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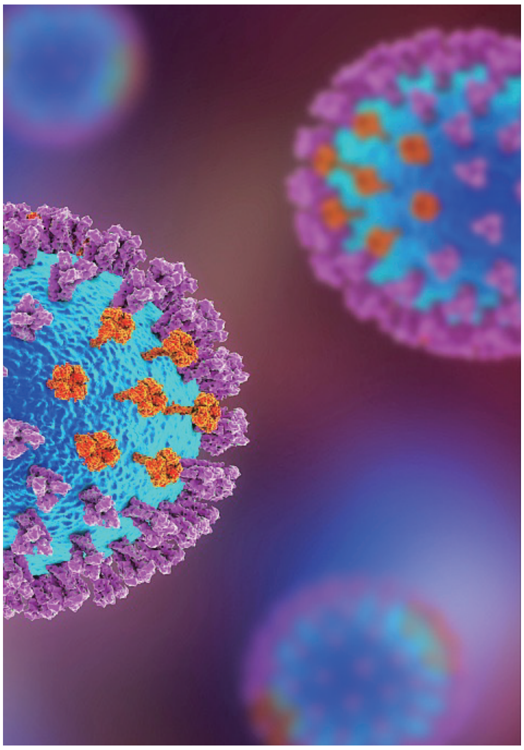

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Cover Image: A model of the influenza virus (adapted from www.vcg.com).

Foreword

Message from Deputy Editor-in-Chief Gabriel M Leung — International Trade and Global Health Protection

It was external trade that first prompted the collection and reporting of surveillance data at the foreign ports from which the US imported goods. So established *Bulletin of the Public Health*—the first precursor to the US Centers for Disease Control's *Morbidity and Mortality Weekly Report* (https://www.cdc.gov/mmwr/index.html). That was in 1878—during the fourth year of Guangxu Emperor's 35-year reign as the penultimate monarch of our country's dynastic legacy. History would have it that it is during a time of Sino-American trade tension, 141 years later, that the Chinese equivalent *China CDC Weekly* was born last month.

China's signature global trade and development partnership—the Belt and Road Initiative (BRI) launched in 2013 by President Xi Jinping—provides a compelling raison d'être for this latest scientific outreach in the form of a new real-time periodical for public health protection along the Silk Road Economic Belt and the 21st-century Maritime Silk Road. It was not so long ago that another continental trade bloc, the European Union, sponsored the pilot issue of European CDC's *Eurosurveillance* (https://www.eurosurveillance.org/) in 1995, two years after the Maastricht Treaty came into force.

If international trade should provide the initial motivation to monitor disease trends and track agents, vectors, and the movement of hosts, the ultimate goal must be to protect health, prevent disease, and promote wellness amongst partnering countries. Where there is nothing quite so toxic to health as the toxicity of poverty, trade has lifted hundreds of million out of poverty in China over the past four decades alone. By the same token, commercial and by extension geopolitical determinants can equally pose massive public health challenges, by omission or by commission.

Infectious epidemics provide the most vivid example. Pathogens respect no borders, as H5N1 (*1*) and SARS (*2*) had recently demonstrated in Hong Kong since 1997. In addition to our longstanding status as one of the world's busiest trading ports, first of clothing, toys, and watches, then latterly of financial, legal, and MICE[*] services, Hong Kong's role as a global commercial hub also made us vulnerable as an epicenter of disease outbreaks. Roads linking otherwise remote villages have accelerated the spread of emerging infections with development. Mega airports, shipping container ports, and super highways—infrastructure characterizing the prosperity of global commerce—are conduits for superspreading events at global proportions. The SARS epidemic, with patient zero originating from Foshan in neighboring Guangdong province, in November 2002 subsequently seeded the province-wide spread but did not transmit outside of Chinese borders until it hit Hong Kong and quickly went on to re-export the virus to Canada, Singapore, and Vietnam (*3*).

While infections are often associated with gripping immediacy that capture the public's fear and imagination, non-communicable diseases (NCDs) impose the largest disease burden by far (*4*). Microbial triggers of NCDs, particularly cancers, are increasingly established. Much more importantly, however, NCDs are caused by lifestyle and behavioral factors that are contemporaneously and inter-generationally (epigenetically) acquired. These have been shown to "spread" assortatively amongst peer groups and in complex social networks (*5*). Such social links between populations are anticipated corollaries of trade that are now accelerated by technology. Perhaps of greatest relevance to the incidence of NCDs, trade and balance of payments between nations ultimately drive consumption patterns thus lifestyle.

Finally, climate change is the most vexed challenge with the direst potential impact that could pose an existential threat to some populations in the medium term and all eventually. Here a non-dichotomous third way other than prosperity vs sustainability must be found. Countervailing geo- and national politics will interfere that would require wise politicians, Virchow's "practical anthropologists", to neutralize thereby protecting the public's health.

I have outlined why and how trade and health are inextricably intertwined. While the challenges are enormous and can appear overwhelming, we hope that *China CDC Weekly* will in time provide a popular platform to

[*] Meetings, incentives, conferences and exhibitions

communicate with our partners worldwide and to help us all in preventing and mitigating these public health challenges before they become another statistic that goes into our reports.

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Vital Surveillances

Morbidity Analysis of the Notifiable Infectious Diseases in China, 2018

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Summary

What is already known about this topic?

Annual morbidity analysis reports that summarized trends and changing epidemiology for notifiable diseases were published in 2013 and 2015 (*1*,*2*).

What is added by this report?

In 2018, the morbidity of national notifiable diseases was 559.41 per 100,000 population, an increase of 12.88% compared with the average rate between 2015–2017. The five notifiable diseases with the highest reported morbidity were hand, foot, and mouth disease (HFMD), infectious diarrhea, hepatitis B, tuberculosis, and influenza. The five regions with the highest reported morbidity of infectious diseases were Zhejiang Province, Guangxi Autonomous Region, Guangdong Province, Beijing Municipality, and Xinjiang Autonomous Region.

What are the implications for public health practice?

Evidence on notifiable disease morbidity trends and changing epidemiology should help disease control and prevention agencies and medical institutions direct their response and prevention efforts. In addition, this report demonstrates the continued need for surveillance systems and high-quality data to identify focal points for disease control.

Abstract

Introduction Notifiable infectious disease surveillance is important for understanding the trends in morbidity for certain diseases, especially detection of acute infectious disease outbreaks and changing epidemiology. A web-based reporting system was deployed in January 2004, which has improved data collection and speed tremendously. This report provides an updated analysis for reports published in 2013 and 2015.

Methods Data from the National Notifiable Disease Reporting System (NNDRS) was used. The NNRDS shows data from 39 notifiable diseases split into three categories (A, B, and C) based on severity and importance. A descriptive analysis was conducted to analyze the morbidity of notifiable diseases in China.

