ISSN 2096-7071
CN 10-1629/R1

CHINA CDC WEEKLY

Vol. 5 No. 22 Jun 2, 2023

CCDC weekly

中国疾病预防控制中心周报

WORLD FOOD SAFETY DAY ISSUE

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Cover Image: adapted from the World Health Organization, https://www.who.int/campaigns/world-food-safety-day/2023.

This week's issue was organized by Guest Editor Yongning Wu.

Vital Surveillances

Epidemiological Features of Foodborne Disease Outbreaks in Catering Service Facilities — China, 2010–2020

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ABSTRACT

Introduction: In terms of food preparation settings, catering service facilities have been identified as locations with the highest incidence of foodborne disease outbreaks in China. Since 2010, the China National Center for Food Safety Risk Assessment has established the Foodborne Disease Outbreak Surveillance System (FDOSS) to monitor foodborne disease outbreaks. Consequently, data from the FDOSS has provided a more accurate depiction of the epidemic characteristics of outbreaks within these facilities.

Methods: From 2010 to 2020, the FDOSS gathered data related to the prevalence of outbreaks, cases, hospitalizations, and deaths linked to foodborne disease outbreaks in catering service facilities. This study examined the temporal and geographical distribution, pathogenic factors, and contributing variables of these outbreaks over the course of the decade.

Results: From 2010 to 2020, China's catering service facilities reported 18,331 outbreaks, which resulted in 206,718 illnesses, 68,561 hospitalizations, and 201 deaths. The second and third quarters of the year accounted for 76.12% of the outbreaks and 72.93% of the cases. The primary pathogenic factors were pathogenic organisms, which caused 4,883 (26.64%) outbreaks, 94,047 (45.50%) cases, 32,170 (46.92%) hospitalizations, and 21 (10.45%) deaths. There were 5,607 (30.59%) outbreaks in restaurants, 2,876 (15.69%) outbreaks from street vendors, and 2,560 (13.97%) outbreaks in employee canteens in China.

Conclusions: The implementation of relevant control methods, including health education and promotion, is critical for addressing foodborne diseases in catering service facilities. Regular food safety training sessions for restaurant personnel and managers are essential to ensuring the effective management of these health risks.

Outbreaks of foodborne diseases are of global concern, posing significant impacts on both human health and the economy (*1*–*2*). In the USA, an estimated 9.4 million cases of foodborne disease caused by identified pathogens occur annually (*3*). One of the most prevalent locations for foodborne illness outbreaks is a catering service facility. The estimated cost of a single outbreak of foodborne illness in a restaurant may exceed 1 million US dollar (USD) (*4*). Research has shown that factors such as inadequate time-temperature control, insufficient kitchen hygiene, and the presence of disease carriers among food handlers in catering service facilities, including restaurants, contribute to foodborne illnesses (*5*). The primary cause of these outbreaks is often faulty operation. Increasing awareness of food hygiene, etiologies, and contributing factors of foodborne diseases can serve as a guide for preventing foodborne outbreaks (*6*–*7*).

The China National Center for Food Safety Risk Assessment established the Foodborne Disease Outbreak Surveillance System (FDOSS) to collect data on foodborne diseases. The CDCs at various levels throughout China are responsible for conducting on-site investigations during outbreaks and entering relevant data into the FDOSS. The purpose of this study is to analyze the epidemiological characteristics of foodborne disease outbreaks occurring in catering service facilities between 2010 and 2020 using data from the FDOSS.

METHODS

Between 2010 and 2020, data were gathered on all foodborne disease outbreaks involving two or more patients or at least one death, which occurred in catering service facilities within China, not including Xizang (Tibet) Autonomous Region. These outbreaks were investigated and reported to FDOSS by local CDCs. The information collected included the timing and location of the outbreaks, the number of cases, hospitalizations, and fatalities, as well as the causes, pathogens, and food production environments involved.

Prior to inclusion in the FDOSS database, all outbreak incidents occurring in catering service establishments underwent rigorous auditing and verification by both the prefecture- and the provincial-level CDCs. Data processing and storage were performed using Microsoft Excel 2019 (Microsoft Corporation, Redmond, Washington, USA). For analysis purposes, dichotomous variables were summarized by counts and percentages, whereas continuous variables were represented by means.

RESULTS

The FDOSS reported a total of 18,331 outbreaks in catering service facilities in China between 2010 and 2020, which resulted in 206,718 cases, 68,561 hospitalizations, and 201 deaths. Among all foodborne outbreaks reported in the same period, these figures accounted for 50.87% of total outbreaks, 75.36% of total cases, 66.04% of total hospitalizations, and 13.65% of total deaths during this period. The median number of patients per outbreak was 15, with a median of 3 hospitalizations per outbreak.

Temporal Distribution

The number of outbreaks and cases climbed rapidly from 2010 to 2018, with a peak of 3,610 outbreaks and 31,230 cases in 2018. The third quarter demonstrated the highest frequency of outbreaks and cases, while the combined second and third quarters represented 76.12% of annual outbreaks and 72.93% of annual cases (Figure 1).

Geographic Distribution

Pathogenic organisms were the primary cause of outbreaks in southern (55.11%), northwestern (26.51%), eastern (26.40%), central (22.78%), and northern regions of China (20.44%), while toxic animals, plants, and poisonous mushrooms were the leading causes of outbreaks in northeastern (22.49%) and southwestern regions (29.54%), respectively. Chemical-related incidents resulted in the highest number of fatalities in northeastern (87.50%), northwestern (58.33%), central (55.00%), and northern regions of China (30.00%), whereas toxic animals and plants were the leading cause of deaths in southern (47.06%) and eastern regions (29.03%). Poisonous mushrooms accounted for the highest fatality rates in the southwestern region (30.00%).

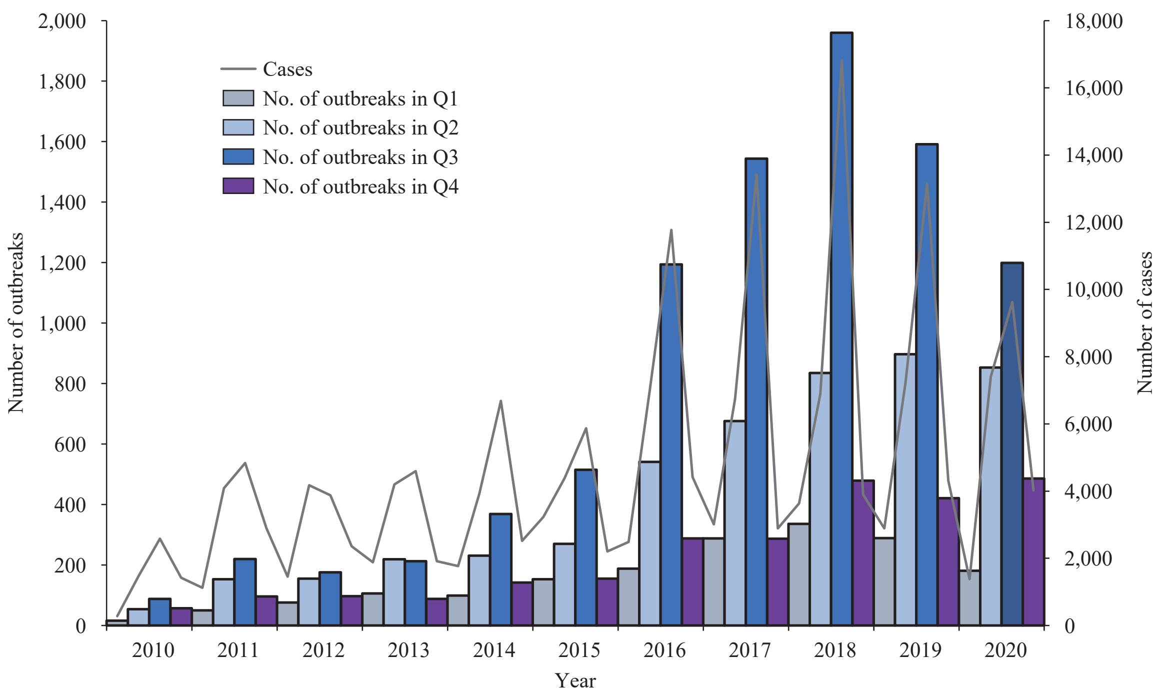

FIGURE 1. Number of reported foodborne disease outbreaks and cases in catering service facilities by quarters, China, 2010–2020.

Pathogenic Factors

The primary factors contributing to outbreak occurrences were pathogenic organisms, accounting for 4,883 (26.64%) outbreaks, 94,047 (45.50%) cases, 32,170 (46.92%) hospitalizations, and 21 (10.45%) deaths. Following this, toxic animals, plants, and mushrooms were responsible for 3,279 (17.89%) outbreaks, 30,698 (14.85%) cases, 12,338 (18.00%) hospitalizations, and 95 (47.26%) deaths (Table 1). Chemical substances, such as methanol and nitrite, caused the majority of fatalities (63). *Vibrio parahaemolyticus*, *Salmonella* spp. (species), and *Staphylococcus aureus* were the most prevalent pathogens, resulting in 3,333 outbreaks, 60,520 cases, 21,491 hospitalizations, and 9 deaths. The susceptibility of various food types to outbreaks was multifaceted, with meat products, aquatic goods, and vegetables associated with 2,724 (14.86%), 1,595 (8.70%), and 1,571 (8.55%) outbreaks, respectively, between 2010 and 2020.

Setting of Food Preparation

Catering service facilities encompass a range of establishments, including restaurants, street vendors, canteens, food stores, and rural banquets. Between 2010 and 2020, foodborne disease outbreaks in these facilities accounted for 5,607 (30.59%) incidents in restaurants, 2,876 (15.69%) in street vendors, and 2,560 (13.97%) in staff canteens (Figure 2). Among all catering service facilities, rural banquets and street vendors were associated with the highest mortality rates, with 64 (31.84%) and 34 (16.92%) deaths, respectively.

A cross-tabulation analysis revealed that the leading causes of outbreaks in restaurants were incorrect processing (655), accidental ingestion (263), and cross-contamination (240). Conversely, the primary causes of outbreaks in street vendors were accidental ingestion (775), improper storage (250), and inadequate processing (227). Similarly, staff canteens experienced outbreaks mainly due to undercooking (737), accidental ingestion (369), and improper processing (191). The majority of deaths resulted from accidental ingestion (89) and improper processing (35).

Combinations of Factors

Using a multidimensional analysis approach, we identified outbreaks by determining pathogenic factors and associated food sources, comparing them with the corresponding settings, and selecting combinations responsible for more than 50 outbreaks. Our analysis revealed that aquatic products contaminated with *Vibrio parahaemolyticus* at restaurants (resulting in 342 outbreaks and 5,345 cases) and rural banquets (leading to 110 outbreaks and 2,062 cases), as well as bean poisoning caused by Phaseolus vulgaris in staff canteens (triggering 725 outbreaks and 9,739 cases), were the primary contributors to food-borne disease

TABLE 1. Foodborne disease outbreaks, cases, hospitalizations, and deaths by pathogenic factors in catering service facilities, China, 2010–2020.

