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Incidence trend and disease burden of seven vaccine-preventable diseases in Shandong province, China, 2013–2017: Findings from a population-based observational study



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ABSTRACT

Introduction: Although vaccines provide a cost-effective solution to vaccine-preventable diseases (VPDs), the disease burden of VPDs is still very high in most parts of the world.

Methods: A population-based observational study was conducted in Shandong province, China, from 2013 to 2017, giving an insight into the epidemiological characteristics and disease burden of seven VPDs. The incidence trend was estimated using the *Poisson* regression model. The disease burden was calculated using the disability-adjusted life years (DALYs).

Results: Most VPDs included in the China's National Immunization Program had higher incidence density (ID) in inland cities. The ID of mumps decreased significantly, while herpes zoster increased (both P < 0.05). The top three causes of the disease burden as assessed with DALYs included tuberculosis, herpes zoster, and hepatitis B, with the rates of 72.21, 59.99, and 52.10 DALYs/100 000, respectively. The disease burden of influenza and herpes zoster were relatively high in people aged > 50 years, while highest DALYs of hepatitis B were found in young adults.

Conclusion: Inequalities in the vaccine coverage by geography, socio-economic status, and targeted population contribute to the increasing incidence and high burden of VPDs and call for renewed and sustained immunization strategies in China.

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Background

As part of a comprehensive intervention package for disease prevention and control, vaccination prevents approximately 2.5 million deaths each year globally [1]. Since 2007, the Chinese government has actively expanded the National Immunization Program (NIP), which included 15 vaccine-preventable diseases (VPDs) [2], and has led to a sharp reduction in the total number of cases of VPDs nationwide. However, the disease burden of VPDs

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is still heavy, posing a huge threat to the public health in China. Understanding the epidemiological characteristics of VPDs is the most important task for controlling them and reducing their disease burden [3].

From 2004 to 2013, the three infectious diseases with the highest incidence were hand, foot, and mouth disease, hepatitis B and tuberculosis in China [4,5]. Hand, foot, and mouth disease was particularly widespread in Asia and was estimated to cause 96 900 age-weighted Disability Adjusted Life Years (DALYs) per annum in eight high-burden countries in East and Southeast Asia [6]; HBV accounted for 700 000 deaths and 21.8 million DALYs globally during 2007–2017, of which East Asia was the worst [7]; Tuberculosis was estimated to cause 122 million DALYs globally in 2019, of which countries in Southeast Asia and Africa were more serious [8]. Influenza was the main cause of morbidity and mortality worldwide, including in China [9], and the disease burden of influenza was beyond respiratory illness [10]. Although mumps and

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measles were included in the NIP in China, there is still a high incidence of these two infections among children [11]. Increasing prevalence of herpes zoster was observed in recent years, with Asia Pacific as the fastest growing region [12]. Post-herpetic neuralgia (PNH), the most common complication of herpes zoster, represents important public health issue because of the relevant burden among the elderly [12,13], the disease burden due to herpes zoster in China was substantial with the aging of the population intensifying [14].

In this study, we used dataset derived from Shandong Multi-Center Healthcare Big Data Platform (SMCHBDP) [15] to compare the epidemiological characteristics and disease burden of the seven VPDs, involving hand, foot, and mouth disease (HFMD), hepatitis B, tuberculosis, influenza, mumps, measles, and herpes zoster. Among them, four diseases were included in the NIP in China (hepatitis B, tuberculosis, mumps, and measles) [16] and one was non-notifiable infection (herpes zoster). By estimating the Disability Adjusted Life Years (DALYs), a more integrated index of disease burden [17,18], we aimed to explore the high-risk groups, and provide scientific basis for effective control of these infectious diseases.

Materials and methods

Data sources and study population

Patients with each of the seven VPDs were enrolled from the SMCHBDP during January 2013 to June 2017. The SMCHBDP, developed by the Health Commission of Shandong Province in 2017, is a hybrid system involving >5 million residents of Shandong province. The platform is derived from the connection of multiple health-related sources, such as electronic health records, electronic medical records, resident medical insurance payment systems, and death registry, sharing a common resident identity card number. Individual information of each patient was extracted, including demographic characteristics (sex, age, and residence location) and medical history (diagnoses, symptoms, therapies, payment records, history of previous infections, and chronic diseases). After removal of the participants who had duplicate or incorrect resident identity card numbers, or had no time to register into the platform, a total of 3 987 573 participants were included. This study was approved by the Ethics Committee of the School of Public Health, Shandong University. Informed consent was waived owing to the retrospective nature of the study.