Results In 2018, the morbidity of national notifiable diseases was 559.41 per 100,000 population, an increase of 12.88% compared with the average of 2015–2017. The proportion of laboratory confirmed cases was 36.22%, which decreased 4.03% compared with the average of that in the recent three years. Diseases transmitted by direct contact/fecal–oral transmission accounted for the largest proportion, 49.37% of the total reported cases, followed by the respiratory transmitted diseases, blood-borne/sexually transmitted diseases, and the zoonotic and vector-borne diseases with a proportion of 25.18%, 24.60%, and 0.85%, respectively. Pathogenic descriptive analysis showed that the viral-infected cases accounted for 73.78% of the totals, followed by the bacterial-infected and parasitic diseases.

Conclusion The national morbidity of notifiable infectious diseases showed increases in 2018, mostly due to higher morbidity of category C diseases, such as HFMD, infectious diarrhea, and influenza, and these diseases need to be further prioritized in disease control and prevention efforts. Laboratory confirmed cases remain low and need to be improved to improve data quality.

Introduction

The National Notifiable Disease Reporting System (NNDRS) in China was established in the 1950s, and since 2004, compulsory guidelines mandate that medical and health institutions at all levels must report infectious diseases to the NNDRS in real time (*3*). The NNDRS is the most important infectious disease surveillance system in China and has played an important role in infectious disease prevention and control. Timely analysis of outbreak surveillance data and understanding the relevant trends and characteristics are the foundation for the prevention and control of infectious diseases (*4*). Therefore, a descriptive analysis of notifiable diseases in 2018 based on data from NNDRS is invaluable to Chinese public health efforts.

Methods

Data on clinical and laboratory diagnoses between January 1 and December 31 in 2018 were collected from NNDRS. Data from certain regions of China (Taiwan, Hong Kong, and Macau) and cases of foreign travelers are not included in the analysis. A total of 39 notifiable diseases (shown in Supplementary Table S1, available in http://weekly.chinacdc.cn/) are required to be reported under the regulations and management of the Law of the People's Republic of China on the Prevention and Treatment of Infectious Diseases (*5*), These diseases are divided into three categories: Class A, B, and C. Descriptive analysis was conducted by Microsoft Excel 2010, and ArcGIS 10.2 was used for geo-analysis.

Results

Overall, 7,770,749 notifiable diseases cases were reported through the NNDRS, and the morbidity of notifiable diseases was 559.41 cases per 100,000 population, with an increase of 12.88% compared with the average of the recent three years. There were no cases of plague, severe acute respiratory syndrome associated coronavirus disease (SARS), poliomyelitis, avian influenza (H5N1), diphtheria, and filariasis reported in China in 2018. The morbidity of Class A and B notifiable diseases was 220.51 cases per 100,000 population, which was relatively stable in the recent years with only 0.03% higher than that of the recent three years. However, the morbidity of Class C was 338.90 cases per 100,000 population, with a remarkable increase of 23.18% compared with the recent three-year average. The top five notifiable diseases with the highest reported morbidity were HFMD, infectious diarrhea, hepatitis B, tuberculosis, and influenza, accounting for 80.10% of the total morbidity and HFMD alone accounting for 30.28%. Compared to the average of 2015-2017, the diseases with the highest increase in reported morbidity were pertussis, influenza, and Japanese encephalitis, while the diseases with the highest decline in morbidity were human infection with H7N9, schistosomiasis, and measles (Table 1).

TABLE 1. The morbidity of notifiable diseases and the proportion of laboratory confirmation proportion in China, 2018 and 2015-2017.

Disease	2018			The Average of 2015-2017			Compared with the Average of 2015-2017	
	Cases	Morbidity (1/100,000)	Laboratory Confirmed Proportion (%)	Cases	Morbidity (1/100,000)	Laboratory Confirmed Proportion (%)	Percent Change in Morbidity (%)	Percent Change in Laboratory Confirmation (%)
Classifications								
Class A, B, and C	7,770,749	559.4101	36.22	6,794,496	495.5761	37.74	12.88	−4.03
Class A and B	3,063,049	220.5065	71.28	3,022,320	220.4416	68.34	0.03	4.30
Class C	4,707,700	338.9036	13.41	3,772,176	275.1345	13.23	23.18	1.36
Transmission routes								
Direct Contact/Fecal-oral Transmitted Diseases	3,836,152	276.1616	12.55	3,398,466	247.8769	13.16	11.41	−4.64
Respiratory Transmitted Diseases	1,956,719	140.8627	25.58	1,472,774	107.4210	18.34	31.13	39.48
Zoonotic/Vector-Borne Diseases	65,865	4.7415	81.07	86,082	6.2786	71.41	−24.48	13.53
Blood-Borne/Sexually Trans-mitted Diseases	1,911,909	137.6368	93.04	1,790,671	130.6077	92.65	5.38	0.42
Pathogen								
Viruses	4,787,198	344.6264	32.15	4,021,239	293.3007	35.16	17.50	−8.56
Bacteria	1,693,219	121.8928	57.26	1,671,194	121.8933	52.95	0	8.14
Parasitic	8,062	0.5789	54.17	13,057	0.9523	25.70	−39.21	110.78

TABLE 1 (continued)