Pathogenic Factor	Outbreak	Proportion (%)	Case	Proportion (%)	Hospitalization	Proportion (%)	Death	Proportion (%)
Pathogenic organism								
Vibrio parahaemolyticus	1,638	8.94	26,180	12.66	5,749	8.39	2	1.00
Salmonella spp.	1,118	6.10	25,248	12.21	12,027	17.54	5	2.49
Staphylococcus aureus	577	3.15	9,092	4.40	3,715	5.42	2	1.00
Bacillus cereus	347	1.89	7,432	3.60	2,585	3.77	1	0.50
Escherichia coli	308	1.68	6,842	3.31	2,468	3.60	1	0.50
Others	895	4.88	19,253	9.31	5,626	8.21	10	4.98
Toxic animals and plants	1,816	9.91	22,615	10.94	8,142	11.88	49	24.38
Poisonous mushrooms	1,463	7.98	8,083	3.91	4,196	6.12	46	22.89
Chemicals	616	3.36	7,564	3.66	5,076	7.40	63	31.34
Mycotoxin	5	0.03	103	0.05	46	0.07	1	0.50
Parasite	11	0.06	125	0.06	10	0.01	0	0.00
Other factors	1	0.01	2	0.00	0	0.00	0	0.00
Unknown reasons	9,536	52.02	74,179	35.88	18,921	27.60	21	10.45
Total	18,331	100.00	206,718	100.00	68,561	100.00	201	100.00

outbreaks in catering operations (Table 2).

CONCLUSIONS

Due to shifts in dietary patterns and the fast-paced nature of modern life, an increasing number of individuals have opted to dine at foodservice establishments in recent years. Consequently, these establishments have become the leading source of foodborne disease outbreaks in numerous regions. It has been documented that a variety of food safety risks exist in foodservice facilities, such as restaurants, including those associated with food ingredients, handling practices, storage, and transportation. These risks may contribute to the occurrence of foodborne disease outbreaks. Moreover, the number of cases and hospitalizations associated with each outbreak at these facilities tends to surpass those resulting from household settings, ultimately leading to a more significant disease burden.

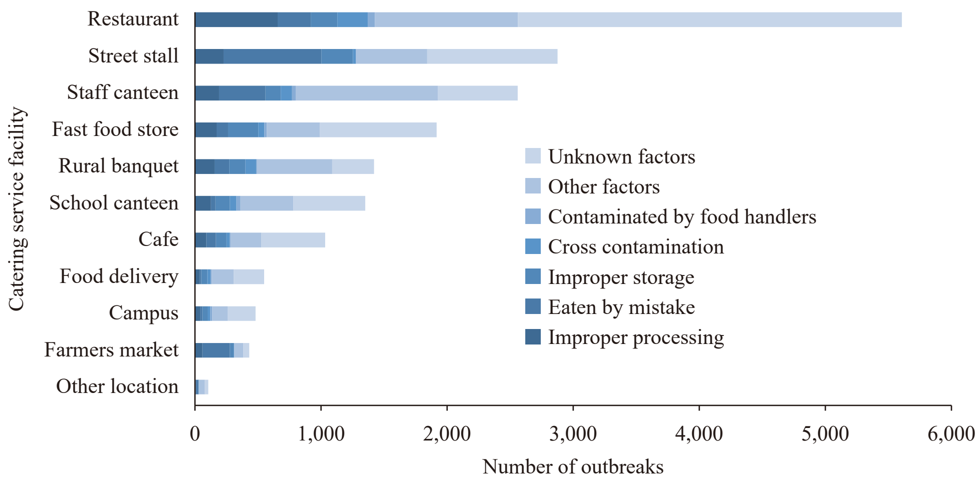

FIGURE 2. Reported foodborne disease outbreaks in catering service facilities by setting and causative factors in China, 2010–2020.

TABLE 2. Multidimensional analysis of settings, pathogenic factors, and food sources in foodborne disease outbreaks at catering service facilities in China, 2010–2020.

Settings	Pathogenic factor	Suspicious food	Outbreak	Case	Hospitalization	Death
Restaurant	*Vibrio parahaemolyticus*	Aquatic products	342	5,345	1,582	0
	Poisonous mushrooms	Mushrooms	175	1,107	550	0
	Salmonella spp.	Meat products	93	2,345	1,365	0
	Bean poisoning	Phaseolus vulgaris	87	718	231	0
Staff canteen	Bean poisoning	Phaseolus vulgaris	725	9,739	2,812	0
	Poisonous mushrooms	Mushrooms	249	1,783	899	15
Street vendor	Poisonous mushrooms	Mushrooms	622	2,322	1,118	10
	Bean poisoning	Phaseolus vulgaris	75	415	123	0
	Nitrite	Meat products	54	320	245	3
	Salmonella spp.	Egg foods	54	269	196	0
Farmers market	Poisonous mushrooms	Mushrooms	256	995	559	6
Rural banquet	*Vibrio parahaemolyticus*	Aquatic products	110	2,062	387	0
	Salmonella spp.	Meat products	101	3,603	2,482	2
	Poisonous mushrooms	Mushrooms	58	1,240	789	9
School canteen	Bean poisoning	Phaseolus vulgaris	73	1,931	712	0
	Bacillus cereus	Flour and rice products	51	1,489	751	0
Fast food store	*Salmonella* spp.	Cakes and pastries	58	1,035	525	0

In recent years, there has been a steady increase in the number of foodborne disease outbreaks and cases in catering service facilities due to the expansion of the reporting network. However, in 2020, there was a decrease in these incidents, with the primary pathogenic factor, *Vibrio parahaemolyticus*, dropping from first to second place, being replaced by *Salmonella* spp. This shift may be attributed to the impact of coronavirus disease 2019 (COVID-19) and its related prevention and control measures, which reduced the number of residents gathering and dining outside. Additionally, the decline in consumption of cold-chain transported aquatic products may have also played a role in this trend.

The peak of outbreaks and cases in catering service facilities occurred annually during the second and third quarters, aligning with the period of bacterial foodborne disease epidemics. This may be attributed to the increased temperature and humidity during this season, promoting bacterial growth and reproduction. *Vibrio parahaemolyticus*, *Salmonella* spp., and *Staphylococcus aureus*, the primary pathogens associated with outbreaks in food service facilities, also demonstrated increased activity during the summer and autumn. Concurrently, meat and aquatic products contaminated with bacteria were more prone to spoilage. The higher number of outbreaks and cases in eastern China may result from economic growth and a heightened focus on epidemiological investigations. Similar epidemiological characteristics have been observed in foodborne disease outbreaks in coastal regions (provinces, autonomous regions, and municipalities directly under the Central Government with coastline) (*8–9*). The findings suggest that targeted population education should be reinforced in catering service facilities in China.

Various pathogenic agents and food combinations, including *Vibrio parahaemolyticus*-contaminated aquatic products and *Salmonella*-contaminated meat items, have been found to be susceptible to causing outbreaks of foodborne illnesses in catering establishments. The primary causes of these outbreaks were related to food preparation management, such as improper processing, accidental consumption, and cross-contamination. Despite the presence of food safety management systems in many restaurants and cafeterias, their implementation was not always effective. To address this issue, it is recommended that the responsible departments enhance food safety management efforts among street vendors and rural banquets.

Accidental consumption of toxic mushrooms by Chinese families has been identified as a major cause of fatalities (*10*). Ingesting harmful chemicals, such as methanol and nitrite, along with poisonous mushrooms and improper food processing, contributed to most deaths in catering service facilities. This situation warrants the attention of authorities, as swift intervention could mitigate the related challenges.

Numerous interventions have demonstrated high effectiveness; thus, it is essential to implement control measures that integrate population science and management. Such measures include public health education on foodborne diseases in catering service facilities and regular food safety training for restaurant employees and managers. By mitigating cross-contamination and ensuring proper cooking and storage practices, the comprehensive implementation of exemplary sanitation procedures during food processing should decrease the incidence of foodborne disease outbreaks (*11*).

While there remain unidentified causes for numerous instances in the system, the data analyzed may not encompass all actual outbreaks. A thorough examination of high-risk factors necessitates an accurate attribution analysis, which relies on the collection of more specific information and samples throughout the investigation. Alternatively, the rapid detection technology of multi-pathogens, along with pulsed-field gel electrophoresis and whole-genome sequencing, could potentially enhance the laboratory diagnostic capabilities for outbreaks and provide confirmation for the results of epidemiological inquiries (*12*).

Acknowledgements: All members at all participating CDCs.

Conflicts of interest: No conflicts of interest.

Funding: Supported by the National Key Research and Development Program of China (Grant No. 2022YFC2602303).

doi: 10.46234/ccdcw2023.091

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Submitted: March 21, 2023; Accepted: May 29, 2023

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Perspectives

Contamination and Transmission of SARS-CoV-2 Variants in Cold-Chain Food and Food Packaging

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INTRODUCTION

The emergence of coronavirus disease 2019 (COVID-19) has posed a significant threat to global health and well-being. Vaccination serves as a vital strategy in preventing and mitigating the severity of clinical symptoms. However, due to natural selection, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has evolved, resulting in various mutations (*1*). Currently, the World Health Organization (WHO) has identified five variants of concern, including Alpha, Beta, Gamma, Delta, and Omicron (*2*). Of these, only Omicron remains in circulation and has already produced nearly one thousand sub-lineages or subvariants. These mutating variants demonstrate increased infectivity and vaccine breakthrough rates, as well as more pronounced antibody escape rates (*3*).

COVID-19 is primarily a respiratory illness, with its main transmission routes being direct contact and the spread of droplets or aerosols (*4*). The Food and Agriculture Organization of the United Nations (FAO) has reported that the likelihood of SARS-CoV-2 transmission via food or food packaging is low, as the virus cannot multiply on such surfaces. In addition, upon exposure to environmental factors, viral particles degrade and become less infectious (*5*). Despite this, emerging epidemiological evidence suggests that imported cold-chain foods and their packaging may contribute to outbreak occurrences.

According to the literature, there have been seven reported outbreaks in China associated with exposure to cold-chain food and food packaging contaminated with SARS-CoV-2. For instance, viral strain analysis revealed that the virus isolated from the outer packaging of imported cod was linked to the SARS-CoV-2 infections found among dock workers during the 2020 Qingdao outbreak (*6*). Moreover, several COVID-19 outbreaks have occurred in meat processing facilities overseas, with a diagnosis rate of 18.2% among workers in some states of the United States (*7*). Individuals working in cold, humid, and crowded environments are at an increased risk for both contracting and transmitting the virus.

