

RESEARCH ARTICLE



Evaluating the impact of the vaccination prescription program on herpes zoster vaccine coverage in Ningbo, China: An interrupted time series analysis

Jianmei Wang^a, Jiaxin Wang^b, Ning Li^a, Dongkai Du^c, Dandan Zhang^a, and Rui Ma^{id a}

^aDepartment of Immunization Program, Ningbo Municipal Center for Disease Prevention and Control, Ningbo, Zhejiang, China; ^bSchool of Public Health, Peking University, Beijing, China; ^cSchool of Public Health, Hangzhou Medical College, Hangzhou, Zhejiang, China

ABSTRACT

As the population ages, herpes zoster (HZ) and postherpetic neuralgia, which are associated with a substantial disease burden, are expected to increase. Ningbo began to implement the Vaccination Prescription Program for community individuals in April 2022. The anonymized HZ vaccination records of individuals aged above 50 during 2020–2023 were extracted from the Ningbo Immunization Information Management System. We applied interrupted time series analyses controlling for long-term trends and seasonality to assess the effects of the program on HZ vaccination coverage. Effect modification from demographic characteristics was investigated. Totally 18,133 doses of the HZ vaccine were administered. The cumulative coverage increased from 0.16‰ to 2.97‰, and the full series cumulative coverage from 0.04‰ to 2.48‰. Relatively higher coverage and full series coverage were observed among residents, females, individuals residing in inner districts and high socioeconomic regions, and those aged 50–59 years. During the transition period, a 468.7% increase in HZ vaccination coverage was evident (Rate Ratio [RR], 5.687; 95% Confidence Interval [CI], 2.334–13.857), and significant impact was detected among all demographic characteristics. During the post-implementation period, a 261.3% increase in coverage was evident (RR, 3.613; 95% CI, 1.202–10.858), while no effect was found among migrants, individuals living in regions with high socioeconomic status, and those aged above 70 years. Although the positive effect of the program, it is imperative to implement key strategies for providing affordable HZ vaccines, such as government funding, subsidies, and vaccination prescriptions from healthcare professionals, alongside peer initiatives and family members' education.

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Introduction


Herpes zoster (HZ) and its common complication, postherpetic neuralgia (PHN), are associated with a substantial disease burden and are expected to increase due to population aging. It is estimated that a cumulative incidence of HZ ranges from 2.9–19.5 cases per 1,000 population, and an incidence rate of HZ ranges from 5.23–10.9 cases per 1,000 person-years worldwide.¹ The estimated pooled incidence of HZ for all ages in China was 4.28 per 1,000 person-years, and it increased as people aged, particularly those over 60, who had an incidence of 11.69 per 1,000 person-years.²

Two kinds of HZ vaccines, the recombinant zoster vaccine Shingrix (RZV, GlaxoSmithKline) and the live attenuated herpes zoster Ganwei (ZVL, Changchun BCBT), have been introduced into the market in China in 2020 and 2023, respectively, priced at approximately USD 193 and USD 225 per dose at the charge of the individuals, respectively. The HZ vaccine has proven effective in attenuating the severity of HZ disease and significantly reducing the incidence of HZ and PHN.³ Many healthcare systems around the world focus on promoting healthy aging. To address this issue, national health agencies, or vaccine committees, in ten different countries have released guidelines about HZ vaccines.⁴ According to the

National Health Commission of the People's Republic of China's 2019 Core Messages for the Prevention of Disability in Older Adults, receiving the HZ vaccine is recommended for older adults.⁵

Ningbo has started to explore the scientific setting and standardized management of adult vaccination clinics since 2010. And the work mechanism and network have developed maturely to improve the accessibility of adult vaccination services.⁶ Besides, over the past ten years, social medical insurance has covered all types of vaccines that are at the charge of the individuals in Ningbo. Even though China licensed the first HZ vaccine in 2020, the coverage among the age-target population in Ningbo is still low⁷. On the one hand, from the demand side, vaccine costs, professional education, credible recommendations, accessibility, and affordability were reported as impediments to HZ vaccination among the elderly.⁸ On the other hand, from the supply side, three to five full-time health workers (PHWs) provide vaccination services to roughly 10,000 individuals in a typical Ningbo community health center (CHC) with a rather heavy workload.⁹ Based on the prevalence of underlying diseases among the elderly and the concerns about medical disputes, PHWs are very cautious when it comes to administering and carrying out

CONTACT Rui Ma  hengmi2021@163.com  Department of Immunization Program, Ningbo Municipal Center for Disease Prevention and Control, No. 1166, Fanjiangnan Road, Haishu District, Ningbo, Zhejiang 315000, China.