Statistical analysis

We compared the incidence density (ID) of each disease, stratified by different sex, age and region categories. ID was defined as the number of annual incident cases of each disease divided by the person-time (per 100 000 person-years).

Poisson regression analysis was used to examine incidence trend from 2013 to 2017 [19,20]. Thematic maps showing the annual ID on a prefecture level were produced with ArcGIS 10.2 (ESRI, Redlands, CA, USA). All analyses were conducted using R software, version 4.0.5 (R Project for Statistical Computing). A two-sided *P* value<0.05 was considered statistically significant.

To compare the disease burden of the seven VPDs, we estimated DALYs using the toolkit (version 0.94) developed by the BCoDE project [21,22]. The toolkit allows the users to supply either a point estimate or a distribution for each input value [23]. DALYs is equal to the sum of years lived with disabilities (YLDs) following the onset of a disease and the years of life lost (YLLs) due to premature mortality compared to a standardized life expectancy [24]. YLDs include the duration lived with disabilities multiplied

by disability weights (DWs). In this study, the DWs were referred to the European disability weight project [25]. Data on life expectancy were derived from the Global Burden of Disease 2015 standard reference life table [26]. Outcome tree models for each disease were constructed and the parameters used were shown in supplementary Table S1 2. To estimate the uncertainty intervals (UIs), the models were run at 1000 iterations of the Monte Carlo simulations without an annual time discount rate for each disease.

Results

During the study period, the total number of reported cases of the seven VPDs was 71 509, with the overall ID of 66.79 cases per 100 000 person-years. Influenza cases accounted for most part of the seven VPDs (62.35%) and was mainly located in the Jiaodong Peninsula (Qingdao, Weihai and Yantai), while the number of mumps and measles cases was relatively low, see in Fig. 1A; The total ID of the seven VPDs varied in different cities, ranging from 12.28 to 279.84 per 100 000 person-years and was relatively high in the city of Qingdao and Weihai (Fig. 1B). The overall ID of diseases included in the NIP was lower than that of diseases not included in the NIP while the diseases included in the NIP had relative higher overall ID in the inland areas compared to other diseases, see in Fig. 1C,D.

Table 1 illustrates the ID trends of the seven VPDs from 2013 to 2017. The overall ID of the seven infectious diseases increased from 35.84 cases per 100 000 person-years in 2013 to 83.27 cases per 100000 person-years in 2017 (P < 0.05). Among them, the ID of herpes zoster showed a significantly increasing trend, while mumps showed a significantly decreasing trend (both P < 0.05). Although the IDs of the other diseases showed stable trends in the whole population, we tested the ID trend of each disease stratified by age groups. The results indicated that the IDs of influenza in population aged over 60 years, hepatitis B in the age group of 40–49 years and tuberculosis in the age groups of 40–49 and over 70 years increased significantly during the study period (all P < 0.05).

Based on the estimation by outcome tree models, a total of 269 deaths (95% CI: 253–290) were attributed to the seven VPDs each year, and influenza, herpes zoster, and tuberculosis accounted for 79.2% of the total estimated deaths. As shown in Table 2, the DALYs due to tuberculosis in this population was 2879.55 DALYs/year, which generated a highest rate of 72.21 DALYs per 100 000 population. The estimated annual disease burden was from high to low: tuberculosis, herpes zoster (2392.22 DALYs/year), hepatitis B (2077.37 DALYs/year), influenza (747.23 DALYs/year), HFMD (400.42 DALYs/year), measles (8.25 DALYs/year), and mumps (0.43 DALYs/year).

As shown in Fig. 2, mumps had a relatively low disease burden at both the population level (0.43 DALYs/year, 95% CI: 0.396– 0.456) and the individual level (0.27 DALYs/100 infections, 95% CI: 0.26–0.29), whereas hepatitis B, herpes zoster and tuberculosis had a relatively high disease burden at both the population and individual levels. Influenza and HFMD had high disease burden at the population level but limited disease burden at the individual level.