Cold-chain food and packaging may become contaminated through two primary means: 1) viral shedding from hands coming into contact with food and packaging surfaces, and 2) expelled respiratory particles generated from talking, coughing, sneezing, and singing (*8*). In the investigation of the COVID-19 outbreak in Qingdao, live SARS-CoV-2 strains were successfully isolated and cultured from imported frozen seafood packaging (*9*). This finding suggests that SARS-CoV-2 can survive at low temperatures for several weeks, thereby enabling its spread across borders. Consumers may then transfer infectious particles from contaminated food surfaces and packaging to their eyes, noses, and mouths (*10*). Even during periods of strict control measures, the potential spread of SARS-CoV-2 through frozen food items and packaging, particularly imported frozen food and packaging, warrants close attention.

SARS-CoV-2 VARIANTS CONTAMINATION IN COLD-CHAIN FOOD AND FOOD PACKAGING

The overall contamination level of cold-chain food and food packaging appears to be low. Between May 5, 2020, and September 10, 2020, the Supervision Bureau of Consumer Rights and Citizen Safety Protection of the Russian Federation examined a total of 1,677 cold-chain samples, primarily consisting of vegetables (40%), meat and meat products (26%), and fruits (22%). All samples tested negative for SARS-CoV-2 (*11*). During November 2020 through January 2021, the Food Quality and Safety Administration's Medical Department of the Ministry of Public Health in Thailand randomly tested 117 samples of food (mainly seafood) and food packaging (cans, cartons, etc.), with no SARS-CoV-2 detected in any samples

(*12*).

In 2020, China Customs collected and tested 1,295,692 samples, of which 47 yielded positive results for nucleic acid (0.35/10,000), and the remaining samples tested negative (*13*). Furthermore, over 55.83 million swabs of frozen food-related samples were collected in China, including 31 provincial-level administrative divisions (PLADs) and the Xinjiang Production and Construction Corps (XPCC). More than 20.51 million swabs were related to cold-chain food and packaging materials. Among these, 1,455 (0.26/10,000) swabs tested positive. As shown in Table 1 (*14*), seafood displayed the highest levels of pollution among all food types. The risk of carrying viruses is higher for outer packaging than inner packaging, and the positive sample detection ratio of imported cold-chain food exceeded that of domestic cold-chain food. Imported cold-chain foods might be a potential source for COVID-19 outbreaks related to the cold chain in China.

In conclusion, by analyzing the results of SARS-CoV-2 nucleic acid testing of cold-chain food and food packaging both domestically and internationally, it can be demonstrated that the risk of cold-chain food contamination by SARS-CoV-2 is relatively low.

Persistence of SARS-CoV-2 Variants on the Surfaces of Cold-Chain Food and Materials

The persistence of SARS-CoV-2 variants on various surfaces of cold-chain food products is influenced by the specific food substrate. Table 2 demonstrates that fresh agricultural products, such as grapes and tomatoes, as well as deli products like turkey and cheese, can maintain the infectivity of SARS-CoV-2 variants for up to 21 days at 4 °C. In contrast, avocado shells, avocado pulp, and salami have been found to exhibit antiviral effects (*15*). Certain meats, including salmon, beef, pork, and chicken, can support the survival of SARS-CoV-2 surrogates for 30 days at both 4 °C and −20 °C (*16*).

Additionally, the persistence of SARS-CoV-2 variants on different surfaces of cold-chain food products is affected by the temperature of cold-chain transmission. One study revealed that the persistence of SARS-CoV-2 variants on frozen meat (-20 °C) is longer compared to that on freshly stored meat (4 °C) (*17*). Therefore, SARS-CoV-2 demonstrates a strong survival capacity under refrigerated or frozen conditions. Low-temperature environments during the storage and transportation of cold-chain food products provide favorable conditions for the survival of SARS-CoV-2.

When the cold-chain transmission is maintained and materials are consistently kept at the same temperature, the persistence of SARS-CoV-2 mutations does not increase. One study demonstrated that SARS-CoV-2 variants, specifically Alpha and Delta, can survive on stainless steel surfaces for up to 10 days at 4 °C (*18*). Another study observed consistent persistence levels for three distinct SARS-CoV-2 variants on the same material surfaces and at the same temperature (*19*). As presented in Table 2, persistence levels of the strains SARS-CoV-2L, SARS-CoV-2S, and 229E at 4 °C differ across various materials. The persistence of SARS-CoV-2 variants on porous surfaces like kraft and parchment paper is lower compared to non-porous surfaces such as low-density polyethylene. The persistence of SARS-CoV-2 variants on both kraft and parchment paper is longer at −20 °C than at 4 °C. Lower temperatures are more conducive to the survival of SARS-CoV-2. Furthermore, the persistence and infectivity of the virus can be extended in refrigerated and frozen conditions when materials are exposed to cold-chain transmission in the food industry.

TABLE 1. Contamination of the SARS-CoV-2 variants in cold-chain food and food packaging in China.

Date (region)	Food	No. of positive samples	Percentage of total positive samples (%)
2020.07–2021.07 (31 PLADs and XPCC)	Seafood	753	53.86
	Poultry meat	530	37.91
	Other foods	115	8.23
	Inner packaging material	37	3.25
	Outer packaging material	1,101	96.75
	Imported food and packaging	1,391	99.50
	Domestic food and packaging	7	0.50

Abbreviation: SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; PLADs=provincial-level administrative divisions; XPCC=Xinjiang Production and Construction Corps.

TABLE 2. Persistence of the SARS-CoV-2 variants on cold-chain food and material surfaces.

Classification	Food	Virus	Initial viral load	Temperature	Persistence (day)	Test method	Viral load	Reference
Fresh agricultural product	Avocado shell or pulp	USA-WA1/2020, NR-52281	3.9 log PFU/mL	4 °C	7	qRT-PCR	LOD	(*15*)
	Grape, Tomato	USA-WA1/2020, NR-52281	3.9 log PFU/mL	4 °C	21	qRT-PCR	+	(*15*)
Deli	Turkey, Cheese	USA-WA1/2020, NR-52281	3.9 log PFU/mL	4 °C	21	qRT-PCR	+	(*15*)
	Salami	USA-WA1/2020, NR-52281	3.9 log PFU/mL	4 °C	14	qRT-PCR	LOD	(*15*)
Meat	Oyster	USA-WA1/2020, NR-52281	3.9 log PFU/mL	4 °C	21	qRT-PCR	LOD	(*15*)
	Salmon	Phi6 (COVID-19 surrogates)	9.0 log PFU/mL	4 °C, −20 °C	30	Plaque assay	+	(*16*)
		IVCAS6.7512; NMDCN000HUI	10^4 $TCID_{50}$/mL	4 °C	9	qRT-PCR	+	(*17*)
				−20 °C	20		LOD	(*17*)
	Beef steak, Ground beef	USA-WA1/2020, NR-52281	3.9 log PFU/mL	4 °C	14	qRT-PCR	LOD	(*15*)
	Beef	Phi6 (COVID-19 surrogates)	9.0 log PFU/mL	4 °C, −20 °C	30	Plaque assay	+	(*16*)
		IVCAS 6.7512; NMDCN000HUI	10^4 $TCID_{50}$/mL	4 °C	9	qRT-PCR	+	(*17*)
				−20 °C	20		LOD	(*17*)
	Ground pork, Pork chop	USA-WA1/2020, NR-52281	3.9 log PFU/mL	4 °C	21	qRT-PCR	+	(*15*)
	Pork	Phi6 (COVID-19 surrogates)	9.0 log PFU/mL	4 °C, −20 °C	30	Plaque assay	+	(*16*)
		IVCAS 6.7512; NMDCN000HUI	10^4 TCID50/mL	4 °C	9	qRT-PCR	+	(*17*)
				−20 °C	20		LOD	(*17*)
	Chicken	Phi6 (COVID-19 surrogates)	9.0 log PFU/mL	4 °C, −20 °C	30	Plaque assay	+	(*16*)
Material	SS	Alpha variant	$6.20×10^4$ PFU/mL	4 °C	10	Plaque assay	LOD	(*18*)
		Delta variant	$1.56×10^4$ PFU/mL	4 °C	10		LOD	(*18*)
	Kraft	SARS-CoV-2 L; SARS-CoV-2 S; 229E	4.77±0.04; 4.82±0.05; 4.84±0.05 log $TCID_{50}$/mL	4 °C	2	$TCID_{50}$ assay	LOD	(*19*)
				−20 °C	5		+	(*19*)
	Parchment	SARS-CoV-2 L; SARS-CoV-2 S; 229E	4.77±0.04; 4.82±0.05; 4.84±0.05 log $TCID_{50}$/mL	4 °C	4	$TCID_{50}$ assay	LOD	(*19*)
				−20 °C	5		+	(*19*)
	LDPE	SARS-CoV-2 L; SARS-CoV-2 S; 229E	4.77±0.04; 4.82±0.00; 4.84±0.05 log $TCID_{50}$/mL	4 °C	5	$TCID_{50}$ assay	+	(*19*)
				−20 °C	5		+	(*19*)

Abbreviation: SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; COVID-19=coronavirus disease 2019; RT-PCR=reverse transcription-polymerase chain reaction; + = be detected; LOD=limit of detection; SS=stainless steel; LDPE=low-density polyethylene.

Cold-Chain Food and Food Packaging Causing COVID-19 Outbreaks

Since the outbreak began three years ago, multiple epidemiological findings have indicated the spread of SARS-CoV-2 through imported cold-chain foods and food packaging. Existing literature has reported seven outbreaks in China linked to contact with SARS-CoV-2-contaminated cold-chain food and food packaging (Table 3) (*6*). In another study, viral genome sequence alignment analyses revealed that the SARS-CoV-2 strains causing six outbreaks in China were unrelated to previous local COVID-19 outbreaks. However, some of these strains exhibited high homology with circulating strains abroad, consistent with the countries of origin for imported cold-chain products from the outbreak area (*20*). These findings suggest that cold-chain foods and packaging can facilitate cross-border viral transmission.

The potential transmission of the virus from cold-chain products to humans may occur if workers handling these items do not properly wear personal protective equipment. Workers such as stevedores or wholesalers may experience higher risk for SARS-CoV-2 exposure due to their direct and frequent contact with cold-chain transported goods. For instance, during the 2020 Qingdao outbreak, the virus strain isolated from the outer packaging of imported cod was found to be a precursor of the strain infecting dock workers. The aforementioned traceability investigation and virology results imply that, under specific environmental conditions, the virus present on the surface of goods might infect high-risk populations without adequate protection, such as cold-chain workers (*21*). For consumers, the risk may be lower as goods are often stored and distributed in well-ventilated environments.