Disease	2018 Cases	2018 Morbidity (1/100,000)	2018 Laboratory Confirmed Proportion (%)	The Average of 2015-2017 Cases	The Average of 2015-2017 Morbidity (1/100,000)	The Average of 2015-2017 Laboratory Confirmed Proportion (%)	Compared with the Average of 2015-2017: Percent Change in Morbidity (%)	Compared with the Average of 2015-2017: Percent Change in Laboratory Confirmation (%)
Single notifiable infectious disease								
Plague	0	0	−	1	0	100.00	−100.00	−
Cholera	28	0.0020	100.00	18	0.0013	100.00	53.85	0
SARS-CoV	0	0	−	0	0	−	−	−
Acquired Immune Deficiency Syndrome (AIDS)	64,170	4.6195	99.86	53,961	3.9358	99.64	17.37	0.22
Viral Hepatitis	1,280,015	92.1473	88.14	1,241,316	90.5390	87.55	1.78	0.67
Hepatitis A	16,196	1.1659	79.81	20,942	1.5275	83.52	−23.67	−4.44
Hepatitis B	999,985	71.9881	96.13	959,478	69.9823	94.48	2.87	1.75
Hepatitis C	219,375	15.7926	57.06	209,584	15.2866	62.56	3.31	−8.79
Hepatitis D	356	0.0256	81.18	262	0.0191	77.48	34.03	4.78
Hepatitis E	28,603	2.0591	86.55	28,035	2.0448	89.20	0.70	−2.97
Hepatitis, Unspecified	15,500	1.1158	24.28	23,014	1.6786	28.04	−33.53	−13.41
Poliomyelitis	0	0	−	0	0	−	−	−
Human Infection with H5N1 Virus	0	0	−	2	0.0001	100.00	−100.00	−
Measles	3,940	0.2836	97.08	24,374	1.7778	95.28	−84.05	1.89
Epidemic Hemorrhagic Fever	11,966	0.8614	77.90	10,143	0.7398	80.24	16.44	−2.92
Rabies	422	0.0304	11.61	654	0.0477	7.04	−36.27	64.91
Japanese Encephalitis	1,800	0.1296	92.83	1,003	0.0731	89.73	77.29	3.45
Dengue	5,136	0.3697	76.67	3,934	0.2869	93.42	28.86	−17.93
Anthrax	336	0.0242	16.37	327	0.0238	15.92	1.68	2.83
Dysentery	91,152	6.5620	12.52	123,856	9.0338	15.34	−27.36	−18.38
Tuberculosis	823,342	59.2717	34.01	845,148	61.6433	28.89	−3.85	17.72
Typhoid & Paratyphoid Fever	10,843	0.7806	40.63	11,109	0.8103	45.28	−3.67	−10.27
Meningococcal Meningitis	104	0.0075	68.27	108	0.0079	53.54	−5.06	27.51
Pertussis	22,057	1.5879	35.18	7,544	0.5502	30.02	188.60	17.19
Diphtheria	0	0	−	0	0	−	−	−
Neonatal Tetanus*	83	0.0052	1.20	192	0.0140	1.04	−62.86	15.38
Scarlet Fever	78,864	5.6774	4.22	67,300	4.9087	4.47	15.66	−5.59
Brucellosis	37,947	2.7318	91.32	47,561	3.4690	92.11	−21.25	−0.86
Gonorrhea	133,156	9.5858	100.00	118,041	8.6097	100.00	11.34	0
Syphilis	494,867	35.6251	100.00	449,344	32.7742	100.00	8.70	0
Leptospirosis	157	0.0113	47.77	303	0.0221	62.64	−48.87	−23.74
Schistosomiasis	144	0.0104	10.42	12,751	0.9300	3.69	−98.88	182.38
Malaria	2,518	0.1813	99.56	2,981	0.2174	99.24	−16.61	0.32
Human Infection with H7N9 Virus	2	0.0001	100.00	350	0.0255	100.00	−99.61	0
Influenza	765,186	55.0851	25.90	319,708	23.3188	36.43	136.23	−28.90
Mumps	259,071	18.6503	1.50	203,525	14.8447	1.18	25.64	27.12
Rubella	3,930	0.2829	88.52	4,758	0.3470	79.36	−18.47	11.54

TABLE 1 (continued)

Disease	2018			The Average of 2015-2017			Compared with the Average of 2015-2017	
	Cases	Morbidity (1/100,000)	Laboratory Confirmed Proportion (%)	Cases	Morbidity (1/100,000)	Laboratory Confirmed Proportion (%)	Percent Change in Morbidity (%)	Percent Change in Laboratory Confirmation (%)
Acute Hemorrhagic Conjunctivitis	38,250	2.7536	0.73	34,494	2.5159	0.61	9.45	19.67
Leprosy	225	0.0162	80.89	310	0.0226	77.72	−28.32	4.08
Typhus	971	0.0699	16.68	1,183	0.0863	34.73	−19.00	−51.97
Visceral Leishmaniasis	160	0.0115	65.00	331	0.0242	43.06	−52.48	50.95
Echinococcosis	4,327	0.3115	26.21	4,560	0.3326	27.13	−6.34	−3.39
Filariasis	0	0	−	0	0	−	−	−
Infectious Diarrhea†	1,282,270	92.3096	23.53	1,080,288	78.7939	24.05	17.15	−2.16
Hand, Foot, and Mouth Disease	2,353,310	169.4129	5.19	2,123,020	154.8486	5.38	9.41	−3.53

* The unit of the morbidity of neonatal tetanus is 1/1,000.

† Infectious diarrhea excludes cholera, dysentery, typhoid fever, and paratyphoid fever.

− Denotes the number cannot be counted.

In 2018, 73.78% of all national notifiable disease cases were attributable to viral diseases. The morbidity of viral infectious diseases was 344.63 cases per 100,000 population with an increase of 17.50% compared with the average of 2015–2017. Bacterial pathogens were responsible for 26.10% of all national notifiable disease cases. The morbidity of bacterial diseases was 121.89 cases per 100,000 population, which was nearly same as that of the recent three years. Parasitosis represented 0.12% of the total cases, and the corresponding morbidity was 0.58 cases per 100,000 population, which was a decrease of 39.21% compared with average of 2015–2017. The reported morbidity of schistosomiasis and visceral leishmaniasis has significantly decreased.

The morbidity analysis by the main route of transmission and the reservoir of the organism showed that diseases transmitted by direct contact/fecal–oral transmission are the largest proportion 49.37% of the total cases, and the related morbidity was 276.16 cases per 100,000 population, which was an increase of 11.41% compared with the average of 2015–2017. The major contributors were HFMD and infectious diarrhea.

Respiratory transmitted diseases contributed 25.18% of total cases, and the morbidity of respiratory transmitted diseases was 140.86 cases per 100,000 population, which was an increase of 31.13% compared with 3-year average. The largest contributors in this category were tuberculosis and influenza.

Blood-borne/sexually transmitted diseases accounted for 24.60% of the totals, and the morbidity was 137.64 cases per 100,000 population, which was an increase of 5.38% compared with the 3-year average. Hepatitis B and syphilis were the major contributors.

The smallest contributor for total cases was zoonotic and vector-borne diseases, which accounted for 0.85%, and the morbidity was 4.74 cases per 100,000 population, which was a decrease of 24.48% compared with the 3-year average. These diseases include brucellosis and epidemic hemorrhagic fever (Table 1, Figure 1).