Fig. 3 describes the age and sex specific burden of each disease in the general population. The DALYs of influenza and herpes zoster were higher in older population. Among adults aged > 50 years, the DALYs of influenza increased with increasing age, and peaked at population aged > 85 years. In contrast, the DALYs of herpes zoster decreased with increasing age, with the peak age group of 50– 54 years (Fig. 3A and B). The disease burden of hepatitis B was highest among young adults within the 25–29 years age group (Fig. 3C). For other VPDs, including HFMD, tuberculosis and



Fig. 1. Geographic distribution of the seven vaccine-preventable diseases (VPDs). (A) Geographic distribution of cumulative cases of the seven VPDs. The size of the circles represents the number of cases, and each color represents one disease. (B) Geographic distribution of cumulative incidence density (ID) of the seven VPDs. (C) Geographic distribution of overall IDs for VPDs included in National Immunization Program (NIP) of China. (D) Geographic distribution of overall IDs for VPDs out of National Immunization Program (NIP) of China.

mumps, DALYs of children, especially those under 10 years, accounted for the main part of the total DALYs (Fig. 3D–F). Differently, the DALYs of measles showed two peaks at the age of 25–29 years and < 1 year (Figure 3G). For mumps, most of the disease burden consists of YLDs, while for other VPDs, YLL due to premature mortality accounted for the majority of the total DALYs.

Discussion

We reported 71 509 cases of seven VPDs in Shandong province, China from 2013 to 2017. The VPDs with the highest number during this period was influenza. The overall ID of the seven diseases showed a significant increasing trend (P < 0.05). Tuberculosis had the highest disease burden at both the population and the individual level. Our study used dataset derived from multi-source health related big data, involving approximately 4 million participants. Incidence trend and disease burden of the seven VPDs were estimated.

Between-region variations in incidence were noted in our study. The overall ID of the seven VPDs was higher in the Jiaodong Peninsula, which is the core area of the Shandong province's economy, the relatively good medical conditions and high health literacy of residents, the detection rate of the seven VPDs in the area was relatively high, and influenza cases in this area were significantly higher, the high ID of influenza may also have contributed to it. In China, influenza vaccine is not included in the expanded NIP. Citizens seek the vaccine on their own and the average

coverage of influenza vaccine was just 1.5%-2.2% over the past 10 years [27]. High levels of population density and air pollution, inequities in social and living conditions, and better performance of diagnosis in Jiaodong Peninsula have increased the risk of respiratory infections, such as influenza [5,28]. The overall ID of diseases included in the NIP remained a relatively low level throughout the province. Since implementation, the NIP of China has made great progress in controlling VPDs. Incidence rates of these diseases in China are comparable to those in high-income countries [29]. However, the NIP still faces huge challenges. There are inequalities in immunization coverage by geography, urbanrural, and socio-economic status [30]. The relatively high average ID of diseases included in the NIP in some inland cities of Shandong province, such as Zaozhuang and Taian, may be due to the low level of economic development and the relatively low accessibility of immunization. For diseases out of the NIP, the average ID was lower in inland areas, such as Linyi, Liaocheng and Zibo. Due to the limitation of medical conditions, the inland areas had not paid enough attention to the VPDs out of NIP, in addition, the individual symptoms of the three diseases were relatively mild, resulting in lower admission rate and reported incidence.

With the development of economy and medical system, yearly incidence and mortality of the 18 reported infectious diseases reduced rapidly in China from 1970 to 1990, and changed little between 1990 and 2007 [31]. After the severe acute respiratory syndrome (SARS) outbreak, the overall incidence of the 45 notifiable infectious diseases of China showed an increasing trend

Table 1

Annual incidence density stratified by age groups and results of trend test of the seven vaccine-preventable diseases in the observational population of Shandong province, China, 2013–2017.