In recent years, sporadic reports of COVID-19 outbreaks linked to cold-chain processes have emerged in China in media reports. As indicated in Table 3, two such outbreaks were associated with the SARS-CoV-2 Omicron BA.2 variant, which was traced back to the external packaging of cold-chain food and products. In contrast, the sources of contamination in other outbreaks, primarily in coastal cities, were not identified in relation to cold-chain food and packaging materials.

The Quantitative Microbial Risk Assessment Model for the Transmission of SARS-CoV-2

The risk of non-foodborne SARS-CoV-2 transmission through cold-chain food and food packaging has raised concerns about food facilities as high-risk settings. The transmission risk factors in these facilities include enclosed environments, frequently touched surfaces, and difficulty maintaining physical distancing. Sobolik et al. utilized a quantitative risk assessment model to assess SARS-CoV-2 transmission in enclosed food manufacturing facilities (*28*). Their findings demonstrated that workers are at elevated risk for SARS-CoV-2 infection through close contact (large droplets and small aerosol particles) compared with fomite transmission (cold-chain food and food

TABLE 3. COVID-19 outbreaks associated with cold-chain food and packaging.

Report	Date	Region	No. of cases	Source of infection	Reference
Literature	2020.06	Beijing	402	Imported frozen food	(*6*)
	2020.07	Dalian	135	Outer packaging of imported frozen food	
	2020.09	Qingdao	14	Outer packaging of imported frozen cod	
	2020.11	Tianjin	2	Cold-chain food environment	
	2020.11	Tianjin	10	Cold-chain food	
	2020.12	Dalian	83	Cold-chain food	
	2021.05	Liaoning, Anhui	43	Imported frozen cod	
Media	2020.12.01	Qingdao	1	−	(*22*)
	2022.05.27	Qingdao	1	−	(*23*)
	2022.05.16	Tianjin	28	Imported cold-chain food (Omicron BA.2)	(*24*)
	2022.06.30	Qingdao	13	Outer packaging of cold-chain goods (Omicron BA.2)	(*25*)
	2022.06.21	Jilin	10	−	(*26*)
	2022.08.07	Jilin	1	−	(*27*)

Abbreviation: COVID-19=coronavirus disease 2019.

packaging) and aerosol exposure alone.

SARS-CoV-2 contamination in food and packaging primarily occurs via respiratory particle spray (droplets and aerosols) generated by workers, especially those who are latently infected or asymptomatic (*29*). Droplet transmission is characterized by close contact (less than 2 meters) exposure to large, virus-containing particles (greater than 100 μm diameter) that originate from coughing or sneezing and rapidly fall onto food or packaging surfaces (*29*). Aerosols consist of small particles that can be contacted at close distances and up to 9 meters away. Workers release aerosol particles when breathing, talking, singing, or laughing. Epidemiological studies have demonstrated viral accumulation and persistence in enclosed indoor spaces, with high levels of small aerosol particles in the air leading to food and packaging contamination (*30*).

Moreover, workers involved in cold-chain food processing, packaging, and transportation may spread the virus via contaminated hands, which in turn could result in the contamination of food and packaging (*31*). Table 4 reveals that implementing measures such as increasing physical distancing among cold-chain practitioners, wearing N95 masks, enhancing air exchange rates, and handwashing can significantly reduce the risk of SARS-CoV-2 infection.

Additionally, Huang et al. successfully isolated the first monkeypox virus (MPXV) strain in China (*32*). A qualitative risk assessment of monkeypox transmission suggests that the virus can be spread through food (bushmeat), even though it is not classified as foodborne. However, heat treatment effectively

TABLE 4. Risk assessment models for the transmission of the SARS-CoV-2.

Virus	Transmission route	Simulation of situation		Risk	Reference
SARS-CoV-2; MERS; Influenza A virus	Droplet and aerosol	Enclosed food manufacturing facility (Exposure time 8 h)		0.96	(*28*)
	Fomite			0.26	
	Aerosol exposure alone			0.05	
SARS-CoV-2; MERS; Influenza A virus	Aerosol, droplet, and fomite	Enclosed food manufacturing facility (PD)	1 m	0.98	(*28*)
			2 m	0.15	
			3 m	0.09	
SARS-CoV-2; MERS; Influenza A virus	Aerosol, droplet, and fomite	Enclosed food manufacturing facility (PD: 1 m)	Cloth	0.47	(*28*)
			Surgical	0.35	
			Double mask	0.12	
			N95	0.01	
Recombinant SARS CoV-2 variants; Murine coronavirus strain	Aerosol	Indoor environment	100 cm^2	2.3×10^{-5}	(*34*)
			400 cm^2	5.1×10^{-6}	
SARS-CoV-2 particles	Aerosol	Indoor environment	0 ACH	0.13	(*35*)
			1 ACH	0.065	
SARS-CoV-2; MERS; Influenza A virus	Aerosol, droplet, and fomite	Enclosed food manufacturing facility (PD: 1 m; Double mask)	2 ACH	0.04	(*28*)
			6 ACH	0.02	
SARS-CoV-2	Fomite	Frozen food packaging facility	The absence of interventions, exposure to packaging under cold-chain conditions	$<2.0\times10^{-3}$	(*36*)
			No SARS-CoV-2 immunity from vaccination or prior infection; Without standard infection control interventions	1.5×10^{-3}	
			Standard infection control interventions	1.2×10^{-3}	
			Handwashing	3.9×10^{-5}	
			Handwashing with mask-wearing	8.5×10^{-6}	
			A fully vaccinated workforce, as well as handwashing and mask-wearing	1.4×10^{-6}–8.8×10^{-6}	
			The susceptible worker with two doses of mRNA vaccine and hourly handwashing and mask-wearing	5.2×10^{-7}	

Abbreviation: SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; MERS=Middle East Respiratory Virus; ACH=air changes per hour; PD=physical distancing.

inactivates the monkeypox virus in food (*33*).

CONCLUSIONS

In China, COVID-19 has been reclassified as a Class B infectious disease and is managed accordingly, leading to significant adjustments in epidemic prevention and control strategies. While the relevance of SARS-CoV-2 transmission through frozen food and packaging has diminished in importance, this study remains highly pertinent for preventing other infectious diseases similar to COVID-19. In particular, it offers valuable insight into the transmission of emerging infectious diseases through cold-chain food and packaging.

Conflicts of interest: No conflicts of interest.

Funding: National Key Research and Development Program of China (Grant numbers 2022YFF1103100 and 2019YFC1605900) and 2022 Strategic Research and Consulting Project of Chinese Academy of Engineering.

doi: 10.46234/ccdcw2023.092

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Submitted: March 01, 2023; Accepted: April 03, 2023

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Perspectives

National Action Plan in Antimicrobial Resistance Using Framework Analysis for China

Shanquan Chen[1,2]; Jiahong Zhang[1]; Yongning Wu[2,#]

INTRODUCTION

The emergence of multi-antibiotic-resistant bacteria has turned bacterial resistance into a pressing global issue. Antibiotics that once effectively treated various infectious diseases are now becoming less efficient against a new class of bacteria known as "Super Bacteria," including methicillin-resistant *Staphylococcus aureus* (*1*). It is estimated that one person dies every minute due to drug-resistant strains of disease, and by 2050, drug-resistant bacterial infections could become the leading cause of death in humans (*2*).

Factors contributing to the antimicrobial resistance (AMR) crisis include insufficient development of new antibiotics, irrational antibiotic use, poor pharmaceutical waste disposal, and a lack of public awareness (*3*). Addressing AMR necessitates cooperation across public health departments and comprehensive governance solutions, which should involve increased oversight of environmental protection, medication development, drug production, distribution, and application (*4*).

To confront this critical issue, the World Health Assembly published a global action plan (GAP) in May 2015, which aims to improve awareness and understanding, strengthen surveillance and research, reduce infection incidence, optimize the use of antimicrobial medicines, and promote sustainable financial support (*4*).

China holds the distinction of being the world's largest producer and consumer of antibiotics. Per capita antibiotic use in China is approximately ten times higher than in the United States, and the average daily intake of antibiotics per 1,000 individuals is six times greater (*5*). Since then, AMR management in China has evolved through three major phases: drug control-based management, clinical monitoring-based management, and a comprehensive management strategy involving multiple domains (*6*). In response to its first National Action Plan (NAP) on AMR (*7*), China implemented various policies and devoted significant efforts to enhance AMR monitoring. Following the completion of the first NAP, the NAP for 2022–2025 was released early in 2023.

The Tripartite AMR Country Self-Assessment Survey (TrACSS), administered by the Food and Agriculture Organization (FAO), World Health Organization (WHO), and World Organisation for Animal Health (OIE), aims to monitor country progress in addressing antimicrobial resistance through a questionnaire survey (*8*). To date, there has been no third-party assessment to systematically review and evaluate the efforts made during the first NAP in China. The purpose of this article is to analyze the governance of AMR-related measures since 2016, including the first and updated NAPs implemented by various ministries in China. This analysis will generate insights from the NAP to inform future policy design recommendations.

METHODS

In 2021, a research team from the National University of Singapore introduced a system for assessing the National Action Plan using line-by-line analysis, which is a method involving grounded theory to identify emerging trends from data line by line and develop a previously non-existent framework (*9*). Various sub-objectives are evaluated and discussed in each section of Figure 1, encompassing policy design, implementation tools, monitoring and evaluation, sustainability, and One Health engagement. Policy design concentrates on creating policy and action structures from the government to stakeholders. Implementation tools primarily serve to implement the designed policies, reduce AMR, control antibiotic usage, and raise public awareness. Moreover, monitoring and evaluation pertain to the effectiveness of the policies and the feedback after actions have been conducted, while sustainability focuses on the continuation of future planning. We analyzed the relevant departments in China and summarized them

