitis C	-	-	-	25.0	(12.8 to 38.5)	<0.001	17.3	(7.4 to 28.2)	0.002
Hepatitis E	-	-	-	3.6	(-10.4 to 19.7)	0.596	3.5	(-2.5 to 9.8)	0.223
Unclassified	-0.7	(-5.0 to 3.8)	0.752	-6.3	(-20.1 to 9.9)	0.412	-19.3	(-29.3 to -7.9)	0.005
Tuberculosis	-	-	-	-4.2	(-5.1 to -3.2)	<0.001	-2.2	(-4.8 to 0.4)	0.087
Mumps	-	-	-	-18.5	(-22.9 to -13.7)	<0.001	-5.7	(-9.3 to -2.0)	0.008
Rubella	-	-	-	-33.0	(-68.0 to 40.3)	0.267	-15.4	(-24.8 to -4.8)	0.011
Varicella	-	-	-	-	-	-	5.9	(2.1 to 9.8)	0.006
HFMD	-	-	-	-	-	-	11.8	(4.9 to 19.0)	0.003
Total	-7.8	(-11.7 to -3.7)	<0.001	-8.7	(-15.4 to -1.6)	0.020	9.5	(6.2 to 12.8)	<0.001

VPDs: vaccine-preventable disease; EPI: The Expanded Program on Immunization; ECM: Epidemic cerebrospinal meningitis; JE: Japanese encephalitis; HFMD: hand, foot, and mouth disease; APC: Annual percentage changes.

Values that consist of a single hyphen (-) indicate missing data.

Values that consist of a forward slash (/) indicate that APC could not be calculated due to years of non-reporting cases.

* values are in percentage (%).

† Hepatitis cases in China have been typed since 1990, first into hepatitis A and hepatitis B, and then into hepatitis C and hepatitis E in 1997, but there are still some cases of hepatitis that have not been classified. Therefore, we combined all hepatitis cases together as one VPD and further divided hepatitis into five subgroups for analysis.

tion (103.8 vs. 1477.5 cases/100,000; chi square value = 8533.0, $p < 0.001$). The age groups with the highest mortality and fatality among 8 VPDs were ≥ 60 years old (1990–2007) and ≥ 80 years old (2008–2018) (Fig. 3B and C). Mortality in the era of Planned Immunization period was higher than that in the era of EPI (1.1 vs. 0.3 cases/100,000; chi square value = 43.8, $p < 0.001$).

From 1990–2018, four VPDs (pertussis, mumps, varicella, and HFMD) had the highest incidence in children, two VPDs (hepati-

tis and tuberculosis) in adults, and another four VPDs (measles, rubella ECM, and JE) had reported cases in all age groups. Compared with the period of 1990–2007 of Planned Immunization, the incidence of mumps, varicella, rubella, JE, hepatitis, and tuberculosis decreased significantly in all ages under EPI, Fig. 3D. During the period 1990–2018, the age groups with the highest mortality were ≥ 65 years old, with hepatitis and tuberculosis accounting for all deaths. The mortality rates for both hepatitis and tuberculosis de-

