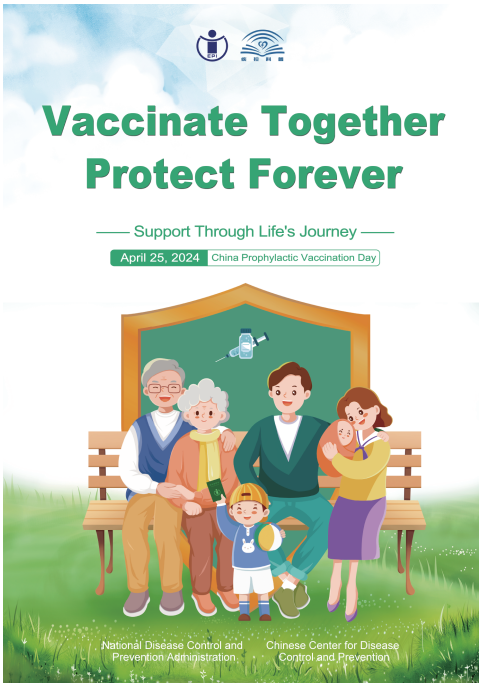
ISSN 2096-7071 (Print)
ISSN 2096-3101 (Online)
CN 10-1629/R1

CHINA CDC WEEKLY

Vol. 6 No. 16 Apr. 19, 2024

中国疾病预防控制中心周报



WORLD IMMUNIZATION WEEK ISSUE

ISSN 2096-7071
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China CDC Weekly

Cover Image: adapted from National Disease Control and Prevention Administration, https://www.ndcpa.gov.cn/jb-kzzx/c100008/common/content/content_1778341757710340096.html.
This week's issue was organized by Guest Editor Huaqing Wang.

Preplanned Studies

Impact of National Immunization Strategies on Vaccine-Preventable Diseases — China, 1950–2021

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Summary

What is already known about this topic?

The incidences of vaccine-preventable diseases (VPDs) included in the Expanded Program on Immunization in China have decreased significantly in recent decades.

What is added by this report?

This study summarizes the national incidences of nine VPDs and the seroprevalence of hepatitis B surface antigen (HBsAg) under different immunization strategies from 1950 through 2021 in China. The sharpest decreases in VPD incidence and under-5-year HBsAg seroprevalence occurred during the latest stage of the National Immunization Program. The decreases in VPD incidence were most prominent among children under five years of age.

What are the implications for public health practice?

These findings provide valuable insights for vaccine value assessment and emphasize the importance of implementing immunization strategies in targeted populations.

Infectious diseases are the largest threat to human health and cause a significant reduction in life expectancy (*1*). Vaccination has proven to be the most effective way to decrease the incidence of infectious diseases and, correspondingly, increase average life expectancy (*2*). China's immunization program has progressed rapidly and comprehensively over the last 70 years, resulting in significant improvements in public health and life expectancy — specifically, in terms of reductions in morbidity and mortality rates due to vaccine-preventable diseases (VPDs). This study aimed to investigate the trends in the number of cases reported and incidence rate of 9 VPDs from 1950 to 2021, as well as the trends in sero-prevalence of hepatitis B surface antigen (HBsAg) from 1980 to 2014, to understand the involving epidemiological patterns and overarching changes in VPDs at the national level. This study's findings indicate that decreases in VPD incidence are most prominent among children under five years of age. In addition, the sharpest decrease occurred during the Expanded Program on Immunization (EPI) stage.

To complete this work, researchers obtained data on reported cases of 9 infectious diseases (diphtheria, hepatitis A, Japanese encephalitis, measles, meningitis, mumps, pertussis, polio, and rubella) from 1950 to 2003 from the Infectious Disease Statistical Report of the Centers for Disease Control and Prevention, China. The data from 2004 to 2021 were obtained from the National Notifiable Disease Reporting System (NNDRS). Population data from 1950 to 2021 were obtained from the Population Division in the Department of Economic and Social Affairs, United Nations (https://population.un.org/wpp/).

The major burden of hepatitis B virus (HBV) is chronic hepatitis B rather than acute hepatitis B; therefore, the prevalence of evidence of HBV infection is a key measure of HBV-related disease burden. This study obtained nationally representative serosurvey data for HBsAg from published scientific documents as evidence of chronic infection. There were 4 national serosurveys in China: one in 1980 (*3*), one in 1992 (*4*), one in 2006 (*5*), and one in 2014(*6*). These surveys covered ages 0–59 years in 1980, 1–59 years in 1992, 1–59 years in 2006, and 1–29 years in 2014. Given that a vaccine against hepatitis B became available in 1985 and was included in the National Immunization Program (NIP) in 2002 and in the EPI in 2008, serosurveys in 1980, 1992, 2006, and 2014 reflect the hepatitis B disease burden in the prevaccine, pre-NIP, NIP, and EPI stages, respectively, as defined below.

This study used Microsoft Excel 2019 (Microsoft Corporation, Redmond, WA, USA) to construct an analytic VPD incidence database and a statistical analysis system (SAS, version 9.4; SAS Institute, Inc., Cary, NC, USA) to perform the statistical analyses.

First, this study's researchers divided the study period into four stages based on vaccine availability, history of disease control, and immunization strategy

implementation: 1) the prenational immunization program (pre-NIP stage, 1950–1977), which was the period in which there was no national vaccination program; 2) the early-stage NIP (early NIP, 1978–1987), in which vaccines against measles, polio, diphtheria, tetanus, pertussis, and tuberculosis were incorporated into the NIP (in 1978) and when, with support from the government and international organizations, the vaccine cold chain system was established and nearly completed; 3) the late-stage NIP (late NIP, 1988–2007), in which vaccination coverage rates (VCRs) steadily increased toward a target of 85% at the provincial level by 1988, the county level by 1990, and the township level by 1995, and during which the hepatitis B vaccine was included in the NIP (in 2002); and 4) the expanded immunization program stage (EPI, 2008–2021), during which vaccines against mumps, rubella, JE, and invasive meningococcal disease were incorporated into the EPI (in 2008).

Between 1950 and 2021, 172,285,377 cases among the 9 study VPDs were reported in China, representing a cumulative average incidence of 230.8 per 100,000 people. Among these patients, 143,599,524 (83.35%) were diagnosed during the pre-NIP stage, 15,468,640 (8.98%) during the early NIP stage, 8,124,496 (4.72%) during the late NIP stage, and 5,092,717 (2.96%) during the EPI stage. The overall average incidences of these 9 VPDs were 701.01, 151.02, 32.98, and 26.43 per 100,000 for the pre-NIP stage, early NIP, late NIP, and EPI, respectively (Table 1).

This study then analyzed the incidences of the 9 VPDs in children under 5 years old using age data that were available from 1997 to 2021 (Table 2). As vaccines against diphtheria, hepatitis A, measles, pertussis, and polio were incorporated into the NIP before 2008, this study divided the examination period for these five diseases into two stages: the pre-EPI stage (1997–2007) and the EPI stage (2008–2021). Vaccines against JE, mumps, rubella, and meningitis were included in the EPI by 2008, so children under 5 years of age would therefore be covered by 2012. This study next divided the period for these diseases into a pre-EPI stage (2004–2012) and an EPI stage (2013–2021). Decreases in the incidences among children under 5 years old were observed for all the VPDs except for pertussis in the EPI stage compared with the pre-EPI stage. The incidence of pertussis increased to 63.77% in the EPI stage compared with the pre-EPI stage. The annual case numbers for children under 5 years old from 1997 to 2021 are presented in Figure 1.

TABLE 1. Number of reported cases and incidence of nine vaccine-preventable infectious diseases in the overall population by immunization stage in China, 1950–2021.

VPDs	Monitoring start (years)	Pre-NIP (1950–1977)		Early NIP (1978–1987)			Late NIP (1988–2007)			EPI (2008–2021)		
		The number of cases	Incidence (/100,000)	The number of cases	Incidence (/100,000)	Decrease* (%)	The number of cases	Incidence (/100,000)	Decrease (%)	The number of cases	Incidence (/100,000)	Decrease* (%)
Diphtheria	1950	1,518,016	7.41	74,990	0.73	90.15	1,891	0.01	99.87	2	<0.01	100.00
Polio	1953	356,743	1.90	49,953	0.49	74.21	14,448	0.06	96.84	0	0	100.00
Pertussis	1950	30,083,436	146.86	4,323,810	42.21	71.26	190,689	0.77	99.48	104,385	0.54	99.63
Measles	1950	101,512,542	495.56	9,243,723	90.25	81.79	1,772,811	7.20	98.55	399,905	2.08	99.58
JE	1950	1,734,057	8.47	327,078	3.19	62.34	279,919	1.14	86.54	21,572	0.11	98.70
Meningitis	1950	8,394,730	40.98	1,449,086	14.15	65.47	114,327	0.46	98.88	3,331	0.02	99.95
Hepatitis A	1990	NA	NA	NA	NA	NA	4,547,133	20.30	NA	364,380	1.89	90.69†
Mumps	2004	NA	NA	NA	NA	NA	1,042,052	19.87	NA	3,776,930	19.60	1.36†
Rubella	2004	NA	NA	NA	NA	NA	161,226	3.07	NA	422,192	2.19	28.66†

Abbreviation: VPD=vaccine-preventable disease; NIP=national immunization program; EPI=expanded immunization program; NA=not applicable.
* Decrease in incidence compared with the pre-NIP.
† Decrease in incidence compared with the late NIP.

TABLE 2. Number of reported cases and incidences of nine VPDs in children under 5 years old by immunization stage in China, 1997–2021.

VPDs	Pre-EPI*		EPI†		
	The number of cases decrease	Incidence (/100,000)	The number of cases decrease	Incidence (/100,000)	Decrease (%)
Diphtheria	29	<0.01	0	0	100.00
Measles	370,648	40.38	221,956	18.33	54.60
Pertussis	41,669	4.54	90,016	7.43	−63.77
Polio	0	0	0	0	NA
JE	16,123	1.92	881	0.13	93.37
Meningitis	2,385	0.28	296	0.04	84.95
Hepatitis A	97,983	10.67	29,603	2.44	77.10
Mumps	486,718	57.91	320,223	46.23	20.17
Rubella	79,538	9.46	6,590	0.95	89.95

Abbreviation: EPI=expanded program on immunization; VPD=vaccine-preventable disease; JE=Japanese encephalitis; NA=not applicable.
* Period from 1997 to 2007 for diphtheria, measles, pertussis, polio, and hepatitis A and from 2004 to 2012 for JE, meningitis, mumps, and rubella.
† Period from 2008 to 2021 for diphtheria, measles, pertussis, polio, and hepatitis A and from 2013 to 2021 for JE, meningitis, mumps, and rubella.