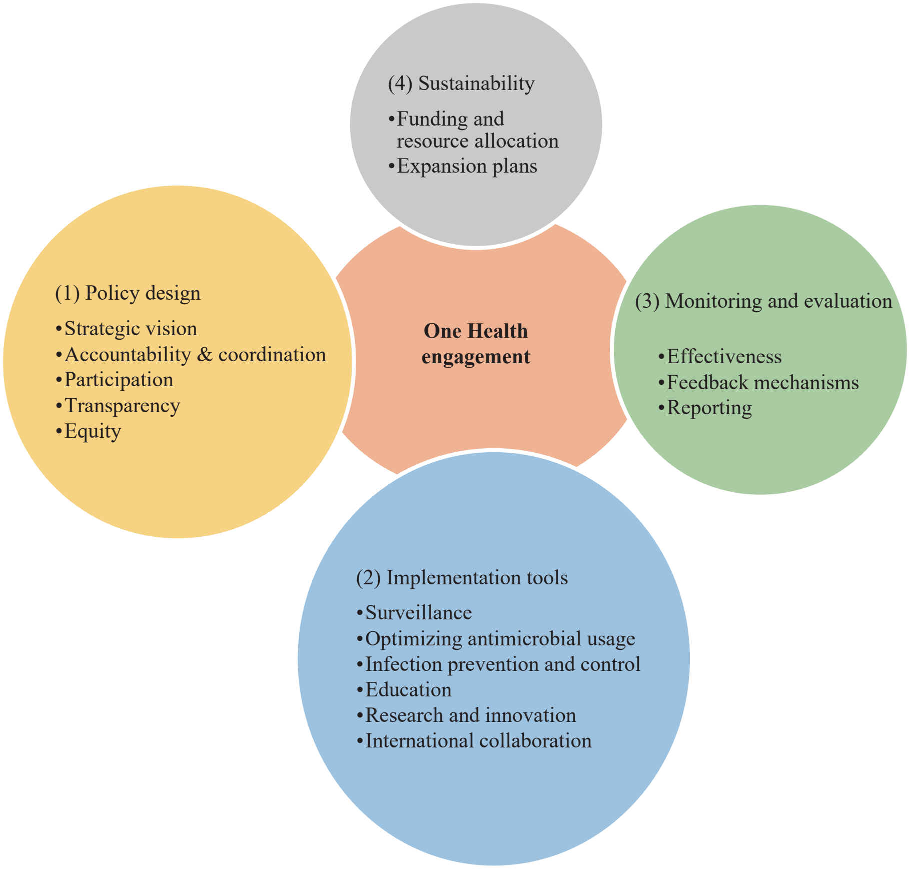

FIGURE 1. The analysis focuses on policy design, implementation tools, monitoring and evaluation, and sustainability toward the goal of One Health engagement.
Note: Analysis framework generated from Chua et al. 2021 (*9*).

in Figure 2, accompanied by a brief introduction of each department in the annotations.

The successful implementation of the NAP requires collaboration among multiple and cross-sectional departments. The initial stage of our study involved identifying departments involved in AMR control, by analyzing their roles, daily operations, and activity participation. Based on the identified departments, we proceeded to follow the primary objectives of the NAP.

Our research team utilized keywords such as AMR, antibiotic resistance, antibiotics, antimicrobials, and specific antibiotics, as well as references to meetings, to search for news articles, public interviews, and government documents. Two researchers then preprocessed the gathered information according to the relevant departments and validated the data by conducting duplicate determinations within the group.

Subsequently, we categorized the actions and developed a framework for the Chinese action plan to facilitate policy analysis. We also conducted a thorough review of the collected resources. An additional proofreading and modification process was performed as we transformed the resources into coherent paragraphs for publication.

RESULTS

The major results are listed below and the details are placed in the supplementary materials with the suggestions for further actions.

Policy Design

Strategic vision: National Health Commission (NHC) conducted AMR situation analysis in clinical surveillance and release the annual report with AMR assessment (*10*).

Accountability & coordination: The Ministry of Agriculture and Rural Affairs (MOA) and the Food Safety Office (FSO) have collaborated on rectification measures to address the issue of excess antibiotic and veterinary drug residues in agriculture (*11–12*). NHC, National Medical Products Administration (NMPA),

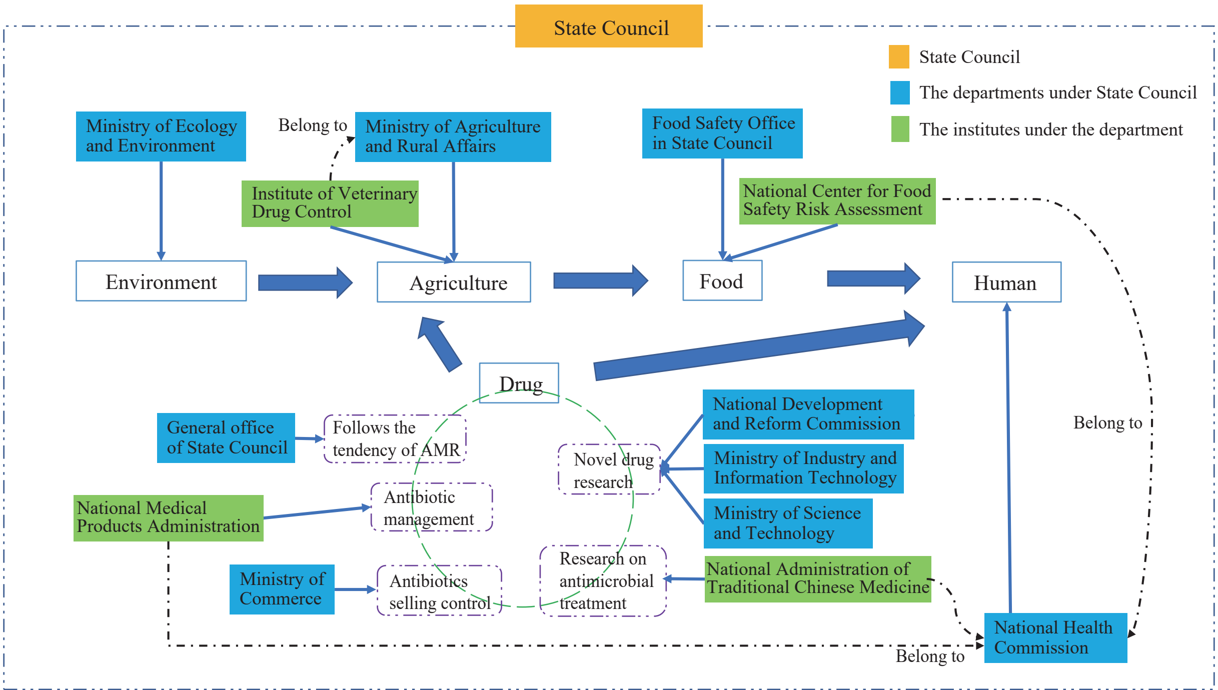

FIGURE 2. Departments chart summarized the involvement based on collected data.

Note: All departments are under the leadership of State Council. MEE takes part in environmental AMR governance. MOA treats AMR problem in breeding, agriculture and graziery. CCVP specifically focuses on the fodder and treatment for animals. FSO in State Council pays part of its attention to AMR as well. CFSA follows the AMR situation in China. NHC develops and organizes the implementation of AMR prevention and control plans. GOSC follows the tendency of AMR domestically. NMPA is in charge of antibiotic management. MOFCOM participates in antibiotics selling control. NATCM has researched on Antibiotics treatment. NDRC focuses on novel drug discovery, MIIT and MOST turn it into practice.

Abbreviation: MEE=Ministry of Ecology and Environment; MOA=Ministry of Agriculture and Rural Affairs; CCVP=Commission of Chinese Veterinary Pharmacopoeia; FSO=Food Safety Office; CFSA=China National Center for Food Safety Risk Assessment; NHC=National Health Commission; GOSC=General Office of State Council; NMPA=National Medical Products Administration; MOFCOM=Ministry of Commerce; NATCM=National Administration of Traditional Chinese Medicine; NDRC=National Development and Reform Commission; MIIT=Ministry of Industry and Information Technology; MOST=Ministry of Science and Technology.

and Ministry of Industry and Information Technology (MIIT) have jointly worked on improving the system for ensuring antibiotic drug supply by enhancing and modernizing the mechanisms associated with antibiotic medication distribution (*13*–*16*). Alongside the National Development and Reform Commission (NDRC), the Ministry of Science and Technology (MOST), and the Ministry of Commerce (MOFCOM), they have issued guidelines that aim to promote the improvement of the antibiotics industry in terms of quality, variety, and volume (*17*).

Participation: NHC improved the management of antibiotics medicine approval, production, and distribution, with a particular focus on antibiotics drug sales in retail (*18*).

Transparency: Transparency pertains to the accessibility of precise and current data (*9*). The MOA has established a database, which is centered on the surveillance of veterinary drug residues and the resistance profile of five key bacterial species (*19*).

Equity: In addition to the stringent regulation of prescription drugs, the NHC implemented reforms in the medical system, which resulted in increased accessibility and availability of over-the-counter medications for the general public (*20*).

Implementation Tool

Surveillance: The Ministry of Ecology and Environment (MEE) has conducted a specialized investigation into the levels of antibiotic pollution in drinking water (*21*). The Global Antimicrobial Resistance and Use Surveillance System (GLASS) offers a standardized methodology for data collection, analysis, and dissemination, as well as supporting capacity building and monitoring the status of national surveillance systems (*22*). GLASS prioritizes pathogens such as *Acinetobacter* spp., *Klebsiella pneumoniae*, *E.*

coli, *Neisseria gonorrhoeae*, *Shigella* spp., *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Salmonella* spp. (*22*). Although China did not participate in GLASS until 2022 (*23*), the NHC has collaborated in efforts to enhance monitoring of adverse reactions to antibiotic drugs (*24*) in China.

Optimizing antibiotic usage: MEE has enhanced control over antibiotic discharge by regulating antibiotic manufacturing and pharmaceutical companies (*25*). MOA has prohibited four antibiotics for use in humans and animals (*26*). NHC has implemented drug classification management and overseen prescription and over-the-counter medications (*27*). Antibacterial medication usage in outpatient clinics in China declined from 19.4% in 2010 to 7.7% in 2017, while inpatient usage decreased from 67.3% in 2010 to 36.8% in 2017 (*13*).

Infection prevention and control: The policies within this section predominantly focus on infection control, with less addressing prevention. The NHC has provided guidance for the clinical use of antibiotic drugs, encompassing both macro-level policies and detailed guidance (*28*).

Education: NHC implemented educational efforts to address misconceptions regarding antibiotic usage and the risks associated with antibiotic misuse (*29*). Hospitals provided training on appropriate antibiotic administration for physicians and nurses (*7*,*30*).

Research & innovations: MOA aims to develop a series of enhanced feed additives by decreasing the proportion of antibiotics and incorporating non-antibiotic agents that demonstrate efficacy in treating bacterial infections, as well as veterinary drugs and vaccines (*31*). Since 2018, NHC has been constructing comprehensive databases and traceability networks for drug resistance genes (*32*), while also promoting medication research and reforming the antibiotic review and approval system. Meanwhile, MOST supports the research and development of novel antibiotics and related technologies (*7*).

International collaboration: China keeps connection with other countries by jointly funding totally 60 million RMB in the field of AMR (*33*).

Monitoring and Evaluation

Effectiveness: The evaluation of policies regarding AMR is not publicly accessible. In addition to modern medicine, MOST and associated departments have assessed the effectiveness of Chinese medicine in combating drug-resistant bacterial infections and examined the underlying mechanisms. The National Administration of Traditional Chinese Medicine (NATCM) has made preliminary progress in promoting innovation and conducting research on antibacterial medications within the realm of traditional Chinese medicine (*10*).

Feedback mechanism: Although the NAP placed emphasis on generating feedback, it has been observed that the majority of actions and departments lack public and transparent feedback mechanisms (*9*).