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HZ vaccinations for the elderly.^{10,11} General practitioners (GPs) are more familiar with the health status of residents due to their medical background and the community's close-knit nature, but GPs rarely recommend vaccination to residents on their own initiative because vaccine promotion is not their duty.¹¹

Health personnel have an important role in promoting vaccination to populations.^{12–14} It was reported that a lack of coordination between GPs and PHWs had a negative impact on vaccine uptake.^{11,15} To address the issue, Ningbo began to implement the Vaccination Prescription Program for community individuals in April 2022 from the perspective of medical and preventive integration. Health personnel in CHCs, including GPs and PHWs, were involved in the program to offer effective vaccination information and education to generate a positive attitude toward vaccination or a specific vaccine during clinical consultations. The program emphasizes the effective communication and cooperation between GPs' and PHWs' efforts in the provision of vaccination, with performance assessment from hospital management.

The program is implemented as follows: (a) PHWs and GPs are required to receive regular training on the most recent scientific evidence regarding vaccines and the diseases they prevent as well as on and misconceptions about vaccination; (b) a supportive environment for vaccination is created by displaying standardized promotional materials, such as boards, and playing scientific videos on the electronic screen in areas of CHCs with high traffic flow; (c) by connecting GPs' Hospital Information System (HIS) and PHWs' Ningbo Immunization Information Management System (NBIIMS), making it possible for GPs to keep track of the types and stock of vaccines in HIS in real time, in sync with NBIIMS, and enabling GPs to prescribe vaccines.

In this study, we applied interrupted time series (ITS) analysis controlling for long-term trends and seasonality based on the HZ vaccination coverage among individuals aged above 50 years during the years 2020–2023 in Ningbo, China, to examine the impact of the Vaccination Prescription Program on that population.

Methods

Data source

Ningbo is an economically developed coastal city in eastern China, with an area of 9816 km² and a population of 9.70 million in 2023. The anonymized individual records of HZ vaccine from September 2020 to December 2023 were extracted from the NBIIMS on January 31st, 2024, including gender, birthdate, district of residence, immigration status, the type of HZ vaccine, and dates of the vaccination. NBIIMS is a computerized, population-based, real-time immunization registration system that has been used in all immunization clinics under the authority of Ningbo Municipal CDC since 2005. The quality of vaccination records has gradually improved over the past five years to ensure compliance with the requirements of the vaccine management law for complete traceability, which is currently regarded as highly complete.

Population figures in 2021 stratified by gender, five-year age groups, calendar year, and region were obtained from the China Disease Control and Prevention Information System (DCPIS), and Gross Domestic Product (GDP) per capita was obtained from the Ningbo municipal bureau of statistics.

Variable definitions

Regarding district of residence, urbanicity was divided into two categories: 1) The urban districts of Haishu, Jiangbei, Yinzhou, Zhenhai, Beilun, and Fenghua were included in the inner districts; 2) Yuyao, Cixi, Ninghai, and Xiangshan were included in the outer districts. We also categorized the socio-economic level of resident areas by Gross Domestic Product (GDP) per capita, based on 2023 statistics from the Ningbo Municipal Bureau of Statistics. Beilun, Zhenhai, Jiangbei, and Yinzhou were categorized as high levels for GDP per capita > GDP per capita of Ningbo city (22,264 USD), while other areas were classified as low levels for GDP per capita. The immigration status was categorized as two types: resident and migrant from other municipalities and the foreigners.

The vaccination coverage was defined as the proportion of vaccinated individuals (≥ 1 dose) aged above 50 years among the target population. Full series coverage was defined as the proportion of individuals aged above 50 years who received full series doses of the HZ vaccine.