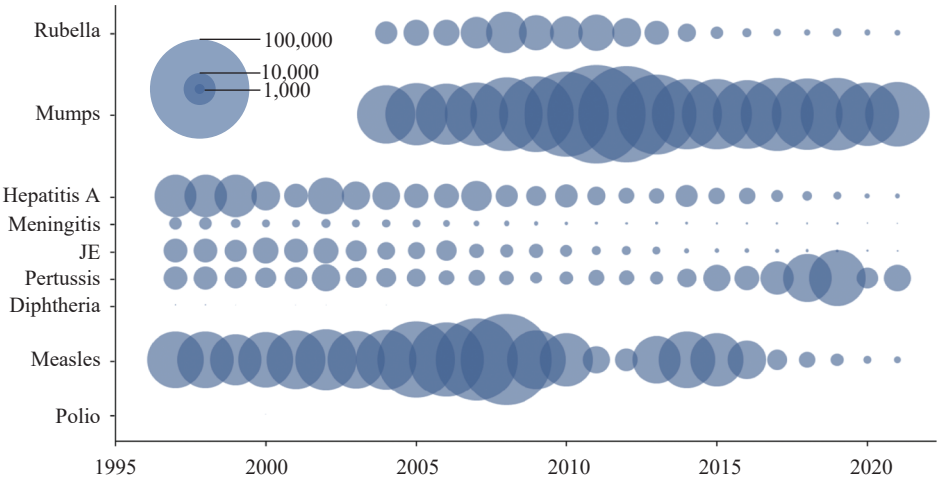

FIGURE 1. Number of reported cases of nine VPDs in children under 5 years old, 1997–2021, represented as bubble diagrams.
Abbreviation: VPD=vaccine-preventable disease; JE=Japanese encephalitis.

The seroprevalence of HBsAg was significantly lower in 2006 and 2014 than in 1980 and 1992, respectively. HBsAg seroprevalences among children aged 1–4 years were 9.24%, 9.67%, 0.96%, and 0.32% in 1980, 1992, 2006, and 2014, respectively (Figure 2).

DISCUSSION

This study explored patterns in case numbers and incidences of ten VPDs in China to evaluate the impact of different immunization strategies on the prevention and control of infectious diseases. Its findings showed that at the national level and within 72 years — from 1950 to 2021 — the annual case numbers and incidences of VPDs decreased significantly across all four stages of immunization, with particularly notable decreases in the late NIP and EPI stages. For measles, pertussis, diphtheria, JE, meningitis, and polio, there was a greater than 98% reduction in the incidence in the EPI stage. In contrast, the decreases in incidence of rubella and mumps were relatively small in the overall population, but there was a larger decrease in the incidences of these diseases in children under 5 years of age than in the overall population during the EPI stage. This could be explained by the EPI vaccination schedule, which included a target population of children under 5 years

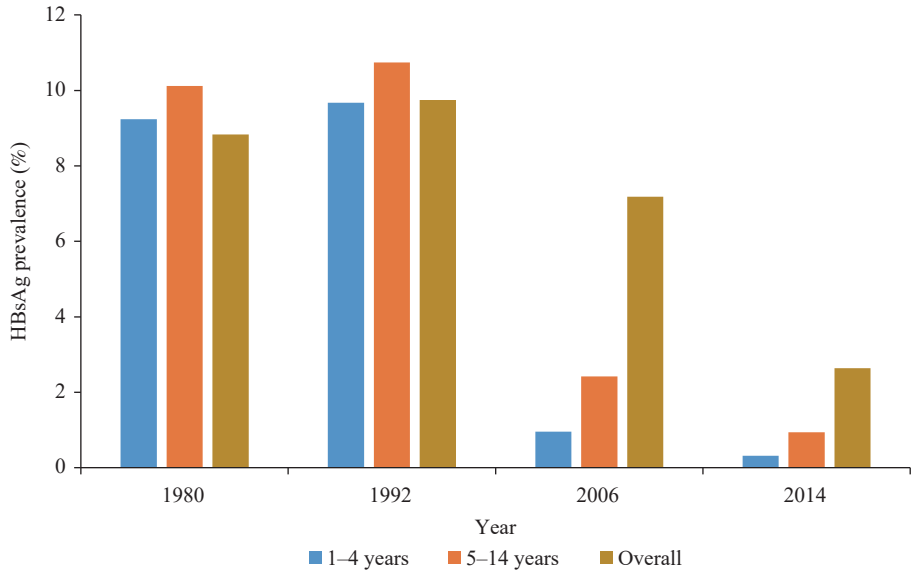

FIGURE 2. HBsAg incidence in China from national serosurveys in 1980, 1992, 2006, and 2014.
Note: The sampled populations were 0–59 years, 1–59 years, 1–59 years, and 1–29 years in surveys conducted in 1980, 1992, 2006, and 2014, respectively.
Abbreviation: HBsAg=hepatitis B surface antigen.

old.

This study's researchers observed notable decreases in HBsAg incidence in different age groups in 2006 and 2014, revealing that increasing hepatitis B vaccine coverage, especially the timely birth dose, has played a major role in the dramatic reduction in HBsAg prevalence in China. These findings are consistent with subnational studies (*7*) and overseas studies (*8*). The introduction and implementation of the NIP and EPI increased vaccine coverage and are the predominant contributors to the dramatic reduction in the incidence of VPDs in China. The reported number of mumps cases has shown an increasing trend in recent decades. Yang and colleagues reported a similar trend of infectious disease incidence from 2004 to 2013 (*9*). Despite the modest decrease in the incidence of mumps during the EPI stage, remarkable decreases were achieved in the late NIP and EPI stages compared with the incidence in the 1990s, based on published data (451.57/100,000) (*10*). This modest decrease may be partially attributable to the improved sensitivity of the reporting system over time. Additionally, only the single-dose mumps-containing vaccine was included in the national EPI before 2020, and this suboptimal regimen would likely lead to a nonsignificant decrease in mumps. In cities where two-dose schedules were used, greater than 50% reductions in mumps incidences were observed in the two-dose era compared with the one-dose era. The low effectiveness of mumps vaccines due to waning immunity may also be a key contributor to the modest decreases in mumps incidence.

This study has several strengths. First, because its surveillance data spans up to 72 years, researchers were able to observe the impact of four different immunization strategies on VPDs at the national level. Second, this study was able to obtain age data, which allowed it to observe that decreases in incidence were most remarkable among children under 5 years of age.

However, this study also has several limitations. First, this study's analyses are largely dependent on reported case data across decades. The quality and completeness of the reporting and reporting systems varied across the four stages. Second, although the Bacillus Calmette Guérin vaccine against tuberculosis was one of the first 4 vaccines incorporated into the NIP in 1978, tuberculosis data were not included in this study due to data availability. Finally, the declines in VPDs observed by this study may not be entirely dependent on vaccination and may reflect improved nutrition, health care, and living conditions. Future research should include additional factors to present a comprehensive assessment of the impact of immunization strategies on VPD control. Additionally, additional attention should be given to the full value of vaccines beyond the reduction of illness and death in future studies.

In conclusion, this study found that the

implementation of immunization strategies significantly contributed to the decrease in incidence of VPDs in China. In particular, declines were observed during the most recent NIP stage because of the maintenance of a high VCR. VPD incidence declines were most prominent among the populations receiving the immunization strategy at the targeted ages. These findings indicate that a high VCR effectively controls the VPDs in the target population. Measures should be taken to maintain the VCR and optimize immunization strategies for VPDs that still circulate in the vaccine target population. Additionally, to better control the VPDs that were not included in the NIP, a holistic plan should be made to assess the feasibility of incorporating them.

Conflicts of interest: No conflicts of interest.

Acknowledgement: We thank Dr. Lance Rodewald, National Immunization Program, Chinese Center for Disease Control and Prevention, for constructive comments on a draft of this manuscript and polishing language.

Funding: Supported by Operation of the CDC Public Health Emergency Response Mechanism in China (131031001000150001).

doi: 10.46234/ccdcw2024.064

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Submitted: January 13, 2024; Accepted: March 18, 2024

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Vital Surveillances

Thirty Years of Experience of Acute Flaccid Paralysis Surveillance for Polio — China, 1993–2022

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ABSTRACT

Introduction: Detecting poliovirus infections proves to be highly challenging due to their asymptomatic nature and infectious potential, highlighting the crucial importance of effective detection methods in the context of polio eradication efforts. In many countries, including China, the primary approach for identifying polio outbreaks has been through acute flaccid paralysis (AFP) surveillance. In this study, we conducted an evaluation spanning three decades (1993–2022) to assess the effectiveness of AFP surveillance in China.

Methods: Data on all AFP cases identified since 1993 and national-level AFP surveillance system quality indicators aligned with the World Health Organization (WHO) standards were collected for analysis. The quality indicators assess surveillance sensitivity, completeness, timeliness of detection notification, case investigation, and laboratory workup. Surveillance sensitivity is determined by the non-polio AFP (NPAFP) detection rate among children under 15 years of age.

Results: Between 1993 and 2022, a total of 150,779 AFP cases were identified and reported. Within this pool, surveillance identified 95 cases of wild poliovirus (WPV) and 24 cases due to vaccine-derived poliovirus. From 1995 onwards, the detection rate of NPAFP cases consistently adhered to the WHO and national standards of ≥1 case per 100,000, falling between 1.38 and 2.76. Starting in 1997, all timeliness indicators consistently achieved the criteria of 80%, apart from the consistency in meeting standards set for the rate of positive specimens sent to the national laboratory.

Conclusions: AFP surveillance has been instrumental in China's accomplishment of maintaining a polio-free status. The ongoing adherence to key performance indicators, ensuring sensitivity and prompt specimen collection, demonstrates that AFP surveillance is proficient in detecting poliovirus in China. As we move into the post-eradication phase, AFP surveillance remains crucial for the sustained absence of polioviruses in the long term.

In 1988, the World Health Assembly endorsed a resolution aimed at the global eradication of polio, leading to the establishment of the Global Polio Eradication Initiative (GPEI). In 2014, the World Health Organization (WHO) designated the international spread of wild poliovirus (WPV) as a Public Health Emergency of International Concern, a status that has been consistently maintained ever since. GPEI has made significant advancements towards the eradication of polio, with the successful elimination of WPV types 2 and 3 in 2015 and 2019, respectively. Furthermore, five out of the six WHO regions have been recognized as polio-free (*1*). China, along with all countries in the Western Pacific region, was accredited as polio-free in October 2000 and has successfully maintained this status to date.