Reporting: NHC published AMR status and report through the national clinic surveillance network for monitoring and evaluation (*10*).

Sustainability

Fund and resource allocation: MOST established some fund and relevant allocation systems for AMR research (*33*).

Expansion plans: This section emphasizes the importance of scaling and ensuring future sustainability in the context of expansion plans. The specific details of these plans will not be disclosed to the public until official publication. Prior research has underscored the significance of implementing NAPs in a manner that is both sustainable and yields a substantial impact (*34*).

ANALYSIS AND DISCUSSION

The NAP analysis framework has demonstrated that in China, the implementation of NAP and the management of AMR-related actions exhibit both horizontal (within each institution) and intersectoral (across institutions) deficiencies in the design, execution, feedback, and regulation of these actions. Furthermore, we incorporated future actions for each governance area, as derived from the NAP analysis framework, into the updated NAP (2022–2025), which can be found in the Supplementary Tables S1–S4 (available in https://weekly.chinacdc.cn/) (*35*).

MOA has placed significant emphasis on monitoring antibiotic usage in growth chemicals or feed and on monitoring resistance in agricultural products (Supplementary Figure S1, available in https://weekly.chinacdc.cn/) (*36*–*38*). However, limited information from sector actions and publicities reflects MOA's efforts in policy design and subsequent implementation tracking. There is a lack of departmental accountability framework for addressing implementation failures. Another design flaw is related to ensuring equity. This component should be incorporated either in the department of action or before the majority of government actions to prioritize interests beyond those of the owners. Moreover, increased efforts could be directed towards developing various vaccines with high short-term efficacy, more injection sites, and addressing safety concerns associated with attenuated vaccinations (*39*). New vaccines should be developed based on the priority of bacterial diseases in each species and integrated with emerging technologies such as adjuvants and delivery (*30–40*). Annually, NHC publishes a status report detailing the issues identified and providing recommendations for improvement. However, MOA lacks an action plan or agenda for future work. Limited data is available from the food and agriculture section, particularly in aquatic animal health and plant health. These findings were also corroborated by the results in TrACSS's report from China (*41*).

The management of antibiotic drugs and antibiotic therapy in the medical and healthcare field in China falls under the jurisdiction of the NHC and the NMPA, with a more multi-sectoral approach. The NHC has enhanced its implementation of drug equity, requiring all levels of the healthcare system to adhere to the principle and arrange for professionals to advise patients on appropriate drug usage. Detailed infection treatment methods and medication guidelines have been published to prevent improper utilization and overdoses throughout the infection diagnosis process. The development of new antibiotic medications has been supported and continues to yield positive results, with multinational collaborations being established. Nevertheless, the relevant literature provides limited information on the specifics of interdepartmental cooperation, role assignment, and required accountability.

Intersectoral Analysis of Actions Among Departments Under the State Council: The core principle of One Health involves the cooperation among various government departments and the inclusion of additional stakeholders to achieve an efficient and large-scale impact. AMR governance cannot be addressed by a single sector or country; the essential requirement is the establishment of a coordinating department for cross-departmental collaboration and assigning responsibility and accountability across multiple departments. These aspects pose significant challenges in China's execution of the NAP and remain the objective for the 2022–2025 NAP (*35*).

There is a lack of intersectoral communication concerning initiatives related to AMR in China. Each department implements its own measures, leading to inconsistencies in the approaches taken. Our study identified considerable disparities in both the quantity and quality of work performed by various departments. The inconsistent attitudes and abilities of the departments contribute to incongruent deployment and completion of AMR-related actions. As a result, there is a need for an intermediary coordinating department at the national level to facilitate cross-sectoral collaboration, reduce resource waste, and improve governance effectiveness. This issue is also emphasized in the updated NAP.

CONCLUSION

In summary, China has made significant progress in AMR governance over the past five years, as evidenced by the development of a comprehensive surveillance and governance framework. A substantial number of publications have emerged addressing clinical usage of antibiotics, animal breeding, and treatment, with considerable investments allocated to AMR research. Despite these advancements, challenges remain due to inadequate interdepartmental collaboration and insufficient policy sustainability, leading to compromised effectiveness in AMR management. Additional efforts are required to address food safety and environmental concerns.

Drawing from the One Health approach and international experiences, such as those provided by the WHO, future initiatives should prioritize interdepartmental cooperation to enhance the sustainability and effectiveness of national action plans. In 2022, China developed its second NAP for 2022–2025, incorporating contributions from several multisectoral departments (*32*). The plan encompasses new areas of focus, including vaccination, AMR treatment in environmental settings, and the establishment of an intersectoral collaboration mechanism.

To further address AMR challenges, China should seek to play a more prominent role in international cooperation by joining global networks and adopting standardized laboratory and surveillance methodologies.

Funding: supported by the National Natural Science Foundation of China (grant No. 22193064), and the Indus-try-University Cooperation Project for Collaborative Education from the Ministry of Education (grant No. 221004439103151).

doi: 10.46234/ccdcw2023.093

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Submitted: May 08, 2023; Accepted: May 29, 2023

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SUPPLEMENTARY MATERIALS

SUPPLEMENTARY TABLE S1. Future actions generated by framework analysis for National Action Plan in China for Governance Area 1: policy design.

Indicator	Result summary	Future actions
Strategic vision	The strategic vision does not include specific, measurable, achievable, relevant, and time-bound (SMART) objectives, which are recommended to be delineated in the ensuing plan.	Make policy and plan consistent with the foreseeability of the global effect
Accountability & coordination	In 2017, MOA introduced a National Action Plan (NAP) with an objective to develop innovative veterinary drugs characterized by low toxicity and minimal residues while simultaneously phasing out high-risk pharmaceuticals. Pursuant to Document No. 194, the production and utilization of feeds containing growth-promoting additives have been prohibited since 2020. A series of guidelines have been established for the development of the pharmaceutical industry, focusing on non-inferior clinical trials for antibiotic drugs, technical requirements for microbiological laboratories involved in clinical trials of antibiotic and anti-TB drugs.	A well-organized coordination and accountability system was absent in the previous NAP, necessitating its implementation in future activities. The updated NAP has recently allocated tasks to specific departments, with the goal of establishing an effective interdepartmental collaboration mechanism.
Participation	The NHC mandated that retail pharmacies, retail companies, and Internet hospitals collaborate in managing antibiotic drug sales under the Measures for Supervision and Administration of Drug Circulation. Unlawful sales of antibacterial medications are subject to penalties, with ongoing policies focused on monitoring antibiotic use and requiring prescriptions for antibiotic sales.	The NAP should focus on promoting public involvement in AMR control efforts. Enhancing public awareness of AMR and emphasizing the importance of combating it through educational initiatives is crucial.
Transparency	MOA built a database based on the surveillance of veterinary drug residues and resistance status of five main bacteria to sixteen veterinary medicines in animal farms housing pigs, poultry, and dairy cows.	The updating process for NAP should be conducted regularly during each specified period, rather than merely providing summary documents in the final stage. It is essential to establish a comprehensive framework and database for AMR in both human and environmental contexts.
Equity	In accordance with the reformation requirements, pharmacists play an essential role in pharmacy settings and are obligated to inform and deliver expert medical advice to customers based on their individual needs.	AMR policy should be more considerate of the real situation in China.

Abbreviation: MARA= Ministry of Agriculture and Rural Affairs; NHC= National Health Commission.

SUPPLEMENTARY TABLE S2. Future actions generated by framework analysis for National Action Plan in China for Governance Area 2: implementation tool.

Indicator	Result summary	Future actions
Surveillance	The MEE primarily focused on two aspects. The first aspect involved antibiotic surveillance and testing. The Eco-Environmental Supervision and Administration Bureau of the MEE conducted antibiotic detection in water bodies within the Haihe River Basin and Beihai Sea Area. The second aspect aimed to bolster antibiotic discharge control and mitigate antibiotic usage. To achieve this, the MEE has strengthened regulations by controlling the approval process for antibiotic manufacturing firms, selecting appropriate locations for pharmaceutical companies, and imposing strict requirements on waste disposal.In terms of controlling the emission to environment from industry, *Synergistic control of antibiotics, resistance genes and conventional pollutants in pharmaceutical wastewater*, was published by China Pharmaceutical Industry Association. The NHC suggests implementing measures to enhance surveillance of adverse reactions related to antibacterial medications, as outlined in the Administrative Measures for Adverse Drug Reaction Reporting and Monitoring. Additionally, since 2018, the organization has been developing a comprehensive whole-genome database to facilitate national traceability networks for antibiotic-resistant genes found in food-borne pathogenic microorganisms.	Cross-sectoral regulatory collaboration is essential for optimal data sharing at the national level, aimed at facilitating real-time oversight across multiple domains. Interdisciplinary exchange on AMR is promoted within the NAP 2022–2025 framework.
Optimizing antibiotics usage	The MEE has enhanced the management of antibiotic discharge by implementing stringent regulations for granting approvals to antibiotic manufacturing firms. Additionally, the selection of pharmaceutical company locations and the imposition of rigorous waste disposal requirements have been emphasized to further control antibiotic discharge. The MOA has implemented a ban on four antibiotics for both humans and animals, which includes lomefloxacin use in food-producing animals, colistin as a feed ingredient, mycobacterium sulfate as a growth-promoting feed ingredient for food animals, and one veterinary antibiotic for growth promotion. As an example, MOA enforced a series of limitations on antibiotics in feed in 2014, with the regulations becoming effective in the farming process in 2015. As a result, China's cattle, poultry, and aquaculture industries have successfully reduced their antibiotic use per kilogram from 353.8 mg/kg in 2014 to 165 mg/kg in 2020 (*25*–*27*).The CCVP aims to halt the use of serial antibiotic veterinary medications, which include arsenic acid, arsine, olaquindox, and others.The NHC prioritized the appropriate use of antibiotics by implementing the Measures for the Classification Management of Prescription and Over-the-Counter Drugs (Trial) in 1999 and establishing a classification management system for prescription and over-the-counter medications through the amended Drug Administration Law in 2001. Throughout the National Drug Safety Twelfth Five-Year Plan, it was mandated that commercial pharmacies employ licensed pharmacists from 2012 onwards, and by 2015, all pharmacists were required to hold a licensed pharmacist certification to provide guidance on antibiotic usage to the public. Furthermore, antibiotic consumption for medical purposes has been subjected to monitoring and regulation via the clinical surveillance network.	Though the clinical research has been finalized, there remains a need to reduce the utilization of drugs in breeding practices. Online pharmaceutical retailers must create stringent policies concerning the prescription of antibiotics. The updated NAP establishes a requirement for all patients to have a prescription prior to purchasing antibiotics. The implementation of fines or sanctions for those who dispense antibiotics without a prescription is essential for compliance.
Inflection prevention and control (IPC)	The NHC has provided guidance for the clinical use of antibiotic drugs through the development and release of the Guiding Principles for the Clinical Application of Antibiotics Drugs (2015 edition). This document offers comprehensive information on the clinical application and management of antibacterial drugs, as well as the treatment of various bacterial infections. It established fundamental guidelines for therapeutic and preventive drug use, and requires medical institutions to create systems for drug classification and management of antibiotic drug applications in clinical settings. Clinical departments are encouraged to establish management teams using real-world examples. Furthermore, the document provides in-depth information on the use of antibacterial agents for numerous bacterial diseases, serving as a reference for the diagnosis and treatment of infectious diseases.	Enhancing preventive measures for humans may be achieved through the development of vaccines for livestock and aquatic animals.