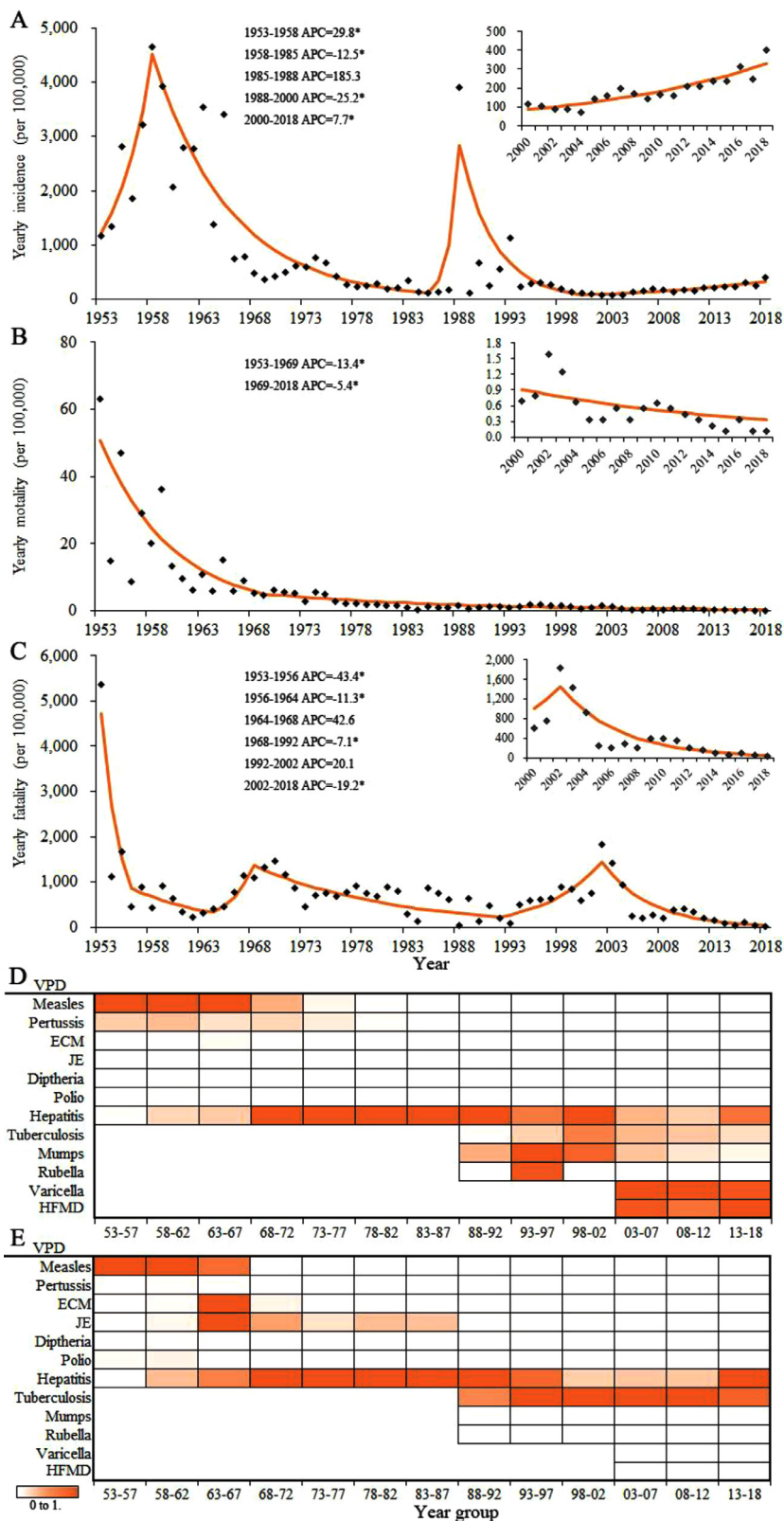


Fig. 2. Annual percentage change and trends in incidence, mortality, and fatality of 12 vaccine-preventable infectious diseases, from 1953 to 2018. APC: Annual percentage change; ECM: Epidemic cerebrospinal meningitis; JE: Japanese encephalitis; HFMD: hand, foot, and mouth disease; VPD: vaccine-preventable infectious disease. (A) Overall yearly incidence, (B) mortality, and (C) fatality. APC for period trends were shown in graphs A, B and C. Black diamonds indicate the observed values and orange curves denote the slope of the APC. Values with * indicate that the APC was significant ($p < 0.05$). Inner small graphs represent a magnified image of the trend in the years 2000–2018. Heat maps for comparison of incidence rates (D), and mortality rates (E) within 5-year intervals. Rates for diseases within each 5-year interval were compared, in which the highest rate was used as the denominator. Values for this proportion ranged from 0 (lowest) to 1 (highest).