Poliovirus infection typically presents asymptomatically and only results in paralysis in less than 1% of infected individuals (*1*). The strategy for eradicating polio involves maintaining a high level of population immunity to the virus, promptly detecting polio outbreaks through identifying infected individuals, and executing substantial outbreak responses. Identifying every child affected by poliovirus is crucial, as a single case can signify an outbreak, potentially indicating numerous asymptomatic infections that are contagious.

Since the initiation of the GPEI, the surveillance of acute flaccid paralysis (AFP) has been instrumental in the detection of polio cases. AFP surveillance helps to identify children with paralysis, who are subsequently assessed for poliovirus infection. In the event of a polio

diagnosis, public health authorities initiate an investigation and implement response measures, such as vaccination campaigns, to halt the transmission of the poliovirus.

The sensitivity of AFP surveillance is of utmost importance and is objectively evaluated by determining if the annual AFP detection rate per 100,000 children under 15 years of age is at or above a specified threshold (one case). Detection rates surpassing this threshold offer reassurance of adequate sensitivity for detecting cases of paralytic polio.

In 1991, China established a dedicated AFP surveillance system aimed at polio eradication, following the development of guidelines in 1992 (*2*–*3*). By 1993, all provincial-level administrative divisions (PLADs), except the Xizang (Tibet) Autonomous Region, had adopted standardized national surveillance protocols that encompassed active AFP surveillance, case investigations, and stool specimen collection for poliovirus detection. The sensitivity and quality indicators of AFP surveillance have consistently remained at high levels, with sensitivity showing a gradual increase over time (*4*–*6*). While there have been epidemiological studies and case reports documenting AFP surveillance activities (*5*,*7*–*8*), a comprehensive overview of the overall progress of AFP surveillance in China has yet to be provided.

Data regarding all cases of AFP identified in China since 1993, and reports of surveillance system quality indicators were obtained. We conducted an evaluation and description of AFP surveillance in China over a 30-year period (1993–2022), assessing aspects such as incidence rates, epidemiological and laboratory investigations, clinical diagnoses, and the effectiveness and quality of the surveillance system.

METHODS

In China, real-time AFP surveillance is a mandatory initiative overseen by China CDC, with the annual submission of results to the WHO Regional Committee. The identification of AFP cases depends on both passive reporting from hospitals and active surveillance conducted by staff at county CDC. Since the inception of a nationwide infectious disease surveillance system in 1991, virtually all hospitals at or above the county level have been reporting AFP cases. County CDC personnel thoroughly investigate each AFP case, gathering stool specimens that are later transported to provincial laboratories for virus isolation. Positive isolates are subsequently forwarded to the National Poliovirus Laboratory at China CDC, recognized as a WHO regional reference laboratory, for intratypic differentiation and genome sequencing. All data are meticulously recorded in the AFP Surveillance Information Reporting and Management System.

Assessment of AFP Surveillance Quality

Annually, quality indicators are computed at the national level and juxtaposed with WHO criteria. These indicators assess the sensitivity, comprehensiveness, and promptness of notification, investigation, and laboratory examinations.

The sensitive threshold for AFP surveillance set by the WHO aligns with China's AFP surveillance guidelines, requiring the detection of at least one AFP case per 100,000 individuals under 15 years per year. Adherence to the WHO protocol for sample collection, necessitating the retrieval of two adequate stool samples within a 14-day period, stands at 80% efficiency (*1*). In accordance with China's AFP surveillance guidelines, key criteria include an 80% rate for prompt investigation within 48 hours of case identification, timely receipt of stool samples within seven days, availability of poliovirus isolation results within 30 days, and the swift shipment of poliovirus-positive specimens to the national laboratory within a 30-day window.

Definitions

Clinically compatible polio cases are defined as AFP cases lacking stool specimens or having inadequate stool specimens without detection of WPV or vaccine-derived poliovirus (VDPV). These cases cannot be definitively ruled out for polio by provincial expert diagnostic teams, irrespective of residual paralysis, death, or loss of follow-up.

Excluded polio cases refer to AFP cases falling into one of two categories: 1) cases presenting with eligible stool specimens wherein neither WPV nor VDPV are identified; 2) cases lacking suitable stool specimens or presenting with inadequate specimens, with no detection of WPV or VDPV, yet conclusively ruled out as polio cases by regional expert diagnostic teams, irrespective of any residual paralysis, mortality, or loss of follow-up.

Statistical Analysis

Descriptive statistics were utilized to summarize the

demographic characteristics of AFP cases. Data on non-polio AFP (NPAFP) detections and population statistics were sourced from the China CDC information system. The analysis was performed using Microsoft Excel (version 2019, Microsoft, Redmond, USA).

Ethical Review

Individual-level, case-based AFP surveillance is required and is not subject to ethical review.

RESULTS

Detection of AFP and Demographic Variables

Table 1 illustrates the results of AFP surveillance and sensitivity indicator values over the 30-year study duration. A total of 150,779 AFP cases were identified and reported, with 149,386 cases (99%) occurring in children under the age of 15. The annual reported

TABLE 1. AFP cases and surveillance sensitivity indicators in China, 1993–2022.

Year	No. of AFP cases	No. of WPV cases	<15 NPAFP	<15 NPAFP detection rate	No. of clinically compatible polio cases	No. of discarded polio cases	No. of VDPV cases
1993	1,879	63	1,226	0.37	653	–	–
1994	3,142	6	2,790	0.88	307	–	–
1995	4,801	1 (imported)	4,615	1.49	168	–	–
1996	4,372	3 (imported)	4,171	1.38	201	4,171	–
1997	4,730	0	4,730	1.59	42	4,688	–
1998	5,009	0	5,009	1.72	44	4,965	–
1999	5,079	1 (imported)	5,078	1.76	33	5,045	–
2000	5,332	0	5,332	1.85	17	5,315	–
2001	5,395	0	5,395	1.88	19	5,376	0
2002	5,415	0	5,415	1.89	20	5,395	1
2003	5,107	0	5,107	1.79	21	5,086	0
2004	5,285	0	5,285	1.86	19	5,266	2
2005	5,425	0	5,425	1.94	16	5,409	1
2006	5,635	0	5,635	2.02	10	5,625	1
2007	4,986	0	4,986	1.79	1	4,985	2
2008	5,154	0	5,154	1.91	3	5,151	0
2009	4,961	0	4,961	1.79	8	4,948	0
2010	5,285	0	5,285	1.91	3	5,282	1
2011	6,205	21	6,205	2.49	30	6,152	2
2012	6,172	0	6,172	2.76	2	6,168	2
2013	5,623	0	5,623	2.51	1	5,621	1
2014	5,758	0	5,758	2.56	0	5,756	2
2015	5,217	0	5,217	2.31	1	5,216	0
2016	5,691	0	5,691	2.52	0	5,690	1
2017	5,278	0	5,278	2.33	0	5,276	2
2018	5,292	0	5,292	2.31	0	5,292	1
2019	5,183	0	5,183	2.23	0	5,183	2
2020	4,369	0	4,369	1.85	0	4,369	2
2021	4,771	0	4,771	2.02	0	4,771	1
2022	4,228	0	4,228	1.79	0	4,228	0
Total	150,779	–	149,386	–	1619	140,429	24

Note: "–" means not applicable.
Abbreviation: AFP=acute flaccid paralysis; WPV=wild poliovirus; NPAFP=non-polio acute flaccid paralysis; VDPV=vaccine-derived poliovirus.

cases of AFP varied from 1,879 in 1993 to 6,205 in 2011.

During the surveillance period, AFP surveillance identified 63 cases of WPV in 1993 and six in 1994. Additionally, five imported WPV cases were reported in 1995, 1996, and 1999. In 2011, Xinjiang reported 21 cases of WPV associated with AFP. No other instances of paralytic WPV infection were documented throughout the study period.

Among cases of AFP in individuals under 15 years of age, 140,429 (94%) were diagnosed as non-polio, 1,619 (1.1%) were clinically compatible cases that tested negative for poliovirus, and 24 cases were identified as VDPV cases. Eighty-two percent of clinically compatible cases were reported before 2000. The number of clinically compatible polio cases declined from 307 in 1994 to 42 in 1997, further dropping to fewer than 10 cases in 2007, and reaching zero in 2016, with no reported cases since, except for a slight increase in 2011 in Xinjiang attributed to enhanced AFP surveillance during an outbreak.

The surveillance sensitivity indicator for detecting NPAFP among children under 15 years of age showed an increase over the study period, rising from 0.37 cases per 100,000 in 1993 to 2.76 per 100,000 in 2012. The NPAFP detection rate in children under 15 surpassed the criterion of 1 per 100,000 for 28 consecutive years (1995–2022) and exceeded 2 per 100,000 for eleven of those years.

Of the 140,429 cases of NPAFP identified, 55,634 (40%) received definitive diagnoses. Among these, 9,505 cases were attributed to Guillain-Barré syndrome (GBS), 3,024 to non-polio enterovirus (NPEV) infection, 1,158 to transverse myelitis, and 1,116 to traumatic neuritis. The most prevalent category was classified as "others," underscoring the diverse range of factors contributing to AFP in pediatric cases (Figure 1).

Timeliness

Two indicator definitions remained consistent throughout the study period: investigating within 48 hours and collecting an adequate stool sample within 14 days of paralysis. Both indicators have an established criterion of 80%. Investigation timeliness has consistently met or exceeded the 80% target annually since 1995, while stool sample timeliness achieved the 80% target in 1996 and has been maintained at over 80% ever since.

Definitions for three indicators were modified over the study period. The timeframe for receipt of stool samples by provincial CDCs was adjusted from ten days in 1993 to seven days in 1995. Similarly, the timeline for isolation results being available at provincial CDC laboratories was altered from 45 days in 1993 to 30 days in 1995, then to 28 days in 2003, and finally to 14 days in 2015. Despite more stringent criteria, China's AFP surveillance system achieved and maintained 80% targets in 1996 and 1997. The indicator tracking poliovirus-positive specimens shipped to the national polio laboratory (NPL) fluctuated between 35% and 100%, with the timeframe changing from 30 days in 1997 to 14 days in 2003 (Figure 2).