Zhejiang Province, Guangxi Autonomous Region, Guangdong Province, Beijing Municipality, and Xinjiang Autonomous Region are the five regions with the highest reported morbidity of infectious diseases, and the morbidities were 986.47, 981.61, 932.64, 840.72, and 813.49 cases per 100,000 population, respectively. For the top four regions, the leading diseases were mainly HFMD, infectious diarrhea, influenza, all of which belong to Class C. However, hepatitis B, syphilis, and infectious diarrhea were the three leading diseases in Xinjiang Autonomous Region of western China. Combining the regional distribution of infectious diseases with different transmission routes, Guangxi Autonomous Region and Zhejiang Province had higher morbidity of direct contact/fecal-oral transmitted diseases than other regions in China including HFMD and infectious diarrhea diseases. Beijing Municipality, Xinjiang Autonomous Region, and Tibet Autonomous Region reported more morbidity of respiratory infectious diseases like tuberculosis and influenza than other provinces. The morbidity of zoonotic infectious diseases was higher in

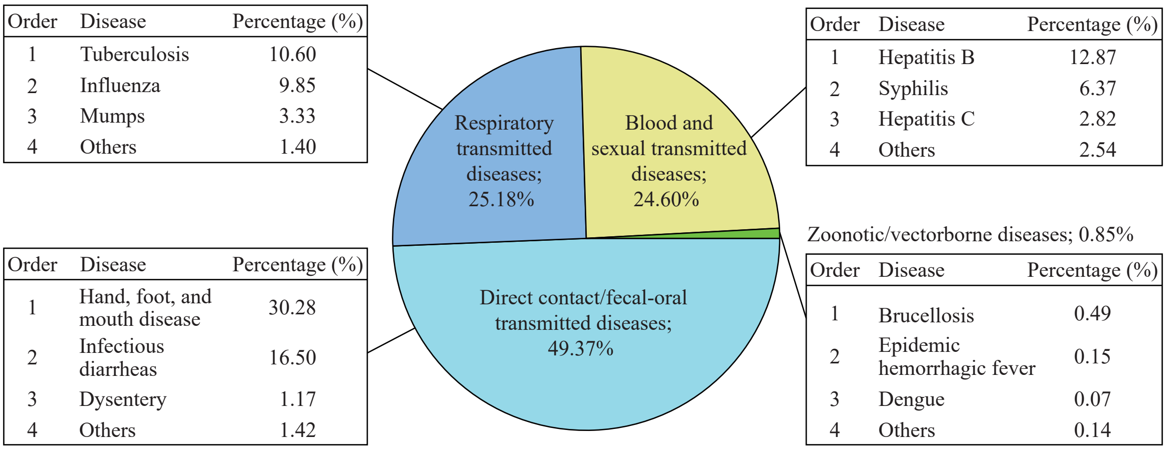

FIGURE 1. The morbidity analysis by the main route of transmission and the reservoir of the organism in China, 2018.

northern regions, including Inner Mongolia Autonomous Region, Ningxia Autonomous Region, and Xinjiang Autonomous Region, than other regions. These diseases include brucellosis and epidemic hemorrhagic fever. Xinjiang Autonomous Region, Hainan Province, and Qinghai Province reported more morbidity of blood and sexually transmitted diseases, including hepatitis B and syphilis (Figure 2).

In 2018, 36.22% of national notifiable disease cases were laboratory diagnosed, 4.03% lower than the average rate between 2015–2017. The proportion of bacterial pathogens with laboratory confirmation was 57.26%, an increase of 8.14% compared to the 3-year average. However, the proportion of viral disease cases with laboratory confirmation was 32.15%, a decrease of 8.56% compared with the average of 2015–2017. The proportion of parasitic cases with laboratory confirmation was 54.17%, an increase of 110.78% compared with the average of 2015–2017. All cases of cholera, H7N9, gonorrhea, and syphilis were laboratory confirmed, but the proportions of scarlet fever, neonatal tetanus, mumps, and acute hemorrhagic conjunctivitis with laboratory confirmation were less than 5% (Table 1).

DISCUSSION

The national morbidity of notifiable infectious diseases showed an increase in 2018 compared with the average of 2015–2017, and all the morbidities of direct contact/fecal-oral transmitted diseases, respiratory transmitted diseases, and blood-borne/sexually transmitted diseases increased, which can be attributed primarily to the higher morbidity of category C diseases, such as HFMD, infectious diarrhea, and influenza. There was 2,353,310 HFMD cases reported in 2018, an increase over 230,000 cases compared with the average of 2015–2017, and this was the largest contributor of direct contact/fecal–oral transmission cases. The HFMD morbidity is higher in eastern and southern provinces of China, and children less than three years old should be the primary targets for interventions (*6*).

There were 1,282,270 infectious diarrhea cases reported in 2018, an increase of over 200,000 cases compared with the average of 2015–2017, becoming one of the great health threats to infants and children since the year of 2008. The seasonal influenza epidemic increased 136.23% in 2018 compared with the average of 2015–2017. Increasing recognition of influenza and increasing awareness of diagnosis and reporting by doctors, espeically in developed provinces such as Beijing, might explain this increase.

Tuberculosis morbidity was reported as 59.27 cases per 100,000 population and contributes the most to the burden of respiratory transmitted diseases. The World Health Organization (WHO) reported over 10 million new tuberculosis cases globally in 2018, and China was one of 20 countries with the highest tuberculosis burden (*7*).

Hepatitis B morbidity was reported as 71.99 cases per 100,000 population, an increase of 2.87% compared with the average of the recent three years, which accounted for the largest proportion of blood/sexually transmitted diseases. The most cost-effective way to control hepatitis B is to prevent a susceptible person from acquiring Hepatitis B virus infection by the interruption of the transmission route and by immunization of susceptible hosts (*8*).

Zoonotic and vector-borne disease morbidity decreased slightly. Brucellosis morbidity was reported