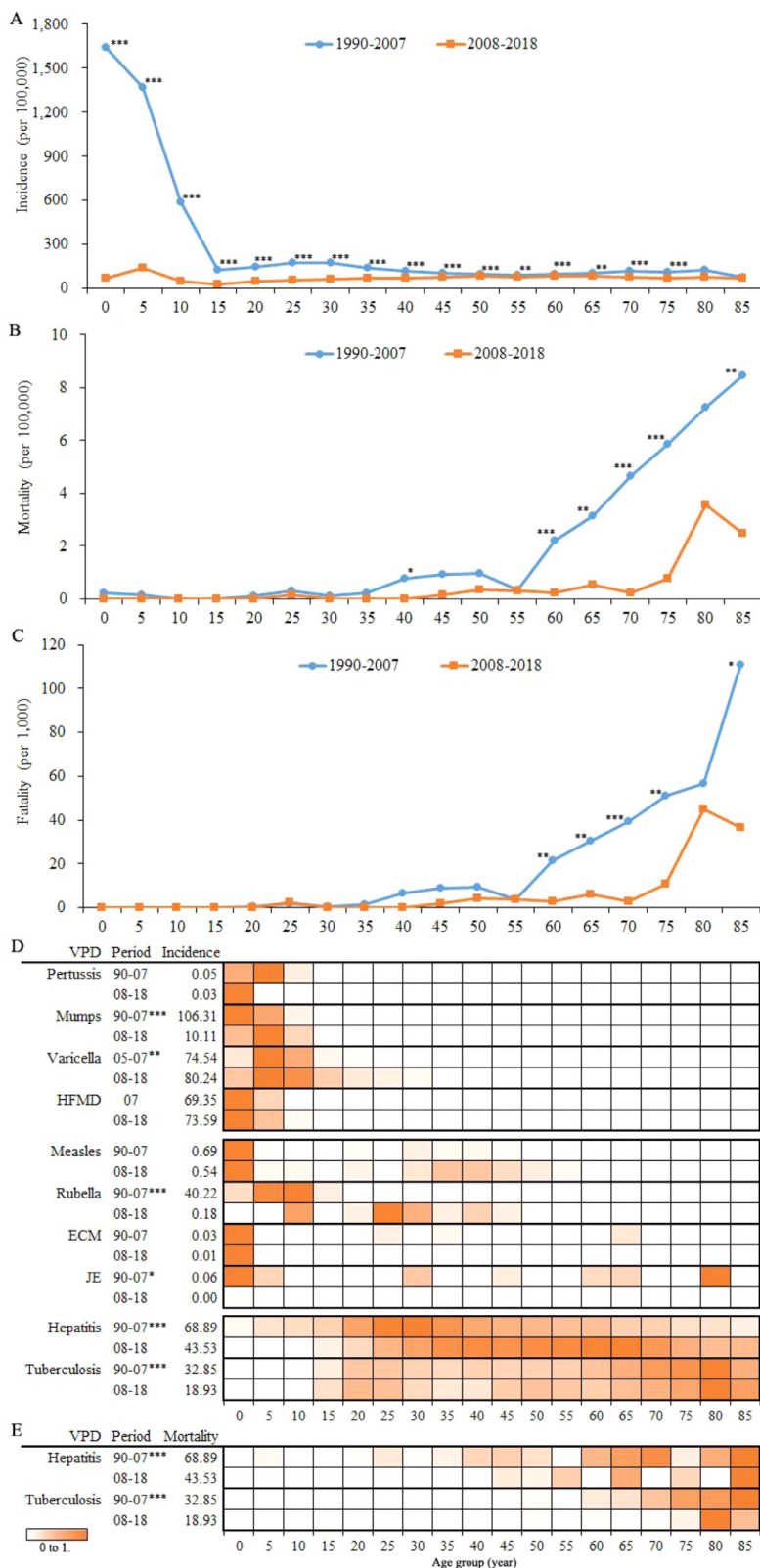


Fig. 3. Trends in incidence, mortality and fatality of vaccine-preventable infectious diseases, by age and vaccination period: 1990–2007 and 2008–2018. ECM: Epidemic cerebrospinal meningitis; JE: Japanese encephalitis; HFMD: hand, foot, and mouth disease; VPD: vaccine-preventable infectious disease; 90–07: 1990–2007 period; 08–18: 2008–2018 period. (A) incidence, (B) mortality, and (C) fatality of eight[†] vaccine-preventable infectious diseases by age and vaccination period. (D) incidence, and (E) mortality for vaccine-preventable infectious diseases among age groups in two different immunization periods, presented as a heat map. These vaccine-preventable infectious diseases are grouped according to whether they had high incidence among children (pertussis, mumps, varicella, and HFMD), high incidence among adults (hepatitis and tuberculosis), and no significant features in terms of incidence by age (measles, rubella, ECM, and JE). Incidence and mortality for diseases within each 5-year age group were compared, in which the highest incidence or mortality rate among all age groups was used as the denominator. The two periods were analyzed separately. Values for this proportion ranged from 0 (lowest) to 1 (highest).

An asterisk (*) indicates a statistically significant difference between the rates of the two vaccination periods.

[†]Diphtheria and polio were not included in the analysis due to no reported cases during 1990–2018. Varicella and HFMD were not included since no data was collected during 1990–2004.

creased significantly during the EPI era compared to 1990–2007, Fig. 3E.

4. Discussion

4.1. Vaccinations and infectious diseases control

We show that within 66 years, from 1953 to 2018, the overall incidence of VPDs in Shanghai has decreased over the three periods of immunization strategy. Correspondingly, mortality and fatality from the 12 VPDs has fallen throughout the periods. At EPI era, the most recent period, there were no reported deaths in ten of the 12 VPDs, and there was a total incidence of less than 1 per 100,000 in seven VPDs. We