DISCUSSION

Since 1995, China's AFP surveillance system has consistently met both the WHO and national sensitivity criteria. From 1993 to 2022, the system

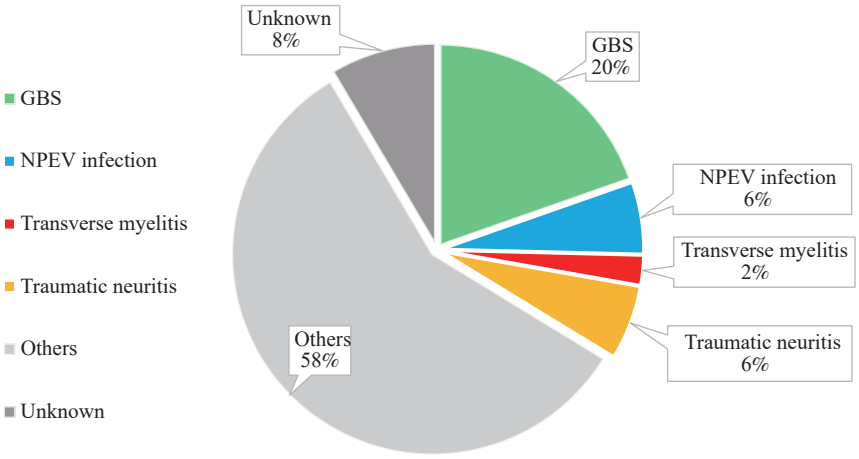

FIGURE 1. Final diagnosis of NPAFP cases <15 years old in China, 1993–2022.
Abbreviation: GBS=Guillain-Barré syndrome; NPEV=Non-polio enterovirus; NPAFP=non-polio acute flaccid paralysis.

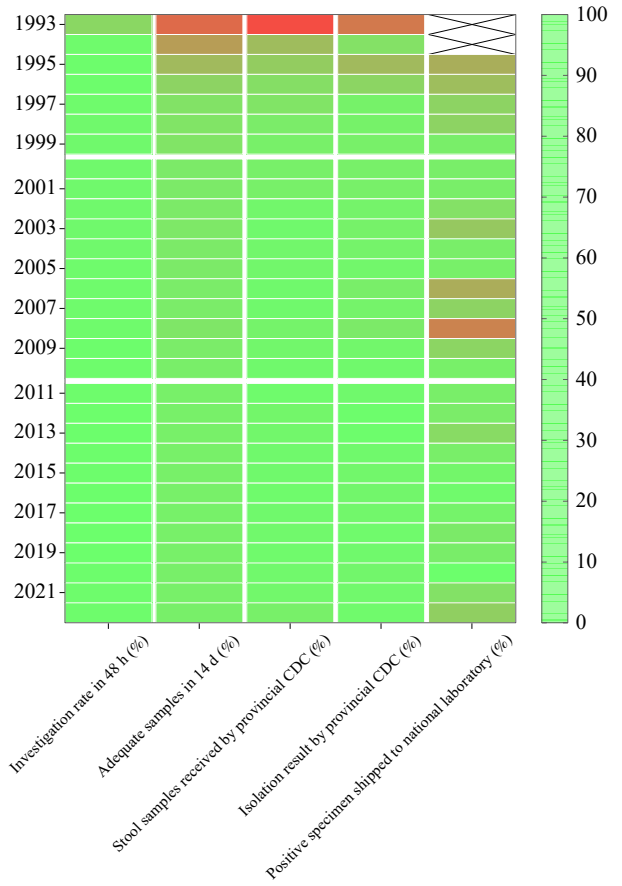

FIGURE 2. Timeliness indicators of AFP surveillance in China, 1993–2022.

identified 95 cases of WPV and 24 cases of vaccine-derived poliovirus among over 150,000 AFP cases. Through thorough investigations, these cases were found not to be polio-related. Maintaining accurate and sensitive polio surveillance is crucial for preserving a polio-free status in both pre- and post-global polio eradication efforts. This study represents the initial account of the results generated by the AFP surveillance system over the years leading up to China's polio-free certification in 2000 and the subsequent years thereafter.

The AFP surveillance system's detections of WPV have been crucial for upholding the polio-free status. For instance, in Xinjiang in 2012, AFP surveillance identified 21 WPV cases, which, through subsequent investigations, were determined to be import-related with evidence of local transmission. The prompt detection facilitated a swift response that safeguarded China's polio-free status (*9*).

AFP surveillance identified 24 VDPV cases, some of which were previously documented (*10*–*11*). Following WHO recommendations, response measures were implemented for each VDPV case. Given the continued use of live poliovirus vaccines, the emergence of VDPVs capable of transmission and causing paralysis is expected, underscoring the importance of AFP surveillance in identifying paralytic cases indicative of VDPV outbreaks. As the global eradication of polio progresses, AFP surveillance will play a pivotal role as an essential element of a robust polio surveillance system.

AFP surveillance, although critical, may not suffice for comprehensive poliovirus detection, as it lacks the ability to identify polioviruses in asymptomatic children. An incident in Shanghai during 2020–2021 illustrated this limitation, where two circulating VDPV (cVDPV) type 3 were detected in a non-paralyzed child and an environmental sample, which genetic analysis revealed genetically linked (*12*). Despite the evidence of poliovirus circulation, no paralysis cases were reported. Similarly, a child diagnosed with a primary immunodeficiency (PID) without paralysis was found to harbor an VDPV, namely iVDPV, in stool samples (*13*). Silent infections like these are beyond the scope of detection by AFP surveillance; however, they can contribute to poliovirus transmission. Therefore, supplementary surveillance methods are imperative, including environmental (wastewater) surveillance and poliovirus monitoring in children newly diagnosed with PID. The evolution of AFP surveillance into an integrated disease surveillance system holds promise for sustained polio control and may yield benefits in managing other infectious diseases (*14*).

In order to enhance quality assurance, our AFP surveillance system underwent enhancements and modernizations concurrent with advancements in surveillance practices and program development. Initially, from 1991 to 1993, AFP cases were documented on paper and in written correspondence. Subsequently, spanning the years 1994 to 2003, case data for AFP were managed at the local level before being transmitted to China CDC via monthly email communications. Between 2004 and 2011, AFP surveillance transitioned to a client-server Internet platform that facilitated data analysis, with provincial CDC personnel submitting case details on a monthly basis. By 2012, the AFP surveillance mechanism had been integrated into China's national disease reporting framework, operating as a real-time online system (*4*).

The evaluation of AFP surveillance quality relies on two key performance indicators: the NPAFP detection rate and the percentage of AFP cases with adequate stool specimens. A NPAFP rate of ≥1/100,000 is deemed sufficiently sensitive for poliovirus detection. The benchmark for AFP cases with adequate stool specimens is set at ≥80%. Our research reveals a swift and

sustained enhancement in surveillance indicators. Amid the COVID-19 lockdown from 2020 to 2022, certain timeliness indicators may have been adversely affected in selected PLADs; nonetheless, national annual indicators consistently met the 80% benchmark. The rapid decline in polio-compatible cases early on signifies improvements in stool sample collection and laboratory diagnosis procedures, signaling the need for continued enhancements. Despite unchanged surveillance guidance since 2006, there persists a subset of AFP cases lacking specific diagnoses or final classifications. The fluctuating proportion of positive samples forwarded to the NPL throughout the study period underscores the necessity for ongoing refinements.

Our study is constrained by the fact that definitions for VDPV cases were modified in 2016, likely resulting in potential underestimation of VDPV cases prior to the alteration. Furthermore, the relatively low counts of "No. of AFP cases" and "<15 NPAFP" in 1993 could be attributable to the nascent stage of the AFP surveillance system at that time.

In conclusion, AFP surveillance has been pivotal in China's effort to attain and uphold polio-free status, identifying 119 polio cases among 150,000 AFP cases over a 30-year period. The significance of AFP surveillance remains paramount, even post global polio eradication. Key performance indicators, such as the NPAFP rate and the proportion of AFP cases with sufficient stool specimens, have consistently met both WHO and national standards, demonstrating the effectiveness of China's AFP surveillance system in detecting polioviruses. Given the ongoing risks associated with WPV and cVDPV importation and transmission, maintaining a highly sensitive and timely AFP surveillance system will be essential to upholding polio eradication efforts in China and worldwide (*15*).

Conflicts of interest: No conflicts of interest.

Acknowledgements: All provincial and local Centers for Disease Control and Prevention in China.

Funding: Supported by the public health emergency response mechanism operated by the Chinese Center for Disease Control and Prevention (No. 102393220020010000017).

doi: 10.46234/ccdcw2024.065

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Submitted: December 06, 2023; Accepted: March 26, 2024

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Methods and Applications

Comparison of Statistical Signal Detection Methods in Adverse Events Following Immunization — China, 2011–2015

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ABSTRACT

Introduction: The current study aims to assess the performance of data mining techniques in detecting safety signals for adverse events following immunization (AEFI) using routinely obtained data in China. Four different methods for detecting vaccine safety signals were evaluated.

Methods: The AEFI data from 2011 to 2015 was collected for our study. We analyzed the data using four different methods to detect signals: the proportional reporting ratio (PRR), reporting odds ratio (ROR), Bayesian confidence propagation neural network (BCPNN), and multi-item gamma Poisson shrinker (MGPS). Each method was evaluated at 1–3 thresholds for positivity. To assess the performance of these methods, we used the published signal rates as gold standards to determine the sensitivity and specificity.

Results: The number of identified signals varied from 602 for PRR1 (with a threshold of 1) to 127 for MGPS1. When considering the common reactions as the reference standard, the sensitivity ranged from 0.9% for MGPS1/2 to 38.2% for PRR1/2, and the specificity ranged from 85.2% for PRR1 and ROR1 to 96.7% for MGPS1. When considering the rare reactions as the reference standard, PRR1, PRR2, ROR1, ROR2, and BCPNN exhibited the highest sensitivity (73.3%), while MGPS1 exhibited the highest specificity (96.9%).

Discussion: For common reactions, the sensitivities were modest and the specificities were high. For rare reactions, both the sensitivities and specificities were high. Our study provides valuable insights into the selection of signal detection methods and thresholds for AEFI data in China.

Data mining techniques have been widely employed since the late 1990s for identifying safety signals in databases containing spontaneously reported adverse reactions of drugs and vaccines (*1–5*). The primary objective is to generate hypotheses for further evaluation of potential safety concerns. Disproportionality analysis, a case/non-case method that compares observed rates with expected rates, is the most commonly used technique for signal detection (*1–5*). However, the performance of these methods and the impact of different thresholds on their performance in detecting safety signals in adverse events following immunization (AEFI) reports in China remain unknown. It is crucial to assess the performance of each signal detection method to establish a reference for routine vaccine safety signal detection.