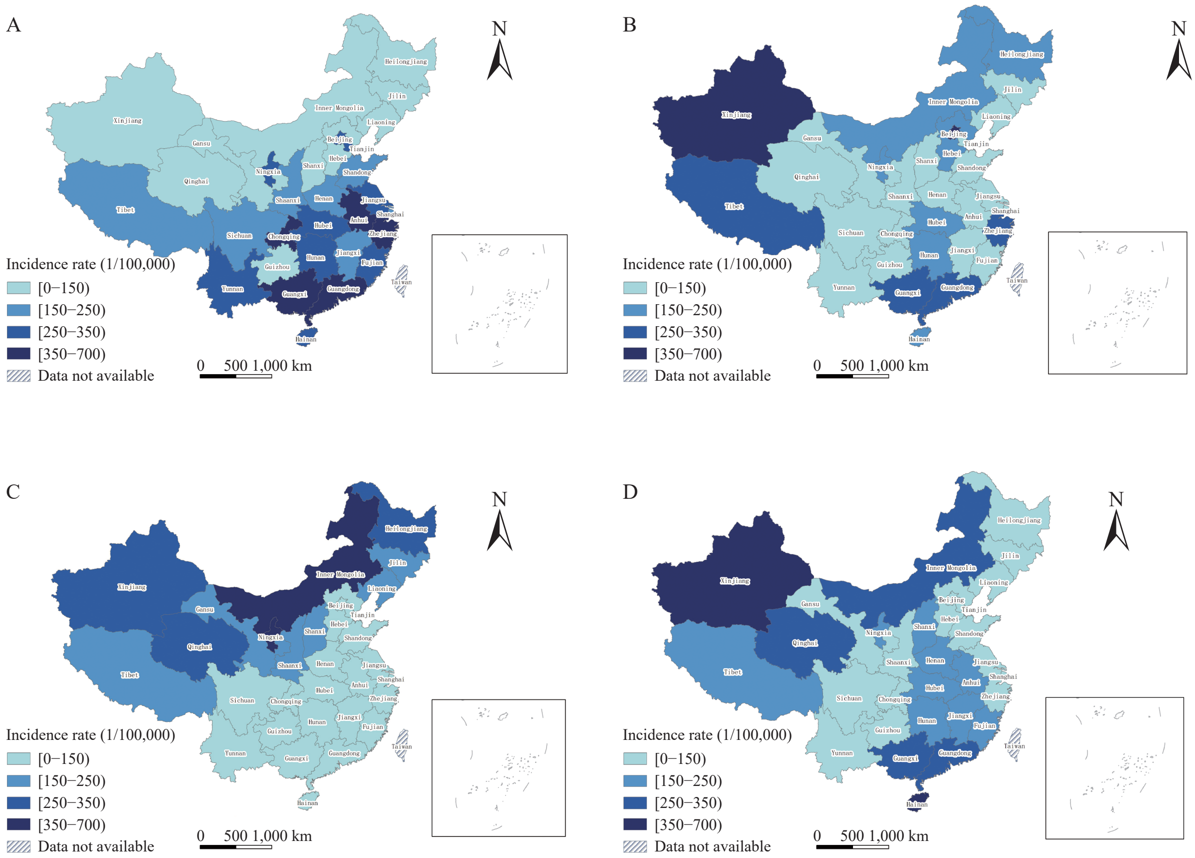

FIGURE 2. Geographical distribution of the morbidity of notifiable diseases in China, 2018. (A) Direct contact/fecal-oral transmitted diseases; (B) Respiratory transmitted diseases; (C) Zoonotic and vector-borne diseases; (D) Blood and sexual transmitted diseases.

as 2.73 cases per 100,000 population and was the leading zoonotic and vector-borne disease. Brucellosis morbidity is high in northern provinces such as Inner Mongolia Autonomous Region, Heilongjiang Province and Xinjiang Autonomous Region, and sporadic outbreaks occured in southern regions caused by infected imported animals from northern regions.

Rabies morbidity was 0.03 cases per 100,000 population and has progressively decreased since 2008. Rabies outbreaks have been effectively controlled. China has the ability to achieve the WHO global goal of eliminating rabies transmission from dog to human by 2030 (*9*).

Dengue fever morbidity increased by 28.86% in 2018, compared with the average of 2015–2017. In recent years, dengue outbreaks occurred frequently in coastal areas, such as Zhejiang Province and Guangdong Province, and most dengue cases in China were imported (*10*).

Overall, the laboratory diagnosis rate of notifiable disease decreased 4.03% compared with the average of 2015–2017. The laboratory diagnosis rate of class C infectious diseases is still lower than that of class A and B infectious diseases. Parasitic infectious diseases had a significantly higher laboratory diagnostic rate in 2018 compared with the average of 2015–2017. However, there is still a big gap in terms of laboratory evidence of pathogen diagnosis between China and western countries (*11*). Even though China has uniform diagnostic standards and reporting requirements for infectious diseases, unbalanced develpoment of laboratory diagnostic facilities and economic status within the country may limit the laboratory confirmation rates, which is reflected in the laboratory diagnosis rate of notifiable disease cases varies across the country. Thus, further strengthening the construction of infectious disease laboratory systems in China and the laboratory testing capabilities are major priorities.

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Authors' contributions: Shuaibing Dong and Xiang Ren contributed equally to this work. Zhongjie Li, Liping Wang, and Lijie Zhang designed and supervised this study; Shuaibing Dong and Xiang Ren wrote the manuscript; Cuihong Zhang, Mengjie Geng, Yuliang Zhu, and Lusha Shi prepared and cleaned the data; Shuaibing Dong, Xiang Ren, and Cuihong Zhang carried out the analysis; All authors interpreted the data and critically revised the manuscript for important intellectual content.

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Notes from the Field

Suspected Yellow Fever Case Determined to be Adverse Vaccine Reaction

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Jiangxi Provincial Center for Disease Control and Prevention (Jiangxi CDC) received an alert at 23:45 on November 7, 2019 from Nanchang Customs that yellow fever virus was detected in a foreign national.

On November 8, county, municipal, and provincial CDCs of Jiangxi Province carried out epidemiological investigations to show that the suspected case was found in a 35-year-old male patient from Addis Ababa, Ethiopia. On November 5, this patient began to have yellow-fever-like symptoms such as onset of fever, chills, and headache. At 16:11 on November 6, the patient and 12 accompanying colleagues arrived in Guangzhou where his temperature was measured at 38.0 ℃. Blood samples were collected by the Guangzhou Customs Laboratory and RT-PCR test results illustrated that the patient was experiencing yellow fever viremia. On November 7, the patient and his colleagues landed in Nanchang, and the Guangzhou Customs Laboratory alerted Nanchang Customs to inform Jiangxi CDC of the patient’s test result.

On November 8, the patient’s temperature had returned to normal and his other symptoms were relieved. None of the patient’s colleagues exhibited any symptoms. Jiangxi CDC tested the patient’s blood sample and the result showed that the yellow fever viremia disappeared. After 24 hours on November 9, the patient’s blood was tested for yellow fever virus a second time, and this result was negative again. Further investigation revealed that the patient received a yellow fever vaccination on November 1, 2019, as indicated by his immunization certificate.

On November 11, the Guangzhou Customs Laboratory finished RNA sequencing of the isolated virus and proved that the detected virus is a strain of the yellow fever vaccine virus. Based on evidence yielded by the investigation, including epidemiological history, onset of relatively mild symptoms, laboratory test results, and vaccination history, the patient’s symptoms were considered to be adverse reactions to the yellow fever vaccination.

Discussion

Yellow fever vaccine is a live-attenuated virus vaccine, a type of vaccine in which the virulence of the pathogen has been reduced, that has been available since the 1930s. The vaccination of yellow fever is required for entry into certain countries (*1*). The viremia may occur in a newly-vaccinated person two to six days following vaccination, and the detectible window for the most people ranges from four to six days after immunization (*2*). The adverse reactions incurred by vaccination are generally mild and include headaches, muscle aches, low-grade fevers (*1*). According to reports by the Vaccine Adverse Event Reporting System (VAERS), the occurrence rate of an adverse event is 43 per 100,000 vaccination (*3*). A mild reaction generally does not require treatment, but in rare scenarios, a newly-vaccinated person may require special healthcare in response to severe or possibly life-threatening reactions (*4*).