believe that the increasing vaccine coverage has played a significant role in the dramatic reduction of incidence, mortality and fatality from VPDs in Shanghai. Our findings in Shanghai, China follow those found nationally [6] and globally, where vaccination programs over time have helped to reduce VPDs in high-income, such as Italy and the United States, [15,16] and low- and middle-income countries, such as Vietnam and others [17,18]. In Vietnam, case-fatality for measles, pertussis, diphtheria and polio declined in 1980 to 2010, and up to 5.7 million disease cases and 26,000 deaths may have been prevented by EPI [18]. In comparison with the period before national vaccination recommendations, the number of reported VPD cases show greater than 99% decline in 2006 in the United States [16]. These reports give us reason to believe that vaccines are one of the greatest achievements of biomedical science and public health.

Strikingly, within the past two decades, the overall yearly incidence of VPDs shows an increasing trend from 2000 to 2018 in Shanghai. Similarly, Yang et al. have reported nation-wide increasing trend on incidence of infectious diseases from 2004 to 2013 [19]. The main reason was that the incidence of two newly managed VPDs (varicella from 2005 and HFMD from 2007) are on the rise during EPI era. In addition, this is also likely due to more efficient reporting and improvements in detection and diagnostic technologies at hospitals and clinics. Moreover, the increase in VPDs incidence likely reflects the post-severe acute respiratory syndrome (2003) epidemic, where there is more awareness, funding, and stricter government mandates about reporting infectious diseases [19]. In China, the annual total health expenditure increased from RMB 11 billion in 1978 to RMB 5912.2 billion in 2018 [20]. Since 2002, the Chinese government has increased its annual budget for tuberculosis detection, reporting and prevention from USD \$300 000/year to \$4.8 million [21]. This is affirmed with the decreasing trend in annual fatality and mortality from 2000 to 2018 despite higher incidences of VPDs.