We evaluated the performance of safety signal detection algorithms in detecting AEFI using data collected in China from 2011 to 2015. The number of signals detected and the operating characteristics of these algorithms were analyzed. Sensitivity and specificity were estimated using published data as gold standards, with different threshold values for each algorithm (*2–7*). The findings of this study can guide the selection of suitable detection methods and threshold values for vaccine safety surveillance in China.

METHODS

Data Sources

The study utilized spontaneous AEFI reports from the national AEFI information system (*8*) from 2011 to 2015. Data preparation involved several steps, including the removal of confidential information (*9*) and duplicate reports, as well as reports without valid AEFI clinical diagnosis that would not contribute to the vaccine-AEFI pair. Additionally, reports with multiple AEFI clinical diagnoses or suspected vaccines were separated into multiple individual reports, each with a unique AEFI clinical diagnosis and suspected vaccine (*10*). The AEFI clinical diagnoses were coded

using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary, version 24.0 (*11*). All vaccines and AEFI clinical diagnoses were included in the analysis.

Signal Detection Methods and Thresholds

Statistical signal detection was performed by analyzing the reporting rates of specific adverse events associated with specific vaccines. Four commonly used methods for analyzing disproportionality were applied: proportional reporting ratio (PRR) (*4*), reporting odds ratio (ROR) (*2–3*), Bayesian confidence propagation neural network (BCPNN) (*1*,*3*), and multi-item gamma Poisson shrinker (MGPS) (*5*). PRR and ROR are frequentist methods, while BCPNN and MGPS are Bayesian methods. The computation techniques for each method can be found in the supplementary table S1 and relevant publications (*1–5*).

The disproportionality analysis is based on a 2×2 table (Table 1). In this table, cell a represents the number of reports containing both the vaccine of interest and the AEFI of interest. Cell b represents the number of reports containing the vaccine of interest with AEFIs other than the AEFI of interest. Cell c represents the number of reports containing the AEFI of interest with vaccines other than the vaccine of interest. Cell d represents the number of reports containing AEFIs and vaccines other than the ones of interest.

TABLE 1. Two-by-two contingency table for signal detection.

	AEFI of interest	Other AEFIs	Total
Vaccine of interest	a	b	a+b
Other vaccines	c	d	c+d
Total	a+c	b+d	N

Note: "a" means number of reports containing both the vaccine of interest and the AEFI of interest; "b" means number of reports containing the vaccine of interest with AEFIs other than the AEFI of interest; "c" means number of reports containing the AEFI of interest with vaccines other than the vaccine of interest; "d" means number of reports containing AEFIs and vaccines other than the ones of interest.
Abbreviation: AEFI=adverse events following immunization.

Table 2 presents the signal detection methods and the threshold values to be assessed. Each signal detection method was evaluated using up to three signal threshold values. Vaccine-AEFI combinations with statistical values exceeding the threshold values were deemed as positive signals.

Performance Evaluation

We calculated the operating characteristics (sensitivity and specificity) of each signal detection algorithm to classify each vaccine-AEFI combination as either a signal or a non-signal. We used published reference standards as our gold standards (*14*).

Two sets of reference standards based on the global manual on the surveillance of adverse events following immunization by the World Health Organization (WHO) (*15*) and safety signals from previous studies (*16–20*) were created (Table 3). Sensitivity and specificity were determined and presented in Table 4.

$$\textbf{Sensitivity} = \frac{A}{A+C} \times 100\%$$

$$\textbf{Specificity} = \frac{D}{B+D} \times 100\%$$

TABLE 2. Signal detection methods and thresholds to be evaluated.

Signal detection method	Signal detection algorithm*	Threshold†
PRR	PRR1	Lower limit of 95% *CI* of PRR > 1(7) and a ≥ 3
	PRR2	Lower limit of 95% *CI* of PRR > 1(7) and a ≥ 5
	PRR3	PRR > 2 and $\chi^2 \geq 4$ and a ≥ 3 (7)
ROR	ROR1	Lower limit of 95% *CI* of ROR > 1 and a ≥ 3 (7,12)
	ROR2	Lower limit of 95% *CI* of ROR > 1 and a ≥ 5 (12)
BCPNN	BCPNN	Lower limit of 95% *CI* of IC > 0 (12)
MGPS	MGPS1	5th percentile of EBGM (EB05) > 2 (7)
	MGPS2	5th percentile of EBGM (EB05) ≥ 1.8 and EBGM ≥ 2.5 (12)
	MGPS3	EBGM ≥ 2 (7,13)

Abbreviation: PRR=proportional reporting ratio; ROR=reporting odds ratio; BCPNN=Bayesian confidence propagation neural network; MGPS=multi-item gamma Poisson shrinker; *CI*=confidence interval; IC=information component; EBGM=empirical Bayesian geometric mean.
* The number refers to various thresholds.
† The variable "a" represents the number of reports that include both the specific vaccine being studied and the AEFI being investigated.

TABLE 3. Reference standard for performance evaluation.

Reference standard	Vaccine	AEFI
Reference standard 1	All vaccines (*15*)	Fever (temperature ≥38.6 ℃)
(common events)	All injectable vaccines (*15*)	Vaccination site erythema (diameter >2.5 cm), Vaccination site induration (diameter >2.5 cm)
Reference standard 2 (rare events)	Live-attenuated Hepatitis A vaccine (*16–20*)	Anaphylactic shock
	Varicella vaccine (*16–20*)	Anaphylactic shock
	BCG (*15*)	Vaccination site abscess, lymphadenitis, disseminated BCG infection
	Live-attenuated oral Polio vaccine (*15*)	Vaccine-associated paralytic poliomyelitis
	Measles containing vaccines (*15*)	Thrombocytopenic purpura
	Measles containing vaccines (*15*)	Rash morbilliform

Abbreviation: AEFI=adverse events following immunization; BCG=Bacillus Calmette-Guérin.

TABLE 4. Two-by-two contingency table for performance evaluation.

Test	Reference standard		Total
	Positive	Negative	
Positive	True positive (A)	False positive (B)	A+B
Negative	False negative (C)	True negative (D)	C+D
Total	A+C	B+D	N

Note: "A" means number of vaccine-AEFI combinations listed in reference standard and detected in this study; "B" means number of vaccine-AEFI combinations not listed in reference standard but detected in this study; "C" means number of vaccine-AEFI combinations listed in reference standard but not detected in this study; "D" means number of vaccine-AEFI combinations not listed in reference standard and not detected in this study.

Analyses

The baseline characteristics of AEFI data were analyzed to assess disproportionality. We examined the number of signals detected by each signal detection algorithm and calculated the cumulative distribution of signals for each algorithm. The distribution of signals was determined by dividing the number of signals with a specific number of reports by the total number of signals detected by each algorithm. Sensitivity and specificity for each detection method were also determined as described previously. Analyses were conducted using R software (version 4.3.1, The R Foundation for Statistical Computing, Lucent Technologies, Auckland, New Zealand) and the PhViD package (version 1.0.8, The R Foundation for Statistical Computing, Lucent Technologies, Auckland, New Zealand).

RESULTS

The original dataset consisted of 587,149 reports documenting AEFI. After removing 762 duplicate records and 15,844 records without a valid AEFI clinical diagnosis, these unique records were further separated into individual reports, resulting in 871,647 records that contained both an AEFI and a suspected vaccine. After removing 485 records without a valid vaccine name and 132 records with duplicate AEFI-vaccine pairings, the final analyzable data set consisted of 871,030 records. This data set included 41 different vaccines, 771 specific AEFI events, and 3,893 unique combinations of vaccines and AEFI events.

Table 5 presents the number of signals detected by each signal detection algorithm. PRR1 and ROR1 identified the highest number of signals, while MPGS1 identified the lowest number of signals. MPGS methods detected fewer signals compared to PRR, ROR, and BCPNN.

PRR3, PRR1, ROR1, and MGPS3, exhibited the highest number of signals detected when the number of reports was five or fewer. Conversely, MGPS1 did not detect any signals when the number of reports was 5 or fewer. Among the signals detected by PRR3, 38.9% had a number of reports equal to or less than 5, while for MGPS3 this percentage was 33.7%. On the other hand, PRR1, PRR2, ROR1, ROR2, and BCPNN identified the greatest number of signals when the number of reports exceeded five.

Algorithm Performance

Table 6 presents the sensitivity and specificity values for each signal detection algorithm using two reference

TABLE 5. Cumulative distribution of number of reports for signals detected by each signal detection algorithm using AEFI in China from 2011–2015.

Number of reports*	PRR1 *n* (%)	PRR2 *n* (%)	PRR3 *n* (%)	ROR1 *n* (%)	ROR2 *n* (%)	BCPNN *n* (%)	MGPS1 *n* (%)	MGPS2 *n* (%)	MGPS3 *n* (%)
a≤3	84 (14.0)	0	86 (18.3)	84 (14.0)	0	25 (5.0)	0	0	42 (12.0)
a≤4	139 (23.1)	0	141 (30.0)	139 (23.1)	0	74 (14.8)	0	0	88 (25.1)
a≤5	181 (30.1)	42 (9.1)	183 (38.9)	181 (30.1)	42 (9.1)	106 (21.2)	0	0	118 (33.7)
a≤6	217 (36.0)	78 (16.8)	218 (46.4)	216 (35.9)	77 (16.7)	136 (27.1)	2 (1.6)	4 (2.8)	146 (41.7)
a≤7	241 (40.0)	102 (22.0)	242 (51.5)	240 (39.9)	101 (21.9)	158 (31.5)	3 (2.4)	6 (4.2)	163 (46.6)
a≤8	271 (45.0)	132 (28.5)	271 (57.7)	270 (44.9)	131 (28.4)	182 (36.3)	11 (8.7)	19 (13.2)	184 (52.6)
a≤9	284 (47.2)	145 (31.3)	284 (60.4)	283 (47.1)	144 (31.2)	195 (38.9)	16 (12.6)	25 (17.4)	194 (55.4)
a≤10	300 (49.8)	161 (34.8)	297 (63.2)	299 (49.8)	160 (34.6)	208 (41.5)	21 (16.5)	32 (22.2)	201 (57.4)
a>5	421 (69.9)	421 (90.9)	287 (61.1)	420 (69.9)	420 (90.9)	395 (78.8)	127 (100)	144 (100)	232 (66.3)
a>10	302 (50.2)	302 (65.2)	173 (36.8)	302 (50.2)	302 (65.4)	293 (58.5)	106 (83.5)	112 (77.8)	149 (42.6)

Note: %=Number of signals in each category divided by the total number of signals detected by each method multiplied by 100. The number after each method refers to various thresholds.
Abbreviation: PRR=proportional reporting ratio; ROR=reporting odds ratio; BCPNN=Bayesian confidence propagation neural network; MGPS=multi-item gamma Poisson shrinker.
* A represents the number of reports containing both the vaccine of interest and the AEFI of interest.

standards: reference standard one for common adverse events and reference standard two for rare adverse events. Based on reference standard one, the algorithms PRR1 and PRR2 demonstrated the highest sensitivity at 38.2%, closely followed by ROR1 and ROR2 at 37.3%. MGPS1 exhibited the lowest sensitivity at 0.9%. On the other hand, MGPS1 exhibited the highest specificity at 96.7%, followed by MGPS2 at 96.2%. MGPS sensitivity was significantly lower than that of PRR, ROR, and BCPNN, while its specificity was higher than that of PRR, ROR, and BCPNN.