Statistical analysis

The interrupted time series (ITS) study design is increasingly being used for the evaluation of public health interventions. It is particularly suited to interventions introduced at a population level over a clearly defined time period that target population-level health outcomes.^{16,17}

According to practical organization, we divided the implementation of the Vaccination Prescription Program into three time periods: pre-implementation (September 2020–March 2022), transition (April 2022–December 2022), and post-implementation (January 2023–December 2023). We analyzed coverage for the HZ vaccine during the transition and post-implementation periods compared to the pre-implementation period, adjusting for seasonality and long-term trends. Models were based on time series of monthly vaccination coverage, which were assumed to follow a Poisson distribution, allowing for overdispersion. We modeled the seasonal variations of vaccination for the HZ vaccine using harmonic functions of time.^{17,18}

The following segmented regression model is used:

$$Y_t = \beta_0 + \beta_1 T + \beta_2 X_{t1} + \beta_3 TX_{t1} + \beta_4 X_{t2} + \beta_5 TX_{t2} + \text{Fourier}(T) + \varepsilon_t$$

where Y_t , the coverage of vaccinations at time t , is a dependent variable. T is the time elapsed since the start of the study, with the monthly unit representing the coverage of vaccinations. X_{t1} is a dummy variable, with the period before transition coding 0, and the period after transition coding 1. X_{t2} is a dummy variable, with the period before post-implementation coding 0, and the period after post-

implementation coding 1. $Fourier(T)$ is a Fourier term to adjust for seasonality. ε_t is the error term at time t representing random variability, which cannot be explained by the model. β_0 , the y-axis intercept, indicates the vaccinations at the initial moment of the time series. β_1 , the slope, is the trend of vaccinations during the pre-implementation period. β_2 is the level change reflecting the immediate effect during the transition period. β_3 is the slope change indicating the gradual effect during the transition period (using the interaction between T and X_{t1} : TX_{t1}). β_4 is the level change reflecting the immediate effect during the post-implementation period. β_5 is the slope change indicating the gradual effect during the post-implementation period (using the interaction between T and X_{t2} : TX_{t2}).

All statistical tests were two-tailed, and P values < 0.05 were considered statistically significant. Statistical analyses were performed using R software (version 4.2.0).

Result

From September 2020 to December 2023, a total of 18,133 doses of the HZ vaccine were administered in Ningbo, China. There were 680 doses administered in 2020, 1,787 in 2021, 6,544 in 2022, and 9,122 in 2023. Table 1 displays the number of HZ vaccine doses and the cumulative coverage by demographic characteristics and calendar year. The cumulative coverage increased from 0.16‰ in 2020 to 2.97‰ in 2023 (18.56 times), and the full series cumulative coverage increased from 0.04‰ in 2020 to 2.48‰ in 2023 (62.00 times). These findings indicate a consistent annual increase in coverage.

Table 2 indicates that both vaccination coverage and full series rate for the HZ vaccine through the end of 2023 were significantly higher in inner districts compared to outer districts ($P < 0.001$), in regions with high socioeconomic status compared to those with low socioeconomic status ($P < 0.001$), among females compared to males ($P < 0.001$), and among residents compared to migrants ($P < 0.001$). Additionally, coverage varied by age group, with the highest rates observed in individuals aged 50–59 years and the lowest rates in those over 70 years ($P < 0.001$).

Data are depicted in Figure 1 on a monthly basis, together with the predicted regression curves. We observed an increase in coverage for the HZ vaccine immediately after the implementation of the Vaccination Prescription Program. During the transition period, there was an immediate 468.7% increase in total coverage of vaccination for the HZ vaccine (Rate Ratio [RR], 5.687; 95% Confidence Interval [CI], 2.334–13.857) compared with that during the pre-implementation period. A statistically significant impact during the transition period was detected among all demographic characteristics (Table 3).

During the post-implementation period, a 261.3% increase in HZ vaccination coverage was evident (RR, 3.613; 95% CI, 1.202–10.858). Notably, there was an increase in coverage among individuals residing in inner districts (RR 3.759; 95% CI 1.118–12.642) and outer districts (RR 3.618; 95% CI 1.464–8.944), as well as in regions with low (RR 4.120; 95% CI 1.415–11.996) socioeconomic status and among residents (RR 3.819; 95% CI 1.239–11.775). Furthermore, an increase was observed among both female (RR 3.520; 95% CI 1.154–10.739) and male (RR 3.817; 95% CI 1.279–11.392) populations. However, no significant impact of HZ vaccination coverage was detected among migrants (RR 2.032; 95% CI 0.760–5.436), living in regions with high socioeconomic status (RR 3.376; 95% CI 0.973–11.714), and those aged above 70 years (RR 3.309; 95% CI 0.720–15.204) during the post-implementation period. Additional information can be found in the supplementary materials.