4.2. EPI strategy in controlling infectious diseases among children

We have identified that the highest incidence of VPDs in all periods is generally among children. During the most recent period (EPI), there have been significant reductions in incidence of VPDs among children under 15 years of age compared to 1990–2007 of the Planned Immunization era. This is largely attributed to the dramatic decline in the incidence of rubella and mumps in children as a result of the introduction of MM, MR, MMR since 2002–2003 and the inclusion of MMR in the national immunization program since 2008. However, the top two infectious diseases with the highest yearly incidence are varicella and HFMD, which are also highly prevalent among children. In childcare institutions and schools, outbreaks of varicella [10] and HFMD occur frequently. In addition, both diseases are associated with complications, posing as public health burdens and should not be ignored [22].

In Shanghai, although one-dose varicella vaccine coverage for schoolchildren aged 3–15 years in 2011 was 88.1% [10] it has not

prevented breakthrough cases or school outbreaks [10]. A two-dose varicella vaccine strategy may be the answer. Two-dose strategies, either short (<1 year) or long interval (≥ 4 years) in Germany and Italy, respectively, have been found to significantly reduce varicella-related hospitalizations [23]. A two-dose strategy has been included into Shanghai's immunization program since August 2018 [10]. In Shanghai, the first dose varicella vaccine is targeted to children aged 1 years old and the second dose at 4 years old, with a 99.6% total coverage for 4-year-olds in 2018. This two-dose strategy may be very useful for the prevention of future varicella cases in China if it can be included in the national immunization program.

The current HFMD vaccine, administered since 2016, was only developed to prevent severe HFMD caused by the enterovirus EV-A71 strain, and not other emerging strains [24]. Moreover, the coverage of the HFMD vaccine in Shanghai and other provinces was relatively low [25] as it is not in the national immunization program and many parents' insufficient awareness of HFMD has likely lead to their unwillingness to vaccinate their children [26]. It is estimated that the incidence of severe HFMD and EV71 HFMD decreased by 52% and 60%, respectively, after introduction of HFMD vaccine in Chengdu, China [25]. Therefore, improving public knowledge of HFMD, accelerating the process of developing multivalent HFMD vaccines, and integrating new vaccines into national immunization programs would help increase immunization coverage to decrease the burden of HFMD.

4.3. The importance of controlling adult VPDs

Although in our report the highest incidence of VPDs is among children, the highest mortality from VPDs is among people over 60 years of age. This remains true for the 2008–2018 period, even though mortality has decreased drastically compared to the 1990–2007 period. Currently, the disease burden among the elderly population is mainly from hepatitis and tuberculosis, with high incidence and mortality. In China, the proportion of infected HBV individuals aged more than 55 years increased from 11.0% in 2004 to 25.2% in 2014 [27]. Shanghai has a high proportion of elderly; roughly 23% are aged 65 years or older [35], which is above the estimated national proportion of 11.9% [20] (in 2018). Moreover, vaccination of the elderly can directly help decrease healthcare costs by preventing VPDs and expensive complications that may arise from these [28]. This emphasizes that with the ageing population, more care in prevention of hepatitis and tuberculosis are needed in the elderly.

For younger and middle-aged adults, aged 20–60 years old, there is a higher incidence of hepatitis and tuberculosis compared to other VPDs. Notably, the incidence of hepatitis has remained within the top three infectious diseases with the highest incidence and it is the VPDs with the highest increasing trend from 2008–2018. Consistent with other national surveillance data, we found that hepatitis B continues to dominate the incidence of hepatitis cases and that hepatitis C continues to increase in Shanghai [19,27]. In addition, in China, the reported incidence of hepatitis E is gradually increasing in people older than 20 years of age, and the reported incidence increases with age [29]. In this age group, mortality is also only from hepatitis and tuberculosis. Therefore, more efforts to control the incidence and fatality of hepatitis and tuberculosis in adults are needed. Although the HBV surface antigen prevalence declined 52% in 2014 after 3 decades of escalating vaccination policy in China [30], the prevalence of HBV infection in adults older than 20 years was still as high as 7% [31]. To reduce the incidence of hepatitis, HepB and HepE should be considered in adults, especially in high-risk groups [29,32]. BCG is the only TB vaccine that is available for human use. It is effective in preventing TB in children and infants [33], however this protection is likely lost in adulthood [34]. This stresses the need for novel TB vaccines

or more effective BCG vaccines and government-led immunization programs for the adult population.