Based on reference standard 2, the diagnostic tests PRR1, PRR2, ROR1, ROR2, and BCPNN exhibited the highest sensitivity (73.3%), while PRR3, MGPS1, MGPS2, and MGPS3 showed a lower sensitivity (53.3%). Among the tests, MGPS1 demonstrated the highest specificity (96.9%). Although MGPS had lower sensitivity compared to PRR, ROR, and BCPNN, its specificity was higher than those three tests.

DISCUSSION

Our study aimed to assess the main features of commonly employed algorithms for detecting signals in spontaneous reporting datasets. Specifically, we examined the performance of four signal detection methods in identifying vaccine safety signals within AEFI data collected in China from 2011 to 2015. To do this, we analyzed the data using different thresholds of signal positivity. In order to evaluate the accuracy of the algorithms, we compared their results to reference standards from published scientific analyses, which were considered as the gold standard. From these comparisons, we calculated the sensitivities and specificities of each algorithm.

The number of signals detected varied significantly among the algorithms, which aligns with the findings of Kubota and colleagues (*21*). The PRR and ROR methods identified the highest number of safety signals, while MGPS method identified the fewest signals. Specifically, PRR1 found 475 more signals than MGPS1. The distribution of signals differed significantly among algorithms when the number of reports was five or fewer, but not when the number exceeded five. PRR1 and ROR1 demonstrated similar performance in signal identification, as did PRR2 and ROR2. The variation in the number of signals identified by PRR1, ROR1, and PRR3 was related to the variability in signals for more commonly reported events (i.e., those with more than five reports). On the other hand, the variability in PRR1 (ROR1) compared to PRR2, ROR2, BCPNN, and MGPS was due to differences in signal identification when the number of reports was fewer than five.

The signal-finding algorithms showed considerable variation in sensitivity and specificity. PRR1 and PRR2 demonstrated the highest sensitivity, followed by ROR1, ROR2, and BCPNN, which were also sensitive but to a lesser extent. However, MGPS1 exhibited the highest specificity, but had the lowest sensitivity. Further research is needed to investigate the reasons

TABLE 6. Performance of each signal detection algorithm.

Signal detection method	No. of signals	True positive (A)	False positive (B)	False negative (C)	True negative (D)	Sensitivity (%)	Specificity (%)
Based on reference standard 1							
PRR1	602	42	560	68	3,223	38.2	85.2
PRR2	463	42	421	68	3,362	38.2	88.9
PRR3	470	5	465	105	3,318	4.5	87.7
ROR1	601	41	560	69	3,223	37.3	85.2
ROR2	462	41	421	69	3,362	37.3	88.9
BCPNN	501	40	461	70	3,322	36.4	87.8
MGPS1	127	1	126	109	3,657	0.9	96.7
MGPS2	144	1	143	109	3,640	0.9	96.2
MGPS3	350	2	348	108	3,435	1.8	90.8
Based on reference standard 2							
PRR1	602	11	591	4	3,287	73.3	84.8
PRR2	463	11	452	4	3,426	73.3	88.3
PRR3	470	8	462	7	3,416	53.3	88.1
ROR1	601	11	590	4	3,288	73.3	84.8
ROR2	462	11	451	4	3,427	73.3	88.4
BCPNN	501	11	490	4	3,388	73.3	87.4
MGPS1	127	8	119	7	3,759	53.3	96.9
MGPS2	144	8	136	7	3,742	53.3	96.5
MGPS3	350	8	342	7	3,536	53.3	91.2

Note: "A" means number of vaccine-AEFI combinations listed in reference standard and detected in this study; "B" means number of vaccine-AEFI combinations not listed in reference standard but detected in this study; "C" means number of vaccine-AEFI combinations listed in reference standard but not detected in this study; "D" means number of vaccine-AEFI combinations not listed in reference standard and not detected in this study.

Abbreviation: PRR=proportional reporting ratio; ROR=reporting odds ratio; BCPNN=Bayesian confidence propagation neural network; MGPS=multi-item gamma Poisson shrinker. The number after each method refers to various thresholds.

behind this finding. When using the reference standard for rare side effects, PRR1, PRR2, ROR1, ROR2, and BCPNN were more sensitive than PRR3, MGPS1, MGPS2, and MGPS3. MGPS1 was found to be the most specific. In summary, our study indicates that PRR, ROR, and BCPNN are more sensitive than MGPS for detecting safety signals, while MGPS is more specific. These findings align with previous studies (*12*,*21*–*22*).

The initial analysis of our data highlighted the significance of data preparation. The standardized processing of data is crucial for ensuring consistent signal detection analyses (*9*). In order to perform signal detection analyses, it is necessary to preprocess spontaneous AEFI reports. This involves eliminating duplicate and invalid records, as well as separating AEFI-vaccine pairs in reports that contain multiple pairs.

Variations in the number of reports, as well as sensitivity and specificity, can be attributed to several factors. First, computation methods differ when dealing with a small number of reports (*21*–*22*). Bayesian shrinkage calculations used by BCPNN and MGPS result in more stable but conservative results compared to PRR and ROR. Second, variations arise from the different thresholds selected (*21*). Future research should systematically evaluate the impact of threshold values on sensitivity and specificity. Therefore, the variations observed in the number of reports and sensitivity and specificity highlight the importance of selecting appropriate signal detection methods and threshold values based on specific use case scenarios.

To the best of our knowledge, this is the first study to investigate the reference standard for performance evaluation. We systematically evaluated the variation in the number of reports, as well as the sensitivity and specificity of the signal detection method, using the AEFI database in China. Our findings can offer valuable insights for the selection of signal detection

methods and corresponding threshold values for the routine signal detection system in China's AEFI data. It is important to strike a balance between sensitivity and specificity when choosing signal detection methods and threshold values, while considering factors such as the ability to investigate detected signals (*12*), the severity of the AEFI under investigation, and the potential impact on public health if a true safety signal is missed.

Based on our study and an extensive review of relevant scientific literature, we propose different approaches for the detection of AEFI, depending on the severity and prevalence of the events, as well as the type of vaccine. For common or mild AEFIs, we recommend utilizing more specific signal detection methods such as the BCPNN or the MGPS, along with more stringent thresholds such as PRR2 or ROR2. These methods and thresholds can effectively reduce the number of false positives. In contrast, for rare or severe AEFIs, or for new licensed vaccines, we advise using more sensitive signal detection methods like the PRR or the ROR, along with less stringent thresholds. These approaches are designed to minimize the risk of missing true signals.

This study has some limitations. First, there is no universally accepted gold standard for evaluating the performance of signal detection (*12*). In this study, we used reference standards based on the World Health Organization's global manual on surveillance of adverse events following immunization (*15*) and safety signals identified in previous studies (*16*–*20*) as the gold standards. Second, AEFI data are collected through a passive surveillance system, and the quality of the reports may affect the detection of signals. Additionally, AEFI data is subject to known limitations, such as under-reporting, selective reporting, or over-reporting (*23*). Therefore, safety signals identified solely based on AEFI data in this study cannot determine causality and should be interpreted cautiously.

In our study, we conducted a comprehensive analysis of the number of signals detected and the performance of various methods for vaccine safety signal detection. The analysis was based on data from a passive, spontaneously reported database of AEFI. We recommend further research to evaluate the specific characteristics of the identified signals and assess the impact of different thresholds on signal detection accuracy. This additional research will provide valuable insights for enhancing the accuracy of vaccine safety signal detection in the context of vaccines used in China.

Conflicts of interest: All authors declare no competing interests.

Acknowledgments: Dr. Lance Rodewald for his review and valuable feedback.

Funding: Supported by the Beijing Natural Science Foundation (L212058).

doi: 10.46234/ccdcw2024.066

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Submitted: November 28, 2023; Accepted: January 24, 2024

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SUPPLEMENTARY TABLE S1. Computation and application of each signal detection method.

Method	Computation	Advantages (*1*)	Limitations (*1*)
PRR (*2*)	$PRR = \frac{a/(a+b)}{c/(c+d)}$ $95\%CI = e^{ln(PRR)\pm1.96\times SE(lnPRR)}$ $= e^{ln(PRR)\pm1.96\times\sqrt{\frac{1}{a}-\frac{1}{a+b}+\frac{1}{c}-\frac{1}{c+d}}}$	1. Easily applicable; 2. Easily interpretable; 3. More sensitive as compared to Bayesian method*.	1. Can not be calculated for all vaccine-AEFI pairs, e.g. PRR can not be calculated if cell c is 0, 95% CI can not be calculated if cell a or c is 0; 2. Low specificity*.
ROR (*3*–*4*)	$ROR = \frac{a/b}{c/d} = \frac{ad}{bc}$ $95\%CI = e^{ln(ROR)\pm1.96\times SE(lnROR)}$ $= e^{ln(ROR)\pm1.96\times\sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}}$	1. Easily applicable; 2. Easily interpretable; 3. More sensitive as compared to Bayesian method*; 4. Different adjustment for covariates in logistic regression.	1. Can not be calculated for all vaccine-AEFI pairs, e.g. ROR can not be calculated if cell b and c are 0, 95% CI can not be calculated if cell a or b or c or d is 0; 2. Low specificity*.
BCPNN (*4*–*5*)**	$\log_2 a\times(a+b+c+d)/(a+b)\times(a+c)$	1. Always applicable; 2. More specific as compared to the frequentist method*.	1. Computation is complex; 2. Low sensitivity*.
MGPS (*6*)***	$\frac{a}{\frac{(a+b)\times(a+c)}{a+b+c+d}}$	1. Always applicable; 2. More specific as compared to frequentist method*.	1. Computation is complex; 2. Low sensitivity*.

* when commonly cited thresholds are used.