| Vaccine-preventable diseases | Year | Incidence density (per 100 000 person-years) * | | | | | | | | |
|------------------------------|-----------|--|--------|--------------|--------|--------|--------|--------|---------|----------|
| | | 0-9 | 10-19 | 20-29 | 30-39 | 40-49 | 50-59 | 60–69 | 70- | All ages |
| Influenza | 2013 | 33.02 | 4.05 | 45.23 | 118.13 | 110.64 | 217.42 | 183.44 | 660.30 | 139.76 |
| | 2014 | 33.81 | 7.25 | 45.86 | 131.82 | 139.95 | 309.25 | 256.93 | 753.60 | 174.83 |
| | 2015 | 259.86 | 212.59 | 161.77 | 263.60 | 377.11 | 594.90 | 549.48 | 1009.68 | 388.05 |
| | 2016 | 161.37 | 153.64 | 120.39 | 217.15 | 353.71 | 608.46 | 653.32 | 1045.26 | 371.43 |
| | 2017 | 161.19 | 213.06 | 142.72 | 204.49 | 377.72 | 554.25 | 589.90 | 1044.48 | 375.51 |
| | β | 38.39 | 56.44 | 26.95 | 25.81 | 74.79 | 97.29 | 120.93 | 106.00 | 38.39 |
| | Р | 0.26 | 0.07 | 0.12 | 0.22 | 0.05 | 0.07 | 0.04 | 0.03 | 0.26 |
| Herpes zoster | 2013 | 0.67 | 2.03 | 7.10 | 17.92 | 21.21 | 51.99 | 70.21 | 105.25 | 28.76 |
| | 2014 | 2.02 | 1.73 | 10.29 | 21.18 | 29.13 | 58.40 | 93.74 | 135.81 | 36.91 |
| | 2015 | 7.78 | 9.81 | 28.80 | 48.86 | 57.01 | 113.29 | 1/2./5 | 236.13 | /3./1 |
| | 2010 | 9.04 | 19.47 | 45.94 | 08.20 | 82.85 | 147.48 | 211.42 | 321.39 | 100.29 |
| | 2017 R | 3.00 | 4.57 | 12.00 | 17.05 | 21.80 | 32.57 | 247.75 | 61.02 | 23 73 |
| | р Р | 0.00 | 4.57 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.01 | 0.00 |
| Henatitis B | 2013 | 0.00 | 3 24 | 29.01 | 51.89 | 55.24 | 65.58 | 46 70 | 17 17 | 38.00 |
| riepatiat 2 | 2013 | 3.18 | 3.80 | 33.42 | 49.39 | 57.59 | 48.93 | 45.20 | 22.32 | 36.77 |
| | 2015 | 3.22 | 5.05 | 39.18 | 53.00 | 64.85 | 87.38 | 68.42 | 38.20 | 48.28 |
| | 2016 | 3.55 | 3.42 | 32.90 | 55.81 | 66.63 | 73.89 | 59.42 | 40.96 | 45.08 |
| | 2017 | 2.58 | 1.94 | 35.18 | 66.73 | 70.05 | 64.71 | 72.68 | 31.93 | 47.23 |
| | β | 0.55 | -0.30 | 1.18 | 3.61 | 3.87 | 2.32 | 6.62 | 4.82 | 2.68 |
| | Р | 0.28 | 0.48 | 0.39 | 0.07 | 0.00 | 0.67 | 0.07 | 0.15 | 0.11 |
| HFMD | 2013 | 173.18 | 2.84 | 1.42 | 1.41 | 0.57 | 0.26 | 0.37 | 1.11 | 19.14 |
| | 2014 | 382.57 | 4.83 | 6.86 | 2.67 | 1.07 | 1.99 | 0.92 | 0.95 | 43.66 |
| | 2015 | 355.33 | 5.65 | 3.10 | 2.23 | 0.17 | 0.61 | 0.00 | 0.41 | 39.13 |
| | 2016 | 349.39 | 5.79 | 3.52 | 5.08 | 1.78 | 0.38 | 1.22 | 2.65 | 39.06 |