Discussion

We conducted a search in the NBIIMS electronic vaccination registries, encompassing all immunization clinics across Ningbo, to examine HZ vaccination coverage from September 2020 to December 2023. Besides, we divided the implementation of the Vaccination Prescription Program according to practical organization into three time periods: pre-implementation, transition, and post-implementation, and applied ITS, which is one of the most efficient quasi-experimental approaches, to conduct the comprehensive assessment of the program on a population level.

Table 1. Cumulative coverage (%) of herpes zoster vaccine by demographic characteristics among individuals aged over 50 years in Ningbo, China, 2020–2023.

Characteristics		2020				2021				2022				2023			
		≥1 dose		full series		≥1 dose		full series		≥1 dose		full series		≥1 dose		full series	
		No.	rate	No.	rate	No.	rate	No.	rate	No.	rate	No.	rate	No.	rate	No.	rate
Urbanicity	Inner	488	0.27	124	0.07	1117	0.63	853	0.48	3647	2.05	2623	1.47	7154	4.01	6019	3.38
	Outer	60	0.04	8	0.00	300	0.18	197	0.12	1584	0.94	1157	0.69	3141	1.87	2551	1.52
Socioeconomic level	High	317	0.28	62	0.05	759	0.66	587	0.51	2396	2.10	1793	1.57	4744	4.15	3957	3.47
	Low	231	0.10	70	0.03	658	0.28	463	0.20	2835	1.22	1987	0.86	5551	2.39	4613	1.99
Gender	Male	186	0.11	43	0.02	464	0.26	347	0.20	1753	1.00	1237	0.70	3613	2.05	2983	1.69
	Female	362	0.21	89	0.05	953	0.56	703	0.41	3478	2.04	2543	1.49	6682	3.93	5587	3.28
Immigration status	Resident	514	0.20	124	0.05	1318	0.50	977	0.37	4846	1.85	3516	1.34	9532	3.63	7930	3.02
	Migrant	34	0.04	8	0.01	99	0.12	73	0.09	385	0.46	264	0.32	763	0.91	640	0.76
Age group (years)	50–59 years	241	0.14	60	0.03	740	0.42	539	0.31	3006	1.71	2168	1.23	5811	3.30	4873	2.77
	60–69 years	235	0.24	58	0.06	522	0.52	398	0.40	1692	1.69	1250	1.25	3267	3.27	2725	2.73
	≥70 years	72	0.10	14	0.02	155	0.22	113	0.16	533	0.76	362	0.51	1217	1.73	972	1.38
Total		548	0.16	132	0.04	1417	0.41	1050	0.30	5231	1.51	3780	1.09	10295	2.97	8570	2.48

Table 2. Cumulative coverage (%) of HZ vaccination by demographic characteristics among individuals aged over 50 years through the end of 2023 in Ningbo, China.

Characteristics		≥1 dose				full series			
		No.	rate	χ^2	P	No.	rate	χ^2	P
Urbanicity	Inner	7154	4.01	1342.402	<0.001	6019	3.38	1210.960	<0.001
	Outer	3141	1.87			2551	1.52		
Socioeconomic level	High	4744	4.15	801.714	<0.001	3957	3.47	676.458	<0.001
	Low	5551	2.39			4613	1.99		
Gender	Male	3613	2.05	1024.801	<0.001	2983	1.69	884.048	<0.001
	Female	6682	3.93			5587	3.28		
Immigration status	Resident	9532	3.63	1581.772	<0.001	7930	3.02	1307.209	<0.001
	Migrant	763	0.91			640	0.76		
Age group (years)	50–59 years	5811	3.30	461.461	<0.001	4873	2.77	428.680	<0.001
	60–69 years	3267	3.27			2725	2.73		
	≥70 years	1217	1.73			972	1.38		
	Total	10295	2.97			8570	2.48		