** Basic computation is listed here. More details regarding Bayesian shrinkage can be found in the paper (*4*–*5*).

*** Basic computation is listed here. More details regarding Bayesian shrinkage can be found in the paper (*6*).

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Review

A Scoping Review of Real-World Study in Vaccine Evaluation

Lei Wang[1,2]; Hong Yang[1,2]; Lanfang Xia[1,2]; Quanwei Song[1,2]; Na Liu[1,2]; Guomin Zhang[1,2]; Fuzhen Wang[1,2]; Huaqing Wang[1,2,#]

Real-world study (RWS) gained prominence starting with a significant investigation on ramipril's impact on hypertension in 1993 (*1*). A key advancement for the Food and Drug Administration (FDA) occurred with the enactment of the 21st Century Cures Act in 2016, emphasizing RWS (*2*). The FDA's Real-world Evidence Program establishes real-world data (RWD) as "data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources", while real-world evidence (RWE) is "clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD" (*3*). The proliferation of big data, electronic medical records (EMR), electronic health records (EHR), and medical claims data offers vast information resources facilitating RWS. Enhanced access to RWD allows for worldwide monitoring of the impacts of various public health initiatives like vaccination programs. While randomized clinical trials (RCTs) traditionally gauge vaccine efficacy and short-term safety, RWS can assess vaccine performance and safety across larger, more diverse populations and are adept at identifying rare events not easily discernible in RCTs due to their infrequency.

The FDA established definitions for RWD and RWE in 2018, yet there is a lack of globally standardized definitions for RWD and RWE (*4*). Given the array of vaccine-preventable conditions and the variety of implementation methods, real-world studies (RWS) on vaccine use draw from a broad range of data sources and employ numerous study designs. Although previous systematic reviews have concentrated on assessing the real-world effectiveness and safety of individual vaccines, some investigations meet the requirements for RWD but do not explicitly incorporate RWD or RWE concepts. Furthermore, there is an absence of an established, overarching definition for RWS, as well as a standardized framework for evaluating vaccines. Consequently, the aims of this study were to: 1) examine the trends and applications of RWS in vaccine evaluation, and 2) describe the study designs and data sources used in RWS concerning vaccine evaluation.

METHODOLOGIC FRAMEWORK

We utilized the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines to conduct our scoping review (*5*), following this method to obtain thorough and relevant results.

Search Strategy

We conducted a literature search on PubMed, Web of Science, CNKI, and Wanfang Database from December 2016 to July 2023. The search included studies in English or Chinese using the keywords "real-world study", "real-world research", "real-world data", "real-world evidence", "vaccine", and "vaccination".

Selection Criteria

The study encompassed human vaccination research on effectiveness, safety, immunogenicity, impact, health economics, vaccination coverage rates (VCR), vaccine hesitancy, and related factors. Excluded were non-human studies, research on methodology, databases, medicine, and treatment, as well as case reports, reviews, perspectives, letters, news articles, and comments.

Data Extraction and Synthesis

Two researchers (WL and YH) reviewed titles, abstracts, and full texts of the articles. Discrepancies were resolved by consulting with the principal investigator (WH). Data were gathered utilizing a standardized Excel sheet, then summarized based on publication date, country, authorship, vaccine type, study purpose, design, population demographics, sample size, and data origin. Findings were delineated and juxtaposed by vaccine types, study methodologies, and data resources.

RESULTS

Literature Screening

The initial search found 792 articles, with 243

duplicates removed. After excluding 271 articles based on title and abstract review, 278 articles underwent full-text screening. Additionally, 12 articles were identified through reference list review and manual search. Ultimately, 154 articles were included in the synthesis (Figure 1).

Trends and Applications of Real-World Study in Vaccine Evaluation

The figure in Figure 2A illustrates the publication trend of studies that mentioned keywords related to RWD/RWE/RWS from December 2016 to July 2023. The number of publications notably increased annually, peaking at 75 studies in 2022. Among the 154 articles, 111 were from high-income countries or regions, according to the World Bank Development Indicators (https://www.worldbank.org). The most researched vaccine, with 111 studies, was the coronavirus disease 2019 (COVID-19) vaccine, followed by the HPV vaccine, the influenza vaccine, and the pneumonia vaccine, each with 9 studies

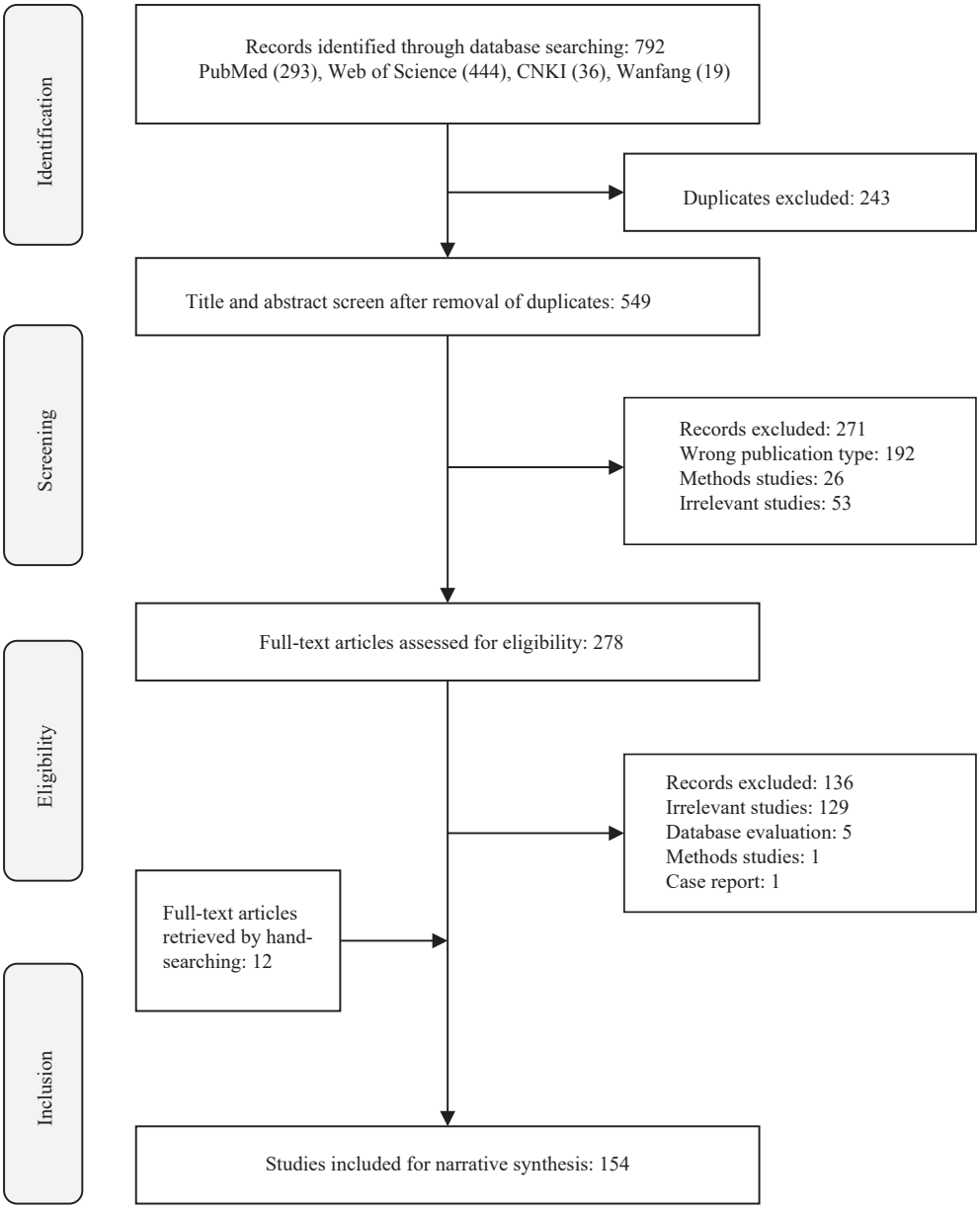

FIGURE 1. Flowchart illustrating the process of identification, selection, eligibility, and inclusion of studies for analysis.
Abbreviation: CNKI=China National Knowledge Infrastructure.
Note: Wrong publication type: reviews, perspectives, letters to the editor, news articles, and comments. Irrelevant studies: studies on animals, databases, medicine, and treatment.