In this case, the patient entered China from a country without yellow fever epidemic. At the time of entry into China, the patient was having viremia and other symptoms associated with yellow fever vaccination. However, before a determination could be made on the patient’s condition, Chinese clinicians and public health professionals were extremely worried that a true yellow fever patient might cause local transmission.

This case report suggests that many clinicians, customs officials, and public health professionals lack essential knowledge and training to properly address infectious disease events such as yellow fever. To use this current case as an example, accurate diagnoses and the implementation of effective control and prevention measures depend on public health professionals’ ability to intensively collect epidemiological information, such as vaccination history, prior two-week travel history, and the infectious disease epidemic situation of countries of origin, etc., and clinicians' ability to make clear and characterized clinical observations. Furthermore, if the presenting symptoms are severe, the viral genome should be sequenced to distinguish vaccine viremia from yellow fever disease as soon as possible.

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Recollections

One Hundred Years of Influenza Since the 1918 Pandemic — Is China Prepared Today?

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Summary
Almost 100 years after the 1918 influenza pandemic, China experienced its largest, most widespread epidemic of human infections with avian influenza A (H7N9), the influenza virus with the greatest pandemic potential of all influenza viruses assessed to date by the United States Centers for Disease Control and Prevention's Influenza Risk Assessment Tool. This historical review describes how China was affected by the 1918, 1958, 1968, and 2009 influenza pandemics, records milestones in China's capacity to detect and respond to influenza threats, and identifies remaining challenges for pandemic preparedness. This review suggests that past influenza pandemics have improved China's national capabilities such that China has become a global leader in influenza detection and response. Further enhancing China's pandemic preparedness to address remaining challenges requires government commitment and increased investment in China's public health and healthcare systems.

Introduction

The centenary of the 1918 Influenza Pandemic is a time to evaluate preparedness for the next pandemic. In 1918, the pandemic spread across the world in three waves, causing an estimated 20–100 million excess deaths (*1*). Almost 100 years later, China experienced its largest, most widespread epidemic of human infections with avian influenza A (H7N9), the influenza virus with greatest pandemic potential of all viruses assessed to date by United States Centers for Disease Control and Prevention's (U.S. CDC) Influenza Risk Assessment Tool (*2*). This historical review describes China's developments in the field of influenza over the past century and asks, what are China's strengths and remaining challenges in pandemic preparedness today?

China's Response to Influenza Pandemics throughout the Century

1918 Influenza Pandemic

In 1918, local newspapers, commercial trade and post office reports first described outbreaks of respiratory illness in China in the southern port cities of Guangzhou and Shanghai. A well-circulated Shanghai daily newspaper published epidemic reports and severe outbreak alerts in early June, announcing the closure of public facilities such as cinemas. At the time, the Republic of China's limited public health capacity was further hampered by political instability, and by December 1918, the pandemic had spread to northeastern provinces. In rural villages, people reportedly suffered fever, cough and muscle pain and died within days. The illness, called 'bone pain plague', 'five-day plague', and 'wind plague' due its severity and transmissibility, caused a shortage of coffins. Villagers sprayed limewater on their roofs to prevent infection, and they used traditional Chinese herbs for treatment (*3*). The pandemic continued until early 1919, when the first national public health agency, the "Central Epidemic Control Division", was established in June 1919. Although Chinese mortality data are limited, an estimated 4-9.5 million died from this pandemic (*4*).

Due to extensive research following the 1918 pandemic, the United Kingdom isolated the first influenza virus [A(H1N1)] in 1933 and the U.S. developed the first influenza vaccine in 1935.

Early Influenza Surveillance Capacity in China 1949–1954

When the People's Republic of China (PRC) was founded in 1949, the central government funded and operated the country's healthcare system. In 1952, the PRC initiated influenza surveillance and founded its first influenza epidemiology office and laboratory in 1954.

1957 Influenza Pandemic

An influenza outbreak detected in Guizhou Province, southwest China, in February 1957 spread to Hong Kong, China in April, resulting in 250,000 cases (*5*) and to Japan and Singapore in May. This pandemic of influenza A(H2N2), known as "Asian flu", caused an estimated 1–4 million deaths globally (*6*–*7*) and became the most severe influenza epidemic recorded in China since the establishment of the PRC. The identification of clusters of sick students prompted several provinces to close public facilities, including schools and cinemas. Although health agencies disseminated influenza prevention messages by newspaper and radio, treatment of infected persons was limited by shortages of medicine. A second pandemic wave spread across China in the latter half of 1957, prompting the government to establish the Chinese National Influenza Center (CNIC) to lead influenza control efforts.

The World Health Organization (WHO) launched the global influenza program in 1947 and established the Global Influenza Surveillance Network (GISN) in 1952. The 1957 pandemic was the first influenza pandemic detected by GISN and occurred before the PRC was a WHO member state.

1968 Influenza Pandemic

The 1968 pandemic virus, influenza A(H3N2), was first isolated in Hong Kong, China in July after a sudden increase of influenza-like illness (ILI) which affected approximately 15% of Hong Kong's population (*8*). The epidemic spread rapidly to India and the Northern Territory of Australia and then to other northern hemisphere countries during the winter of 1968–1969 causing an estimated 1–4 million excess deaths worldwide (*7*). During the Cultural Revolution (1966–1976), most public health data collection in China was suspended; however, reports from CNIC's outpatient ILI surveillance sites in Guangdong, Sichuan, Shanghai, Beijing, Harbin, and Qingdao, suggest that the highest annual number of laboratory-confirmed ILI cases in China during 1968–1992 occurred in 1968 (*9*).

Improvement of Influenza Surveillance in China, 1977–2000

After becoming a WHO member country in 1972, China invested resources in CNIC's research infrastructure and formed international collaborations to strengthen influenza surveillance.

In 1981, China joined the WHO's GISN, now called the Global Influenza Surveillance and Response System (GISRS). In 1988, China initiated influenza laboratory capacity building programs supported by international partners including WHO and U.S. CDC. Since the 1990s, CNIC has sent more than 4,000 circulating and candidate seasonal influenza vaccine viral strains to WHO Collaborating Centers. In 2000, with WHO support, China expanded its influenza surveillance network with more sites.

Public Health Capacity Development Triggered by Novel Respiratory Diseases, 2002–2005

In January 2002, the Chinese Academy of Preventive Medicine that housed CNIC was renamed the Chinese Center for Disease Control and Prevention (China CDC). Later that year, Guangdong Province reported the first cases of Severe Acute Respiratory Syndrome (SARS), which became an outbreak of international concern in early 2003. As a result, China invested in a nationwide network of CDCs at the national, provincial, prefecture and county levels and in April 2004, launched a real-time web-based reporting system for notifiable infectious diseases and emerging public health events to connect 100% of CDCs at all levels and 98% of national, provincial and prefecture health facilities. In the same year, China identified highly pathogenic avian influenza A(H5N1) virus in numerous poultry outbreaks and several human infections (*10*). Early detection of respiratory infectious diseases, including SARS, H5N1 and other novel avian influenza viruses, became a public health priority in China. By 2005, CNIC had further expanded its national influenza surveillance network to all 31 provinces with 63 network laboratories and 197 sentinel hospitals.