TABLE S2. (Continued)

Indicator	Result summary	Future actions
Education	In 2019, the CFSA prioritized public education through the implementation of foodborne illness and antimicrobial resistance book projects.	Enhancing intra-functional communication regarding AMR governance is crucial for fostering awareness within the department. Advocating for more comprehensive dissemination of information within the community can contribute to this effort. Additionally, professional and continuing education in the One Health approach for stakeholders should be emphasized as a focal point of the educational strategy.
Research & innovations	In July 2018, MOA issued the Notice on Printing and Distributing Technical Guidelines for Agricultural Green Development (2018–2023), which aimed to develop a range of green, efficient feed additives, low-toxicity, low-resistance veterinary drugs, and high-efficiency, safe vaccines.Since 2018, the NHC has been conducting research on the development of whole-genome databases and traceability networks for drug resistance genes in food-borne pathogenic microorganisms on a national scale. The NHC has initiated several actions to promote medicinal research and innovation, such as enhancing the antibiotic drug registration management system to encourage innovation and registration through more clearly defined problem orientation and scientifically grounded regulatory concepts. Furthermore, the NHC has continuously reformed the antibiotics review and approval system, ensuring reviews are conducted in a scientifically standardized manner in compliance with relevant laws and regulations.The MOST actively fosters research and development of novel antibacterial drugs within the National Science and Technology Key Project, specifically focusing on “Key New Drug Creation” during the “13th Five-Year Plan” period. To address the challenges associated with limited resources, the MOST prioritizes the advancement of innovative drugs targeting drug-resistant pathogens and infectious diseases, as well as the establishment of new technology platforms for clinical evaluation of these medications.	The organization of scientific research must be systematically structured, taking into account various factors such as drug categories, distinct diseases, and diverse applications. Furthermore, the transition from research to practical implementation should be expedited.
International collaboration	The National Natural Science Foundation of China and the Royal Society collaborated to fund six joint research projects in the area of AMR, providing a total of 15.1445 million CNY in direct funding. These projects covered a range of topics, including resistance mechanisms and their applications, technological platforms, transmission mechanisms, key factors influencing drug usage behaviors, and path research in China.The National Science and Technology Key Project (NSTKP), through the support of MOST, emphasizes the research and development of innovative antibacterial drugs and concentrates on the advancement of novel pharmaceuticals and cutting-edge technology platforms.	In the context of developing novel antibiotics and managing AMR, international drug development can benefit from multi-partnerships that involve collaboration and shared analysis. Adopting and adapting diverse AMR governance models in such collaborative efforts can prove to be efficient. Moreover, pursuing cooperative AMR governance, such as joint initiatives between bordering countries, can facilitate regional or global control of AMR.

Abbreviation: MEE=Ministry of Ecology and Environment; NHC=National Health Commission; MOA=Ministry of Agriculture and Rural Affairs; NAP=National Action Plan; CCVP=Commission of Chinese Veterinary Pharmacopoeia; CFSA=China National Center for Food Safety Risk Assessment; MOST=Ministry of Science and Technology; CNY=Chinese Yuan; AMR=antimicrobial resistance.

SUPPLEMENTARY TABLE S3. Future actions generated by framework analysis for National Action Plan in China for Governance area 3: monitoring and evaluation Analysis.

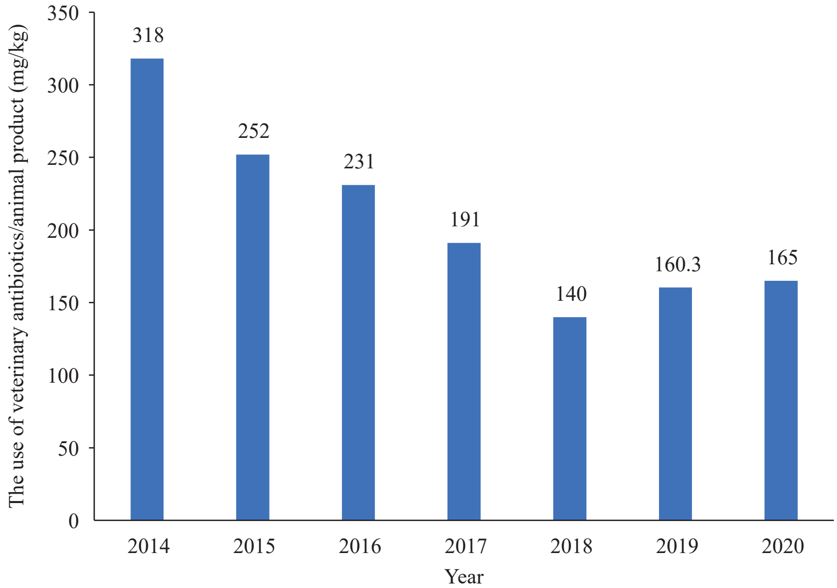
Indicator	Result summary	Future actions
Effectiveness	In 2017, a project was established with a funding of 9.86 million CNY to support teams carrying out a demonstration study on the Application of Antibacterial Drugs in the Reduction of Children's Bacterial Infectious Diseases using Traditional Chinese Medicine. The project aimed to facilitate and conduct exploratory research on innovative Chinese medicine treatments and prescriptions in 2018.	Further methodologies for assessing the efficacy and efficiency of implemented measures must be developed to mitigate potential resource and financial misallocations in subsequent actions. A more comprehensive evaluation mechanism, encompassing objectives, work actions, and system development, is necessary and is also addressed in NAP 2022–2025.
Feedback mechanism		Establishing a feedback mechanism to improve post-action outcomes and strengthen evidence-based governance
Reporting		Currently, only a limited number of departments, such as MOA and NHC, published annual regulatory reports. It is our hope that more departments will release statistical and public reports in a timely manner following the implementation of regulations. Upon establishing interdepartmental collaboration, efforts will be made to generate a comprehensive report aggregating data from diverse sources. This will enable a thorough examination of the national AMR issue and facilitate the identification of macroscopic governance solutions.

Abbreviation: NAP=National Action Plan; MARA=Ministry of Agriculture and Rural Affairs; NHC=National Health Commission; CNY=Chinese Yuan; AMR=antimicrobial resistance.

SUPPLEMENTARY TABLE S4. Future actions generated by framework analysis for National Action Plan in China for Governance area 4: sustainability.

Indicator	Result summary	Future actions
Fund and resource allocation	MOST initiated a project aimed at assisting the pertinent team "Research on the Antibiotics Resistance Mechanism and Transmission Law of Important Foodborne Pathogens", with a funding of 29.8 million CNY.	The allocation of funds and resources could be more transparent and detailed in published documents, clearly indicating the intended purpose or use for significant projects before and after completion. This approach will help ensure the efficient utilization of funds and resources in real-time.
Future expansion of implementation plans		Efforts should be made to identify issues warranting attention and establish annual plans, objectives, and budgets to address these concerns. It is essential to develop robust, locally-driven strategies to determine targeted and sustainable indicators for monitoring antibiotic usage, AMR, and infection prevention and control measures.

Abbreviation: MST=Ministry of Science and Technology; CNY=Chinese Yuan; AMR=antimicrobial resistance.



SUPPLEMENTARY FIGURE S1. Antibiotic usage in animal products in China is getting controlled. Report on the use of veterinary antibiotics in China from MOA published the usage data yearly from 2014 to 2020.
Abbreviation: MOA=Ministry of Agriculture and Rural Affairs.

Policy Notes

Statement on Establishment of A Provisional Health Based Guidance Value for Dietary Exposure to Cadmium in China

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The National Health Commission of the People's Republic of China and the State Administration for Market Regulation have issued the National Food Safety Standard (GB2762-2022), which delineates the maximum limits (ML) of contaminants in food. This standard will be implemented on June 30, 2023. It currently maintains the ML of cadmium in rice (including unhusked rice, husked rice, polished rice) at 0.2 mg/kg, a value first established 40 years ago in GBn238-1984.

Considering the higher ML of 0.4 mg/kg outlined by the Codex Alimentarius Commission (CAC) and the lower limit of 0.15 mg/kg recommended by the European Food Safety Authority's (EFSA) Panel on Contaminants in the Food Chain (CONTAM Panel), a review of the Chinese standard was deemed necessary. The primary objective was to determine whether the current provisional tolerable monthly intake (PTMI) of 25 μg/kg body weight (b.w.) for cadmium, as established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), remains appropriate for China.

To reach our recommendation, we considered additional data on the dietary consumption patterns and corresponding biomarkers of exposure for the Chinese population. We also conducted an updated literature review and examined assessments performed by both JECFA and the EFSA CONTAM Panel. Based on these findings, we recommend maintaining the PTMI of cadmium exposure in China at 25 μg/kg b.w. This recommendation provides a scientific foundation for the newly issued ML of cadmium in rice.

BACKGROUND

Cadmium is classified as a type I carcinogen by the International Agency for Research on Cancer (IARC) (*1*), and exposure has been associated with a range of cancers. Long-term exposure to cadmium primarily exerts toxic effects on the kidneys, but also affects the bones (*2*). Food is the major source of cadmium exposure for the non-smoking general population, contributing up to 90% of the total human cadmium intake (*3*–*4*). Rice is more susceptible to cadmium contamination than other crops (*5*). Furthermore, China is the largest rice-producing and consuming country globally, with rice production accounting for over one-third of the total domestic grain output. Therefore, monitoring cadmium ML in rice is not only a public health measure; it is also part of the nationwide surveillance and control efforts focused on the quality of agricultural products. These practices protect domestic rice traders and contribute to maintaining the safety of food sources in the Chinese mainland.

The ML of cadmium in food was initially established in China in 1984 (GBn238-1984) and has undergone multiple re-evaluations (GB15201-1994, GB2762-2005, GB2762-2012, GB2762-2017), based on the provisional tolerable weekly intake (PTWI) of cadmium set forth by the JECFA (revised to PTMI in 2010). As Table 1 illustrates, the limit values for cadmium in rice range from 0.1 to 0.4 among major rice-trading countries. The ongoing debate regarding the precise allowed level remains unresolved, as evidenced by the current discrepancy between CAC and EFSA guidelines. Given the variability in consumption patterns, cadmium exposure, absorption, and metabolism among diverse populations, a universally accepted standard may not be suitable. As a result, establishing a health-based guidance value (HBGV) for dietary exposure to cadmium in the Chinese mainland is crucial to determine an acceptable cadmium limit in rice for the domestic market.