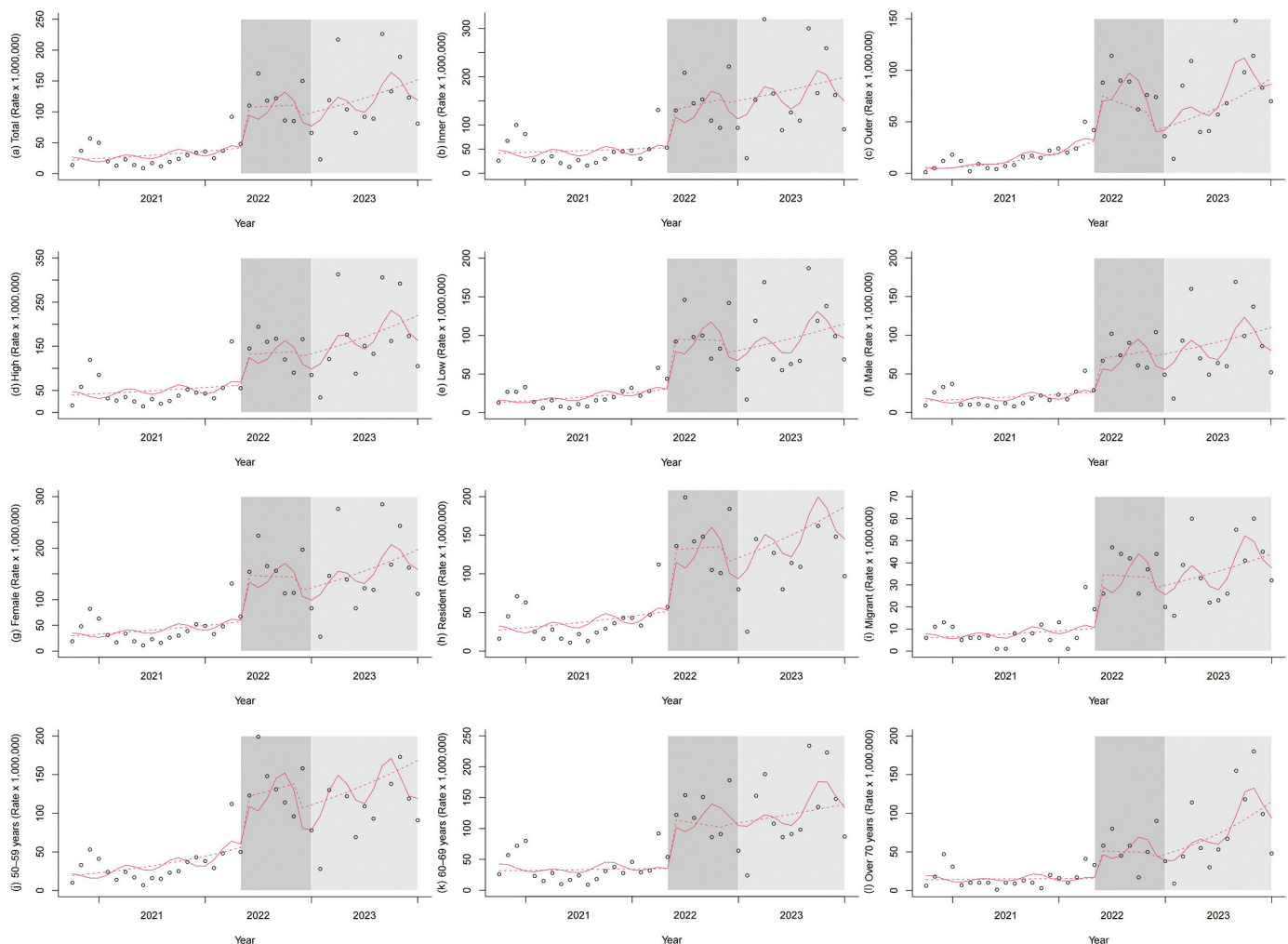
**Figure 1.** Models adjusted for seasonality. The observed data (represented by circles) and the predicted data (represented by solid lines) illustrate the HZ vaccination coverage over time among various demographic groups: the total population (a), individuals in inner districts (b), individuals in outer districts (c), individuals with high socioeconomic status (d), those with low socioeconomic status (e), males (f), females (g), residents (h), and migrants (i), individuals aged 50–59 years (j), those aged 60–69 years (k), and individuals over 70 years (l). The white background represents the pre-implementation period, the dark gray background represents the transition period, and the light gray background represents the post-implementation period of the Vaccination Prescription Program. The dashed lines represent the de-seasonalized trend of HZ vaccination coverage.

Table 3. Estimated level changes in coverage of herpes zoster vaccine stratified by demographic characteristics during the transition period (β_2) and post-implementation period (β_4) of the vaccination prescription program.