2009 H1N1 Pandemic

In April 2009, after a surge of influenza A(H1N1)pdm09 cases was reported from Mexico and the United States, WHO declared a public health emergency of international concern. China first responded with a policy of containment and quarantined foreign travelers and persons with respiratory symptoms in hospitals. After five months, the focus of response shifted to active surveillance for influenza cases (*11*). WHO officials praised China for its transparent response and success in mitigating the outbreak. An estimated 32,500 (95% Confidence Interval 14,000-72,000) of the 100,000-400,000 estimated global excess respiratory deaths occurred in China (*12–13*).

The 2009 pandemic triggered further government investment in China's influenza surveillance network, which, by the end of 2009 included 411 laboratories and 556 sentinel hospitals, one of the largest influenza surveillance networks in the world.

CNIC became a WHO Collaborating Centre for Influenza in 2010

In October 2010 CNIC was designated as the fifth and latest WHO Collaborating Centre for Reference and Research on Influenza. CNIC's surveillance network collects 200,000–400,000 specimens and conducts antigenic analysis on approximately 20,000 viral strains annually. In addition, CNIC disseminates a weekly, online influenza surveillance report in Chinese and English, reports data on ILI, circulating influenza subtypes and the novel influenza virus detections to WHO, and provides training to influenza centers in neighboring countries.

Detecting and Responding to Avian Influenza A(H7N9) 2013–2018

In March 2013, Shanghai Municipality and Anhui Province sent CNIC three human specimens of unsubtypable influenza from patients critically ill with pneumonia. The specimens tested positive for influenza A/H7 and were identified as low pathogenic (causing mild or no symptoms in infected poultry) avian influenza (LPAI) A(H7N9) (*14*). CNIC reported the first three cases of human infection with novel H7N9 virus to WHO within one week of isolation and sequencing and shared the virus with other WHO Collaborating Centers within 7 weeks. From 2013–2017, China has experienced annual epidemics of human infections with H7N9, with a cumulative 1,537 human cases identified through September 2019. The fifth H7N9 epidemic from October 2016–September 2017 was notable for a surge in cases (n=758), wide geographic spread throughout China (27 of 31 provinces affected), and the first detection of highly pathogenic avian influenza (HPAI) H7N9, a virus that causes severe disease in poultry in addition to humans (*15*). Although no sustained human-to-human transmission of H7N9 has been reported to date, both LPAI and HPAI H7N9 infection in humans are associated with severe illness and high mortality (approximately 40%).

Because most (90%) humans infected with avian influenza A(H7N9) have been exposed to live poultry within the two weeks preceding illness onset, China initiated poultry industry reform, including banning live poultry markets in major cities and promoting market sanitation. The animal health sector, led by the Ministry of Agriculture, became increasingly engaged in H7N9 detection in poultry after the emergence of HPAI H7N9 in early 2017. In September 2017, the Ministry of Agriculture initiated a nationwide poultry vaccination campaign with bivalent H5/H7 poultry vaccine. Since that time, only 5 cases of H7N9 human infection have been reported.

China's Critical Role in Global Influenza Pandemic Preparedness

China was affected by all four pandemics in the past century and the 1957 and 1968 pandemics were first identified in China (Table 1). The virus with the highest pandemic potential to date among all influenza viruses assessed, avian influenza A(H7N9), was also identified in China. With 20% of the world's population and the world's largest poultry production of 5 billion chickens and ducks per year, China plays a critical role in global influenza pandemic preparedness

TABLE 1. Estimated mortality of the past influenza pandemics.

Pandemic	Influenza A Virus Subtype	Area of First Detection	Estimated Mortality Worldwide	Estimated Mortality in China	Population in China
1918	H1N1	Unclear	20-100 million(*1*)	4-9.5 million(*4*)	460 million
1957	H2N2	Southern China Singapore/Hong Kong, China	1-4 million(*7*)	225,000-900,000*	646 million
1968	H3N2	Hong Kong, China	1-4 million(*7*)	220,000-881,000*	782 million
2009	H1N1pdm09	North America	100,000-400,000(*13*)	32,500(*12*)	1.33 billion

* No published data available; mortality estimates in China for pandemics in 1957 and 1968 were extrapolated by multiplying the global mortality estimates and the proportions of China's population size in the world.

through continuous surveillance for early detection of novel viruses.

Progress and Remaining Challenges in Pandemic Preparedness and Response

In the past several decades, China has made significant progress in responding to influenza pandemics through public health investment and infrastructure development resulting in an influenza surveillance network covering most of the nation (Figure 1). China's response to the H7N9 epidemics was notable for close public health collaborations with WHO and other international organizations in regular, joint risk assessments to enable the timely dissemination of data to the international community. Additionally, China has demonstrated interest in coordinating surveillance and response efforts with regional partners, and it has the capacity to implement sweeping measures with central government support, such as mass poultry vaccination.

Despite these advances, key challenges remain. Using WHO's "Checklist for Pandemic Influenza Risk and Impact Management" and U.S. CDC's "Preparedness and Response Framework for Influenza Pandemics", China CDC influenza experts summarized recent progress, remaining challenges and proposed actions in five core components of pandemic preparedness (Table 2).

Political Commitment After the 2003 SARS outbreak, recent avian influenza outbreaks and the 2009 H1N1 pandemic, China increased political commitment and financial resources for preventing infectious diseases, enhancing influenza surveillance and response capacity, and expanding the CDC system. As of November 2017, China CDC consisted of 3,481 units and 877,000 public health professionals serving at all levels of government. In addition, a web-based national notifiable infectious disease reporting system was developed to increase timely case reporting.

Nevertheless, growing public health needs have stretched the still limited investments in China's public health system. Low salaries are a significant barrier to the recruitment and retention of high quality professionals, and recently, CDC staffing at all levels has declined. In addition, competing health priorities potentially interfere with high level Chinese government commitment to pandemic preparedness. Improved CDC human resource development is essential, in addition to the government's prompt endorsement of an updated national influenza pandemic preparedness plan.

Multisector Coordination As demonstrated during the recent H7N9 epidemics, China has the capacity to implement sweeping measures and coordinate actions across government levels, sectors, and agencies if prioritized by the central government. For example, mobilization of multiple sectors facilitated mass poultry vaccination, with >85% of all poultry receiving the bivalent H5/H7 vaccine annually since 2017. (*16*) Nevertheless, intergovernmental coordination challenges remain. Improving data sharing and coordination between human and animal health sectors will facilitate a One Health approach to influenza, while enhancing communication between clinicians and public health professionals will improve early detection and the use of influenza vaccine and antiviral medications.