| | 2017 | 175.66 | 2.91 | 3.62 | 6.20 | 0.98 | 1.11 | 0.91 | 0.00 | 19.77 |
| | β | -2.82 | 0.11 | 0.11 | 1.20 | 0.15 | 0.01 | 0.14 | -0.05 | -0.33 |
| Tuborquiocic | P 2012 | 0.95 | 0.85 | 0.89 | 0.02 | 0.51 | 0.97 | 0.45 | 0.90 | 0.94 |
| Tuberculosis | 2015 | 0.67 | 5.27 | 17.24 | 12.05 | 12.01 | 24.55 | 19 45 | 25.62 | 10.54 |
| | 2014 | 1.88 | 15.17 | 22.38 | 21 74 | 17.38 | 29.30 | 36.62 | 55.03 | 24.86 |
| | 2015 | 0.51 | 15.17 | 31.52 | 20.00 | 18 29 | 29.50 | 41 79 | 59.95 | 25.55 |
| | 2010 | 0.52 | 12.14 | 28.28 | 14.26 | 20.49 | 23.02 | 47.50 | 73.41 | 25.09 |
| | β | -0.04 | 2.28 | 3.10 | 0.82 | 2.34 | 1.08 | 5.44 | 10.13 | 2.78 |
| | P | 0.87 | 0.14 | 0.12 | 0.59 | 0.04 | 0.61 | 0.12 | 0.01 | 0.07 |
| Mumps | 2013 | 28.31 | 27.17 | 4.26 | 3.07 | 0.38 | 2.05 | 0.37 | 0.55 | 6.97 |
| | 2014 | 15.90 | 18.98 | 1.08 | 0.62 | 1.07 | 1.99 | 0.31 | 0.00 | 4.18 |
| | 2015 | 18.24 | 8.63 | 1.21 | 0.37 | 1.35 | 1.83 | 1.35 | 2.07 | 3.77 |
| | 2016 | 14.47 | 5.79 | 0.84 | 1.02 | 1.62 | 0.38 | 0.49 | 0.76 | 2.81 |
| | 2017 | 10.34 | 4.86 | 1.09 | 1.24 | 0.98 | 2.60 | 0.46 | 2.71 | 2.68 |
| | β | -3.74 | -5.78 | -0.66 | -0.33 | 0.17 | -0.05 | 0.04 | 0.51 | -1.00 |
| Maaalaa | P 2012 | 0.05 | 0.02 | 0.17 | 0.41 | 0.29 | 0.88 | 0.83 | 0.18 | 0.03 |
| Measles | 2013 | 2.36 | 1.22 | 2.03 | 4.48 | 1.34 | 1.54 | 1.47 | 1.66 | 2.09 |
| | 2014 | 8.07 | 0.69 | 5.25 | 6.99 | 1.95 | 1.55 | 1.01 | 0.95 | 3.90 |
| | 2015 | 12.00 | 2.00 | 5.55 7.55 | 4.04 | 4.03 | 3.63 | 1.00 | 2.49 | 4.05 |
| | 2010 | 3.62 | 2 43 | 1 45 | 1 24 | 0.65 | 1 48 | 0.00 | 0.00 | 1 34 |
| | £017 ß | 0.68 | 0.52 | -0.05 | -0.28 | 0.40 | 0.20 | -0.28 | -0.35 | 0.10 |
| | P | 0.71 | 0.16 | 0.97 | 0.84 | 0.71 | 0.66 | 0.28 | 0.30 | 0.90 |
| Total | 2013 | 34.03 | 6.55 | 15.18 | 29.84 | 28.85 | 51.85 | 47.74 | 116.67 | 35.84 |
| | 2014 | 63.82 | 6.21 | 18.13 | 32.69 | 34.46 | 62.53 | 59.25 | 133.54 | 44.99 |
| | 2015 | 94.01 | 37.08 | 38.74 | 56.31 | 74.46 | 118.34 | 117.96 | 186.80 | 82.93 |
| | 2016 | 78.83 | 29.53 | 34.64 | 53.95 | 75.86 | 122.84 | 137.03 | 200.55 | 83.90 |
| | 2017 | 52.25 | 36.18 | 37.86 | 53.34 | 81.82 | 116.09 | 135.36 | 197.75 | 83.27 |
| | β | 5.14 | 8.26 | 6.19 | 6.83 | 14.74 | 18.88 | 25.30 | 22.92 | 13.38 |
| | Р | 0.56 | 0.08 | 0.06 | 0.07 | 0.03 | 0.05 | 0.02 | 0.02 | 0.04 |