Characteristics		Transition period				Post-implementation period			
		β_2	Z	P	RR (95% CI)	β_4	Z	P	RR (95% CI)
Urbanicity	Inner	1.739	3.372	0.001	5.691 (2.071–15.636)	1.324	2.140	0.032	3.759 (1.118–12.642)
	Outer	1.612	4.569	<0.001	5.010 (2.510–10.002)	1.286	2.785	0.005	3.618 (1.464–8.944)
Socioeconomic level of resident areas	High	1.602	3.157	0.002	4.964 (1.836–13.423)	1.217	1.917	0.055	3.376 (0.973–11.714)
	Low	1.856	4.165	<0.001	6.399 (2.671–15.329)	1.416	2.597	0.009	4.120 (1.415–11.996)
Gender	Male	1.733	3.724	<0.001	5.657 (2.273–14.084)	1.340	2.401	0.016	3.817 (1.279–11.392)
	Female	1.745	3.848	<0.001	5.725 (2.354–13.921)	1.259	2.212	0.027	3.520 (1.154–10.739)
Immigration status	Resident	1.749	3.771	<0.001	5.750 (2.317–14.271)	1.340	2.333	0.020	3.819 (1.239–11.775)
	Migrant	1.681	4.012	<0.001	5.371 (2.363–12.210)	0.709	1.413	0.158	2.032 (0.760–5.436)
Age group (years)	50–59 years	1.669	3.771	<0.001	5.307 (2.229–12.636)	1.196	2.179	0.029	3.305 (1.128–9.686)
	60–69 years	1.878	4.045	<0.001	6.538 (2.632–16.241)	1.493	2.636	0.008	4.452 (1.466–13.516)
	≥70 years	1.604	2.579	0.01	4.973 (1.470–16.828)	1.197	1.538	0.124	3.309 (0.720–15.204)
Total		1.738	3.825	<0.001	5.687 (2.334–13.857)	1.284	2.288	0.022	3.613 (1.202–10.858)

Our findings demonstrate a consistent increase in the number of administered doses and vaccination coverage in each of the four years since the license in China of the HZ vaccine. However, despite this upward trend, the coverage was only 2.97%, and the full series coverage was only 2.48% by 2023, slightly higher than the national average. The extremely low coverage of HZ vaccination among the age-target population in China differs dramatically from the vaccination rates in developed countries, such as 8.4% in Canada,¹⁹ 24.1% and 34.5%, respectively, among adults aged 50 and 60 in the United States,²⁰ and 10.2% to 17.7% in Greece.²¹

To our knowledge, this is the first study in China that reports HZ vaccination in a real-world setting. Significant differences were found in urbanicity, socioeconomic level, gender, immigration status, and age group. Similar to a Canadian study, access and affordability concerns with HZ vaccination were major factors in influencing the vaccination rate (6.2%) among urban compared to rural residents (5.3%).¹⁹ Although there is an adequate supply of the HZ vaccine, the primary obstacle to vaccination was the financial situation, and perceptions of HZ diseases and the HZ vaccine.⁸

The current framework in China for promoting immunizations among the elderly, such as reimbursement policies, exhibits noteworthy regional variations across cities and regions. Price sensitivity plays a key role in acceptance of vaccination among the elderly.²² For the elderly with poor economic status, the HZ vaccine price of around USD 200 per dose was too high to bear, which is an important factor causing the low vaccination rate. In Ningbo, the cost of HZ vaccination can be fully reimbursed by social medical insurance or by mutual assistance between family members.

This study identified that the Vaccine Prescription Program did not have a significant effect on increasing HZ vaccination coverage among several subgroups during the post-implementation period. As for the migrant, the primary reason is that they are not the target population covered by social medical insurance and therefore must bear the financial responsibility for vaccination.²³ In

order to promote future HZ vaccination uptake, it is crucial to offer financial help to the migrant. Individuals with high socioeconomic status are typically wealthier and have more access to a variety of information sources,^{24,25} which can lead to vaccine hesitancy from information overload and exposure to false or misleading rumors. Therefore, personalized health communication from HCWs is required to reduce vaccine hesitancy and foster trust in vaccines like the HZ vaccine. As for individuals aged at least 70 years, they are more isolated than the middle-aged in terms of accurate and professional health knowledge. The elderly exhibited a lack of information-seeking capacity, as well as misinformation, fears, and concerns about vaccinations.²⁶ For improving vaccine uptake among the elderly, creating a supportive environment, such as taking a pay-it-forward format, which is an innovative community-engaged intervention.^{27,28} Interventions that target individuals as peers or family members can be utilized alongside to raise vaccine awareness and vaccination willingness.²⁹