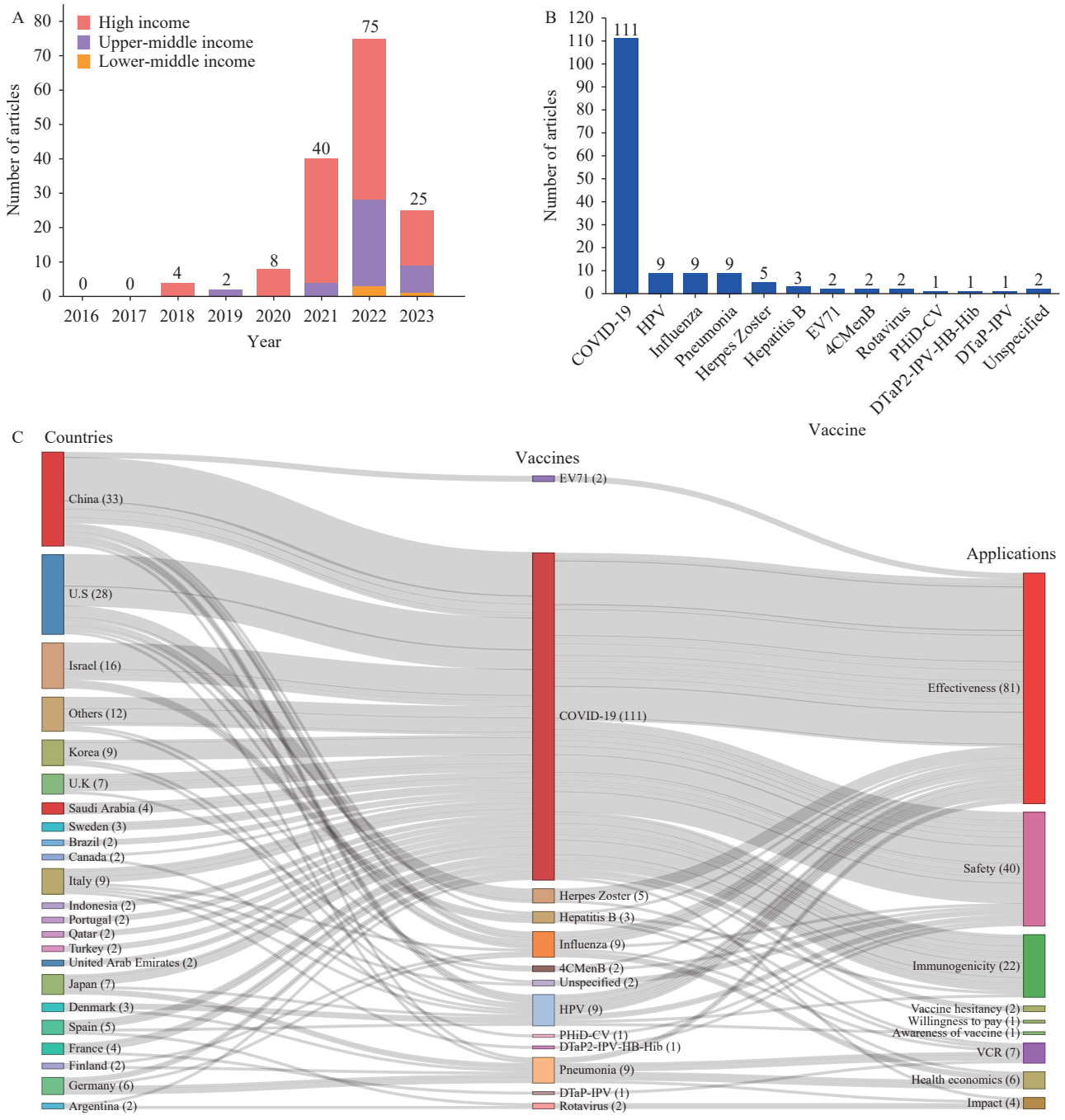

FIGURE 2. Trends and applications of real-world study in vaccine evaluation.
Abbreviation: VCR=vaccination coverage rates.

(Figure 2B). Figure 2C shows that the studies covered 34 countries, with China leading in the number of vaccine-related real-world studies (33 studies), followed by the United States (28 studies). The primary uses of real-world studies were to assess effectiveness (81 studies), safety (40 studies), and immunogenicity (22 studies). Additionally, two studies on the EV71 vaccine were exclusively conducted in China. Real-world studies were also applied to evaluate vaccine coverage rates, health economics, impact, vaccine hesitancy, willingness to pay, and awareness of vaccine evaluations.

Study Designs of Real-World Study in Vaccine Evaluation

The most common study designs in the literature reviewed were cohort studies (86 studies) and case-

control studies (28 studies). Cohort studies were predominantly utilized for assessing effectiveness (45 studies) than safety (15 studies) or immunogenicity (15 studies), while case-control studies, particularly the test-negative design (16 out of 26 studies), were commonly employed for evaluating vaccine effectiveness. Cross-sectional studies were frequently utilized for assessing vaccine safety (21 studies). Additionally, other study designs such as target trial emulation studies, screening methods, ecological studies, and pragmatic randomized clinical trial (PCT) were employed for vaccine effectiveness evaluation. Furthermore, two studies utilized modeling for economic evaluations of vaccines (Table 1).

Data Sources of Real-World Study in Vaccine Evaluation

Table 1 demonstrates that administrative databases were predominantly utilized in 49 studies for assessing vaccine effectiveness in real-world scenarios. For evaluating immunogenicity, survey data from real-world settings were commonly employed in 20 studies. In terms of vaccine safety assessment, researchers frequently examined large-scale datasets from administrative databases (20 studies) and survey databases using RWD tailored for specific research goals (16 studies). Most parameters for economic evaluations of vaccines were sourced from administrative databases, medical claims databases with cost records, and electronic medical records. Among the reviewed studies, only three used administrative databases for the economic assessment of vaccines. In the evaluation of HPV vaccine effectiveness in real-world studies, registry databases were the primary information source for HPV diseases in 4 out of 9 studies. Utilization of claims databases in real-world vaccine evaluations was infrequent, constituting only 4.9% of the total, whereas EMR/EHR accounted for 10.4%.

DISCUSSION

Our analysis revealed a substantial rise in RWSs on vaccines post the FDA's issuance of a regulatory framework in 2018, indicating wider adoption of RWS. The surge may also be linked to the integration of big data in the context of COVID-19, which since 2020 has further stimulated researcher interest and regulatory bodies' willingness to embrace RWSs. These studies primarily originated from affluent regions with possibly better access to reliable data, enabling more robust real-world research. The HPV vaccine received

TABLE 1. Characteristics of real-world studies on vaccines.

Categories	Effectiveness	Safety	Immunogenicity	Impact	Economics	VCR	Hesitancy	Other*	Total
Study design									161†
Cohort	45	15	15	3	3	5			86
Case-control	26	2							28
Cross-sectional		21	7			1	2	2	33
Target trial emulation	4	1							5
Screening method	2								2
Ecological	2			1					3
Model					2				2
PCT	1								1
CRCT		1							1
Data source									163†
Administrative database	49	20	2	3	3	2			79
EMR/EHR	11	4		1	1				17
Claims database	4				1	3			8
Registry	5								5
Survey	13	16	20			1	2	2	54

Abbreviation: VCR=vaccination coverage rates; PCT=pragmatic randomized clinical trial; CRCT=cluster randomized controlled trial; EMR/EHR=electronic medical records/electronic health records.

* Other: Willingness to pay, Awareness of vaccine.

† Certain study designs or data sources involve multiple applications.

considerable attention in this review due to challenges in endpoint event identification in clinical trials caused by low cervical cancer incidence and long latency periods. Therefore, RWSs assessing the HPV vaccine are valuable. The relationship between serological markers and the protective efficacy of the hepatitis B vaccine is well-documented (*6*). Consequently, the vaccine's effectiveness can be determined via serological assessments, reducing the reliance on real-world studies for efficacy evaluation. RWSs regarding influenza and pneumonia vaccines in the elderly mainly concentrate on health economics, driven by the significant economic impact of respiratory infectious diseases in this age group. Studies on childhood immunization program vaccines like diphtheria, tetanus, pertussis, hepatitis B, and polio predominantly focus on vaccine coverage and adherence. Research on novel vaccines like DTaP2-IPV-HB-Hib and PHiD-CV centers on real-world safety evaluation.

Our review of the literature revealed that RWSs commonly employ observational designs, in line with the inherent nature of such studies. Cohort and case-control studies are predominant, along with the increasing popularity of the TND case-control design and screening method design (*7*). The stepped wedge design involves the gradual implementation of a vaccination program to participants over several time periods, enabling a sequential assessment of its effects. Marshall HS utilized this approach to evaluate the safety of the 4CMenB vaccine in adolescents (*8*). A framework termed "target trial emulation study" has been developed to assist in the design and analysis of observational studies using RWD (*9*). Additionally, the target trial simulation design demonstrates promising potential in assessing the real-world effectiveness of the COVID-19 vaccine (*10*).

The assessment of vaccine effectiveness relies on two essential factors: the exposure and outcome variables. Therefore, the choice of a data source is crucial for real-world vaccine research. The electronic health database managed by the Abu Dhabi Health Services Company (SEHA) facilitates the provision of COVID-19 vaccinations to all residents of the United Arab Emirates, oversees the management of vaccine-related complications, and administers all COVID-19 designated hospitals within Abu Dhabi (*11*). This comprehensive database contains essential variables and a range of covariates crucial for the assessment of vaccine effectiveness. Additionally, Clalit Health Services (CHS) represents the foremost integrated payer-provider healthcare organization in Israel (*12*). The data repositories contain an extensive array of information such as demographic details, diagnostic results, pharmacological data, laboratory test outcomes, procedural records, imaging studies, and hospital admission information. These countries, with their advanced systems, can link exposure and outcome variables to swiftly and effectively analyze vaccine efficacy in real-world scenarios.

RWS is a broad term that covers various epidemiological designs, primarily observational and non-interventional studies. Although not included in the FDA guidelines, the concept originates from the National Medical Products Administration (NMPA) guidelines (*13*). The FDA offers detailed procedures for submitting real-world data to inform regulatory decisions on drugs and biological products (*14*). Recommendations for RWS include engaging with the FDA beforehand, assessing data sources, and providing study outcomes. For future real-world vaccine research, it is vital to evaluate the suitability of data sources with extensive exposure variables, outcome variables, and covariates. Reliable data sources and proper analysis are essential for generating high-quality evidence. Encouraging low-income and lower-middle-income countries to conduct vaccine RWS can be cost-effective. Additionally, enhancing basic databases and training scientific researchers in these regions is crucial.

This study is subject to some limitations. First, our research scope was constrained due to the 21st Century Cures Act implemented by the FDA in December 2016. Second, we might have overlooked certain real-world studies that did not explicitly refer to the keywords RWS/RWD/RWE in their text, although we did include numerous nationwide vaccination studies through manual searches. Third, we did not evaluate the quality of the included literature due to the broad definition and absence of specific criteria for RWS. As the body of literature on vaccine real-world studies expands and the standards for RWS become more consistent, we will update our review accordingly.

CONCLUSIONS

RWS have gained significant popularity in vaccine evaluation since 2016 and are particularly prominent in high-income and upper-middle-income countries due to the increased availability and accessibility of RWD. These studies typically rely on observational study designs such as cohort, case-control, and cross-sectional studies, utilizing data from sources like administrative databases, EMR/EHR, and claims

databases. The field of vaccine RWS is continuously evolving, and this review aims to offer guidance for researchers interested in conducting such studies.

Conflicts of interest: No conflicts of interest.

Acknowledgements: Dr. Lance Rodewald from the Chinese Center for Disease Control and Prevention for his valuable comments and assistance with editing the English language.

Funding: Beijing Natural Science Foundation (L212058).

doi: 10.46234/ccdcw2024.067

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Submitted: November 23, 2023; Accepted: January 22, 2024

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Youth Editorial Board

Indexed by Science Citation Index Expanded (SCIE), Social Sciences Citation Index (SSCI), PubMed Central (PMC), Scopus, Chinese Scientific and Technical Papers and Citations, and Chinese Science Citation Database (CSCD)

The inauguration of *China CDC Weekly* is in part supported by Project for Enhancing International Impact of China STM Journals Category D (PIIJ2-D-04-(2018)) of China Association for Science and Technology (CAST).

CCDC weekly

Vol. 6 No. 16 Apr. 19, 2024

Responsible Authority
National Disease Control and Prevention Administration

Sponsor
Chinese Center for Disease Control and Prevention

Editing and Publishing
China CDC Weekly Editorial Office
No.155 Changbai Road, Changping District, Beijing, China
Tel: 86-10-63150501, 63150701
Email: weekly@chinacdc.cn

CSSN
ISSN 2096-7071
CN 10-1629/R1