HFMD: hand, foot, and mouth disease.

* The trend was tested by Poisson regression analysis.

from 2004 to 2013 [5]. In this study, we examined incidence trend of the seven VPDs from 2013 to 2017 and six of them are notifiable infectious diseases in China. During the study period, the ID of mumps decreased significantly, which was consistent with the changing pattern of mumps across the country. It might be due to the combined measles, mumps, and rubella vaccine was added to the list of routine immunization after 2008 in China [11,32]. On the contrary, the ID of herpes zoster increased continuously, with people over 50 years had the highest incidence. The increasing prevalence of herpes zoster is a common public health issue in the Asia-Pacific region and some European countries [12,23,33]. In China, it might be attributed to the increasing aging population problem. There were 240 million people aged \geq 60 years as of 2017 and the number is estimated to be about 255 million by 2020 (accounting for 17.8% of the total population) [34]. It is noted that the IDs of hepatitis B and tuberculosis showed a significantly increasing trend in the age group of 40–49 years. The reasons might be that people of these ages are the main labor force in the society and are struggling under the pressure of everyday life. In addition, the vaccines for tuberculosis and hepatitis B are often

Table 2

Estimated annual burden of the seven vaccine-preventable diseases in the observational population of Shandong province, China, 2013-2017.

| Vaccine- preventable | Median (95% confidence interval) | | | | | | | | | |
|----------------------|----------------------------------|---------------------------------------|-------------------------------|----------------------------------|----------------------------------|----------------------------------|------------------------------|--|--|--|
| diseases | Cases per year | Incidence (per 100 000 population) | Deaths/year | YLDs/year | YLLs/year | DALYs/year | DALYs per 100 000 population | | | |
| Influenza | 47,164 (47164, 47164) | 1182.78 (1182.78, 1182.78) | 61 (61, 61) | 94.81 (88.56, 101.42) | 652.42 (652.42, 652.42) | 747.23 (740.98, 753.84) | 18.74 (18.52, 18.91) | | | |
| Herpes zoster | 2364 (2364, 2364) | 59.27 (59.27, 59.27) | 81 (69, 96) | 121.79 (111.98, 131.32) | 2270.84 (1952.16, 2686.88) | 2392.22 (2075.30, 2804.50) | 59.99 (52.04, 70.33) | | | |
| Hepatitis B | 1754 (1714, 1792) | 43.98 (43.98, 44.94) | 52 (41, 64) | 270.52 (226.27, 328.04) | 1800.76 (1352.76, 2451.73) | 2077.37 (1629.48, 2745.65) | 52.10 (40.86, 68.85) | | | |
| HFMD | 6427 (3910, 8890) | 161.19 (98.05, 222.95) | 3 (2, 4) | 189.31 (109.30, 280.07) | 209.70 (122.69, 309.14) | 400.42 (236.85, 571.30) | 10.04 (5.94, 14.32) | | | |
| Tuberculosis | 912 (912, 912) | 22.86 (22.86, 22.86) | 71 (70, 71) | 562.06 (551.20, 573.11) | 2317.45 (2271.91, 2369.92) | 2879.55 (2831.40,2931.82) | 72.21 (71.00, 73.52) | | | |
| Mumps | 156 (150, 162) | 3.97 (3.76, 4.06) | 0.0023 (0.0022, 0.0024) | 0.31 (0.28, 0.34) | 0.12 (0.12, 0.12) | 0.43 (0.40, 0.46) | 0.011 (0.010, 0.011) | | | |
| Measles | 154 (150, 157) | 3.85 (3.75, 3.95) | 0.12 (0.11, 0.13) | 1.98 (1.65, 2.37) | 6.24 (5.73, 6.83) | 8.25 (7.56, 8.97) | 0.21 (0.19, 0.23) | | | |
| Overall | 58,935 (56414, 61401) | 211.14 (202.11, 219.98) | 269 (253, 290) | 1241.20 (1146.59, 1352.62) | 7258.72 (6667.60, 8109.61) | 8503.99 (7890.02, 9371.50) | 30.47 (28.27, 33.57) | | | |

HFMD: hand, foot, and mouth disease.



Fig. 2. Ranking of the seven vaccine-preventable diseases by estimated burden at population level (DALYs/year) and individual level (DALYs per 100 cases) in Shandong province, China, 2013–2017. The DALYs per year are shown on the x-axis and the DALYs per 100 cases are shown on the y-axis. Both axes are on logarithmic scale, of which the x-axis represents the disease burden at the population level and the y-axis represents the disease burden of the individual level. The size of the bubbles represents the estimated number of cases annually. DALYs: Disability Adjusted Life Years.

given to infants and small children in China. Adults rarely get vaccinated to prevent these diseases, which is also a common barrier in some other countries of Asia [12,35].