Influenza Vaccination Seasonal influenza immunization infrastructure is critical for pandemic preparedness to allow efficient, rapid vaccination with pandemic vaccine. Despite China's domestic seasonal influenza vaccine production capacity, influenza vaccine coverage in China is low (<2%) (*17*), even

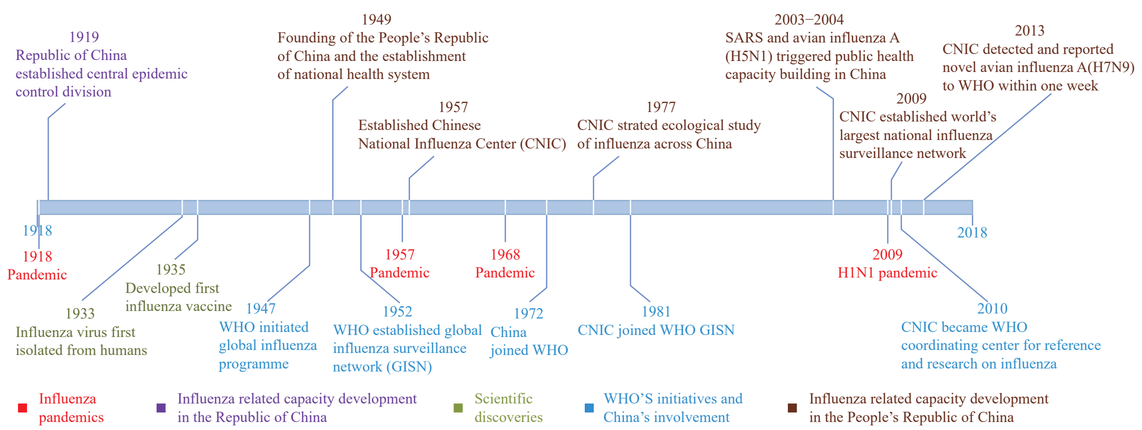

FIGURE 1. Influenza pandemics, scientific discoveries and China's influenza-related capacity milestones, 1918–2018.

TABLE 2. Remaining challenges and recommended actions for influenza pandemic preparedness in China.

Subject	Remaining Challenges	Planned Actions
Political Commitment	- Underinvestment in CDC human resources contributing to difficulties in recruiting and retaining highly qualified public health professionals - Inadequate emphasis on pandemic preparedness at higher government levels due to competing health priorities	- Increase financial investment in the public health system in China particularly with respect to recruiting and retaining highly qualified public health professionals - Prioritize pandemic preparedness and develop an updated national influenza pandemic preparedness plan
Multisector Coordination	- Inconsistent data sharing between animal and human health sectors - Insufficient communication between clinicians and public health professionals	- Convene regular multi-sectoral systematic planning meetings during inter-pandemic periods to promote a One Health approach to influenza - Disseminate key public health messages to clinicians through multiple approaches (e.g., medical education; continuing education; social media) - Develop mechanism for clinicians to communicate with public health professionals (e.g., clinician hotlines; conferences on cross-cutting topics for both public health professionals and clinicians)
Influenza Vaccination	- Significant underuse in all high-risk groups - Inadequate awareness of the influenza vaccine in both health care workers and the public	- Conduct mass media campaigns and continuing education to increase awareness of influenza vaccine in both health care workers and the public - Develop strategies to increase influenza vaccination in health care workers - Develop strategies to encourage health care workers to recommend seasonal influenza vaccine to high risk patients - Expand adult immunization services - Develop free influenza vaccination policy for high risk groups ○ Explore whether insurance can be used to pay for the influenza vaccine for the general public
Medical Care and Countermeasures	- Insufficient healthcare surge capacity ○ In the 2017-18 influenza season there were: ● Temporary antiviral shortages ● Hospitals overrun with patients ● Too few ventilators - Insufficient knowledge of how to prevent, test for and treat seasonal influenza illness, including lack of knowledge about hospital acquired infections	- Improve infrastructure and operational standards at all hospital levels - Improve preparedness and continuity of clinical capacity at all levels (through regular training, continuing education etc.) - Implement early warning systems and develop plans for taskforce management to respond to unexpected surges in healthcare utilization during the influenza season - Improve clinical practice for seasonal influenza prevention, testing and treatment (through regular training, continuing education etc.) - Promote vaccination and PPE among healthcare workers
Risk Communication	- Lack of an official technical framework to communicate seasonal influenza intensity, severity and risks	- Develop an influenza intensity and severity framework based on data collected in recent influenza seasons

among high risk populations recommended for vaccination by China CDC. National policy to encourage influenza vaccine use may increase healthcare worker and public awareness of the vaccine, promote adult immunization infrastructure development, and better prepare China for the next pandemic.

Medical Care and Countermeasures In the past decade, China has increased its capacity to diagnose, manage, and treat avian influenza infections. Gaps remain in testing and treating patients with seasonal influenza. Moreover, during the severe 2017–2018 influenza season, the healthcare system was overwhelmed due to insufficient clinical surge capacity, and several cities reported antiviral medication shortages. Improving preparedness will entail upgrading hospital infrastructures, expanding antiviral stockpiles, building logistical capacity, and improving staff surge capacity. In addition, increasing influenza vaccination coverage and use of personal protective equipment among healthcare workers may protect frontline staff and prevent nosocomial infections.

Risk Communication Risk communication has improved since the 2003 SARS outbreak. During the H7N9 epidemics, China's key government ministries, led by the State Council, collaborated to develop and disseminate H7N9 prevention and control messages through traditional and social media platforms. Government spokespersons provided timely, transparent information-sharing. The 2017–18 influenza season, however, revealed the need to strengthen risk communication about the intensity and severity of influenza seasons using influenza surveillance data.

Conclusion

During the past century, the world's population has quadrupled and humans and animals have become increasingly connected through travel and global supply chains. A novel influenza virus can spread internationally within hours. Pandemic preparedness in China is critical because of its population size, robust poultry industry, and circulating avian influenza A viruses with pandemic potential. In the last decade, China has become a global leader in influenza detection and collaboration, actively engaged with WHO and the international health community. China is ready to undertake greater responsibility for the early detection of and response to influenza threats with pandemic potential. Enhancing China's pandemic preparedness requires government commitment to update the national influenza pandemic preparedness plan, increase investment in China's public health and healthcare systems, promote seasonal influenza vaccination, improve medical care, countermeasures and risk communication during influenza epidemics, and facilitate multisector communication and coordination to promote a One Health approach to influenza.

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