The majority of the elderly attach importance to the opinions of health care professionals and recognize their influence.^{12,13} In fact, Ningbo implements the Vaccination Prescription Program so that GPs and PHWs in the CHCs are able to prescribe vaccination. In order to ensure that GPs' and PHWs' efforts on a way to promote vaccinations for the elderly, rational performance assessment from hospital management and adopting a top-down approach, starting with policy and providing financial support to provide free or reduce the cost of vaccines from health administrations, is the next step in the implementation of the Vaccination Prescription Program.¹¹ There is still a long way to improve funding mechanisms and strengthen publicity and education to promote the widespread implementation and effectiveness of the Vaccination Prescription Program.³⁰

Our study has several limitations. First, we lacked population figures by demographics in 2022–2023, so we utilized 2021 population figures, which may have had a slight impact

on our estimates. However, the impact is minor since the mortality rate of the elderly individuals over 60 was approximately 2.2% in Ningbo. Second, despite the NBIIMS's efforts to collect vaccination records in order to ensure compliance with the requirements of the vaccine management law, there may be potential issues where certain records are missing due to unsuccessful uploads. Nonetheless, it is worth noting that there are very few missing records, and it has minimal impact. Third, while we were able to capture certain demographic characteristics in the NBIIMS, we were unable to explore other motivators and barriers, such as education level, occupation, knowledge, and practices regarding the HZ vaccination among the elderly, because these factors were not recorded in the NBIIMS. Additionally, data constraints hindered our ability to conduct interaction between demographic variables to enhance the clarity of the analysis, allowing our ecological study to solely provide an approximation of HZ vaccine coverage at the population level. Finally, this study had a narrow time frame because of the new introduction of the HZ vaccine in September 2020 in Ningbo.

Conclusion

Our study revealed that HZ vaccination coverage in Ningbo has remained low since the introduction of the vaccine in September 2020. Notable disparities in vaccination coverage were observed across different demographics. Coverage increased significantly following the implementation of the Vaccination Prescription Program. This underscores the critical role of GPs in promoting immunization services and the necessity of ensuring adequate vaccination service capacity among PHWs. However, absolute HZ vaccination coverage remained very low as compared to other countries. To address the issue, it is imperative to implement key strategies for providing affordable HZ vaccines, such as government funding, subsidies, and vaccination prescriptions from healthcare professionals, alongside peer initiatives and family members' education.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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Notes on contributor

Rui Ma was born in Gansu, China, in 1969. In 1992, she received her bachelor's degree from the School of Public Health, Lanzhou Medical College. She worked in the Harbin Municipal Center for Disease Control

and Prevention from 1992 to 2005 and in the Ningbo Municipal Center for Disease Control and Prevention from 2005 until the present, engaging in the control and prevention of vaccine-preventable diseases for 32 years. In 2011, she was appointed as a chief physician with a major in preventive medicine. The National Immunization Advisory Committee Specialized for Varicella Immunization Strategy included her as a member. During the past 10 years, she has successfully organized five sessions of continuing education programs at the national and provincial levels. She has participated in eleven national, provincial, and municipal research projects and has contributed to the writing of 8 books and published more than 20 academic papers. She serves on the editorial boards of PREVENTIVE MEDICINE (Zhejiang, China) and the International Journal of Biologicals (Shanghai, China). From 2019 to 2024, she serves as the vice-chairman of the Ningbo Immunization Advisory Committee.

ORCID

Rui Ma  <http://orcid.org/0009-0006-2379-2313>

Authors' contributions

Conceptualization, Jianmei Wang and Rui Ma; Data curation, Jiaxin Wang and Dongkai Du; Formal analysis, Jianmei Wang and Jiaxin Wang; Methodology, Jianmei Wang and Ning Li; Project administration, Dandan Zhang and Rui Ma; Visualization, Jianmei Wang and Jiaxin Wang; Writing – original draft, Jianmei Wang; Writing – review & editing, Dandan Zhang and Rui Ma. All authors read and approved the final manuscript.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical approval

The study was reviewed and approved by the Institutional Review Board of Ningbo Municipal Center for Disease Control and Prevention (Reference number: 202311). Informed consent was exempted because it was limited to analysis of previously de-identified data collected for public health surveillance purposes.

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