The disease burden of tuberculosis and hepatitis B were 72.21 DALYs/100 000 population and 52.10 DALYs/100 000 population, respectively, which were higher than previous studies in the European Union and the European Economic Area [36,37]. The reason might be that HBsAg prevalence rate in Chinese population, in particular those born before the advent of infant HBV vaccination pro-

gram, is much higher than that in Europe and North America [38]. Another possible reason might be that adults, who had inadequate protective immune barrier against hepatitis B, were resistance to adult vaccination measures (Yang et al., 2015). Therefore, prevention and control of hepatitis B in adults, especially young adults, is still a substantial challenge. For tuberculosis, delayed diagnosis is common in low- and middle-income countries [39], which may increase the incidence of tuberculosis. Besides, tuberculosis patients in Eastern Europe and the Middle East countries are



Fig. 3. Estimated annual disease burden of the seven vaccine-preventable diseases (DALYs per 100 000 population) by gender and age groups in Shandong province, China, 2013–2017. (A-G) The disease burden of influenza, herpes zoster, hepatitis B, hand, foot, and mouth disease, tuberculosis, mumps, and measles, respectively. DALYs: Disability Adjusted Life Years, YLDs, years lived with disabilities, YLLs, years of life lost.

mainly refugees [40], and there might be underreporting issues, resulting in an underestimation of disease burden. On the contrary, our estimates for DALYs of influenza and herpes zoster were lower than other studies [23,37,38]. The reasons might be as follows. A large proportion of cases with influenza and herpes zoster were elderly adults, who may not seek medical service unless they were more severely ill. Additionally, the health statues of the rural elderly is a serious concern in China. The poor medical conditions in rural areas with substantial empty-nesters may lead to misdiagnosis and missed diagnosis issues. Similar to previous studies, the disease burden of measles and mumps remained low [36,37]. Since the continuous advancement of immunization programs in various countries, these two diseases have been effectively controlled [41], and the global disease burden showed a downward trend [42]. However, additional attention should be paid to the children aged under 10 years in China.

Disease burden at the population level discusses how death and loss of health due to a disease within the measured population, while disease burden at the individual level takes into account the severity and impact of disease to a single person. In this study, tuberculosis, hepatitis B, and herpes zoster caused relatively severe illness and had a high burden of disease for each person with the disease (relatively high DALYs per case). Other VPDs, such as influenza and HFMD, may not be as severe at the individual level but, due to the large number of cases, have a greater total burden (relatively high DALYs per year). Mumps and measles had a relatively low disease burden at both individual and population level, due to the much lower number of cases and low severity. Similar results have been reported by European Union and European Economic Area countries [36].

Among the seven VPDs, herpes zoster, influenza, and HFMD have not been included in the NIP of China. Since the population structure and the spectrum of infectious diseases has changed, the disease burden of these disease has exceeded some diseases in the NIP schedule. Thus, vaccine intervention strategies and diseases under the NIP should be adjusted accordingly. Implementation of additional targeted vaccinations for infectious diseases, especially in older adults is under discussion worldwide [43,44]. To reduce both the number of cases and the overall burden associated with these diseases, comprehensive and careful considerations should be given to the introduction of more vaccine eligibility to the NIP of China.

Our study has some main limitations. First, outcome trees were built on available published evidence, and the resulting disease progression pathway may not always fully reflect the definition of a case of the specific disease. Although this might be a source of imprecision, the outcome trees were still the best available approximation [45]. Second, instead of a specific disability weight in China, we used the values from European population [25]. The differences between the Chinese and European races might cause bias in our estimation. Third, we only chosen seven VPDs in this study because of their severity and perceived burden, further researches are needed to estimate the current disease burden of all VPDs in China and assist in prioritization of disease control.

Conclusions

The overall ID of the seven VPDs increased significantly from 2013 to 2017. The IDs of hepatitis B and tuberculosis in middleaged adults increased significantly, and their disease burden were high at both the population and individual levels. Strategies for reaching population who are difficult to reach, and for promoting the full immunization should be developed. The immunization coverage of herpes zoster and influenza vaccination should be improved, especially among the elderly. It is of great necessity to consider whether to expand these vaccination programs into the China's NIP to achieve greater value in public health.

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Ethics

This study was approved by the Ethics Committee of the School of Public Health, Shandong University. Informed consent was waived owing to the retrospective nature of the study.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jvacx.2022.100145.

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