4.4. Strengths and limitations of this study

Several strengths distinguish this study. Our surveillance data span up to 66 years, allowing us to observe the impact on VPDs from three different vaccine immunization strategies. We also analyzed trends in the incidence of varicella and HFMD that were not prevented by the two non-national immunization planning vaccines. In this study, we identified vulnerable populations that can benefit with further public health programs: more targeted care into varicella and HFMD in children under 15 years old, and control of hepatitis and tuberculosis in adults and the elderly.

Our study is also not without several shortcomings. Firstly, VPD monitoring data before 2003 may have been under-reported and incomplete, which led to an underestimation of the effectiveness of vaccines and immunization programs in controlling VPDs. In recent years technological advances has allowed for quicker and more complete reporting, and more accurate diagnoses in hospitals, thus increasing incidence reports of VPDs compared to previous years. Thus, it is likely that the VPD burden in Shanghai has actually reduced more drastically since 1953 than we report. Moreover, early data before 1990 was incomplete, lacking basic information such as age. Thus, age-specific incidence of VPDs was only available for the period of 1990–2018. Secondly, over the 66 years of surveillance, the International Classification of Diseases (ICD) has changed for some infectious diseases, which may affect our findings, albeit slightly since most infectious disease classifications rely on microbiological testing, epidemiological history and not solely on symptoms (Supplementary Table 1). Thirdly, this study includes only the population with household registration in Shanghai. As there are many migrant and unregistered workers in Shanghai, we cannot see the full depiction of the VPDs burden on the entire population. Fourthly, Shanghai has higher public health quality and awareness compared to other areas in China, hence our findings may not be representative of all of China. Fifthly, the decline in VPDs that we report may not entirely be dependent on vaccination, and the effect of improved nutrition, healthcare and living conditions cannot be ignored.

4.5. Conclusions and recommendations

Our study has affirmed that vaccination has a significant effect in controlling incidence, mortality and fatality of infectious diseases. However, there is still room for improvement by reducing VPDs that are on the rise in the recent EPI 2008–2018 period, such as hepatitis, varicella and HFMD, as well as the VPDs with the highest mortality, such as hepatitis and tuberculosis. Therefore, there should be more focus on controlling adult hepatitis and tuberculosis, either by introducing adult booster vaccines or by research into more effective vaccines. In addition, the number of cases of varicella and HFMD are the top two of all 12 VPDs, but vaccines are not currently included in the national immunization program (ie. are not mandatory). With regards to varicella, a two-dose varicella vaccine strategy should be promoted in children and gradually included it into national immunization programs. In addition, there is a need to further increase the coverage of HFMD vaccine among children and to develop a multi-valent vaccine for HFMD. Finally, China needs to include more WHO-recommended vaccines into its national immunization program, such as human papillomavirus vaccine, HepB-Haemophilus influenzae type b conjugate vaccine, oral rotavirus vaccine, pneumococcal conjugate vaccine and influenza vaccine.

Contributors

QW, MZ, YH, and JL designed the study. CW, HG, MS, and JZ collected data. QW and ZX analyzed data. QW and MZ interpreted data and wrote the report. QW, MZ, ZX, CW, HG, MS, JZ, YH, and JL revised the report from preliminary draft to submission. YH and JL supervised the study. All authors contributed to and approved the final version of the manuscript.

Data sharing statement

The study protocol, statistical analysis plan, and deidentified data that underlie the results of this article will be available for investigators after approval by the Academic Board of the Xuhui District Center for Disease Control and Prevention in Shanghai, China. Please email the corresponding author for more information.

Declaration of Competing Interest

We declare no competing interests.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.lanwpc.2021.100092](https://doi.org/10.1016/j.lanwpc.2021.100092).

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