METHODS

The research to establish the provisional HBGV for cadmium exposure in food was proposed by the National Expert Committee for Food Safety Risk Assessment, entrusted by the National Health

TABLE 1. The ML of cadmium in rice in China and other major rice trading countries or organizations.

Nations/regions/ organizations	Cadmium limits in rice (mg/kg)	
	Unhusked rice/husked rice	Polished rice/rice (flour)
China (including Hong Kong SAR)	0.2	0.2
Codex Alimentarius Commission (CAC)	–*	0.4
The European Union (EU)	–*	0.15
The Republic of Korea	–*	0.2
Singapore	–*	0.2
Japan	0.4	0.4
Russia	–*	0.1
Australia	–*	0.1
New Zealand	–*	0.1
Thailand	–*	0.4
Vietnam	–*	0.4

Abbreviation: ML=maximum limits; SAR=Special Administrative Region.

* Data unavailable due to no limit for unhusked/husked rice or undifferentiated limits for rice in those countries or organizations.

Commission, and conducted by the Secretariat of the Expert Committee for Food Safety Risk Assessment in the China National Center for Food Safety Risk Assessment (CFSA).

The CFSA team analyzed data gathered from a representative sample of the Chinese population residing in cadmium-contaminated regions. The data included food consumption, contamination levels in food, cadmium absorption and metabolism characteristics in humans, and recently updated literature information. Renal dysfunction was considered as the primary adverse health outcome from cadmium exposure, using β2-microglobulin (B2M) as a biomarker for renal tubular effects.

A concentration-effect model was established based on the biomarker of exposure (urinary cadmium concentration) and the biomarker of response (B2M concentration) to predict the benchmark dose (BMD) or threshold of urinary cadmium as a reference point (RP). A one-compartment toxicokinetic (TK) model and a physiologically based toxicokinetic (PBTK) model specifically designed for the Chinese population were employed to correlate urinary cadmium concentration with dietary cadmium intake. Consequently, the provisional HBGV was estimated.

The study included a total of 7,152 participants from 6 provincial-level administrative divisions (PLADs) (Sichuan, Hunan, Guangdong, Jiangxi, Zhejiang, and Shanghai). To investigate the chronic toxic effects of cadmium exposure, this research focused on local residents who had consumed locally grown rice for 30 years or more. As a result, 67.0% of the sample population consisted of individuals aged 50 years and above. Food consumption data were acquired using a 24-hour recall method, during which participants provided a detailed account of their food consumption over the previous day via an interview. Morning midstream urine specimens were collected from the participants. Urinary cadmium and food cadmium levels were measured using inductively coupled plasma mass spectrometry, while urinary B2M concentration was assessed through an automatic biochemical analyzer.

RATIONALE AND EVIDENCE

The methodologies employed in this study closely followed those utilized by the EFSA CONTAM Panel and the JECFA (*3*) for deriving the HBGV for dietary cadmium. Both organizations conducted a step-wise toxicodynamic/toxicokinetic assessment (*3*,*6*–*8*). The two primary components of this analysis included a concentration-effect model, which correlated urinary cadmium concentrations with B2M levels, and a toxicokinetic model, which associated urinary cadmium concentrations with dietary cadmium intake. These models were executed and critically assessed to ensure accuracy and reliability in the findings.

The assessments conducted by EFSA and JECFA were based on a meta-analysis derived from a systematic review of epidemiological studies, with reported summary values of urinary cadmium and B2M concentrations. The present study evaluates both individual data from surveys conducted among Chinese residents and summary data from an updated meta-analysis to derive the final HBGV. In addition to the Hill model adopted by EFSA, the piecewise linear model and generalized additive model were also utilized to predict the RP of urinary cadmium. A one-compartment TK model and a more comprehensive PBTK model, optimized with exposure characteristics of non-smoking residents in Shanghai, were employed to derive the dietary cadmium intake from different RPs of urinary cadmium (*9*). Figure 1 illustrates the technical process used to derive the provisional HBGV.

PRESENTATION

The assessment report underwent review and approval during the second meeting of the Sub-Committee on Chemical Hazard, part of the National

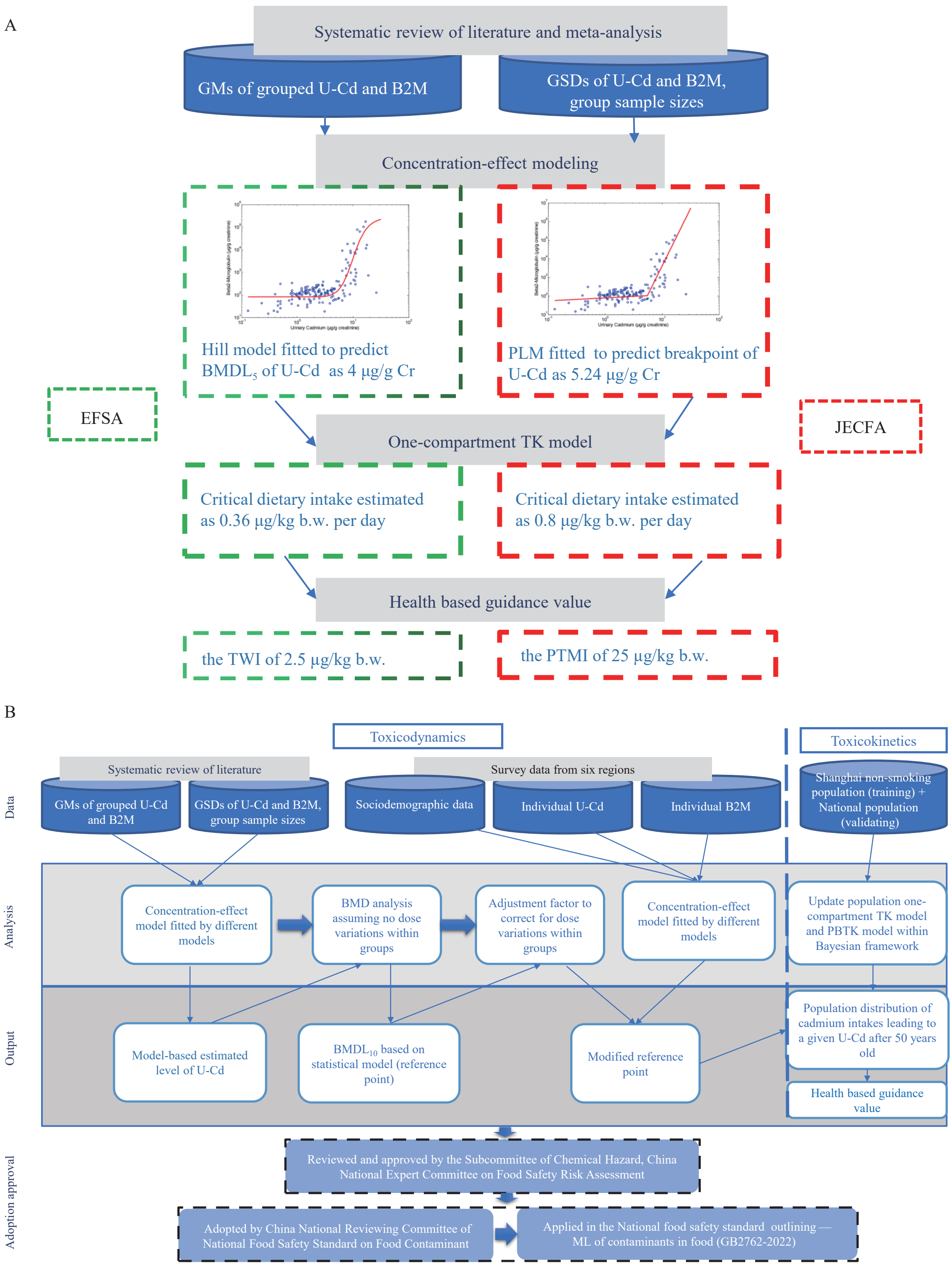

FIGURE 1. The basis and process of establishment of the standard for the ML of cadmium in rice. (A) The process of the HBGV derivation by the EFSA CONTAM Panel and the JECFA. (B) Technical process of the HBGV derivation with procedure of approval and adoption for establishment of the standard for ML in China.

Abbreviation: ML=maximum limits; GM=geometric mean; GSD=geometric standard deviation; U-Cd=urinary cadmium; B2M=β2-microglobulin; $BMDL_5$=benchmark dose lower confidence limit at the benchmark response of 5%; Cr=creatinine; PLM=piece-wise linear model; HBGV=health based guidance value; TWI=tolerable weekly intake; PTMI=provisional tolerable monthly intake; EFSA CONTAM Panel=European Food Safety Authority's Panel on Contaminants in the Food Chain; JECFA=Joint FAO/WHO Expert Committee on Food Additives.

Food Safety Risk Assessment Expert Committee, on May 27, 2021. The results with comparison to EFSA, JECFA, and similar domestic studies (*10*) were listed in Table 2.

The estimated RPs for urinary cadmium in the Chinese population range from 0.71 to 1.86 μg/g creatinine (Cr), with PTMI values of 14.4 to 35.1 μg/kg b.w. based on TK model and 9.0 to 28.5 μg/kg b.w. based on the PBTK model. When considering the $BMDL_{10}$ as an RP with high-dose effects alongside the conservative PBTK model, the calculated PTMI equates to 28.5 μg/kg b.w. In contrast, using the $BMDL_5$ result in conjunction with the TK model yields a calculated PTMI of 16.5 μg/kg b.w. Given the current cadmium exposure status in China, the recommended PTMI for cadmium exposure for the Chinese population is 25 μg/kg b.w., aligning with the recommendation proposed by JECFA.

DISCUSSION

Based on the PTMI value derived from the Chinese population, this study assessed the health risks associated with different cadmium MLs in rice among various regions and age groups in China. The assessment evaluated the level of cadmium exposure in rice and its contribution rate to total dietary exposure using consumption data from the National Food Safety Surveillance (2015–2020), China Nutrition and Health Surveillance (2015–2017), and the Chinese Total Diet Study (2012). Results indicated that the nationwide exposure level to cadmium from rice consumption was generally lower than the PTMI. However, high-consuming populations, children under six years old, and individuals residing in Southern China exhibited higher cadmium exposure levels than the PTMI threshold. Strict implementation of the current cadmium ML of 0.2 mg/kg in rice could reduce dietary exposure to cadmium by 2% to 20% for residents with high dietary cadmium exposure in four southern PLADs in the Chinese mainland. Nevertheless, the potential for a subset of these high consumers to exceed the PTMI remains, indicating that adjusting the ML value from 0.2 mg/kg to 0.4 mg/kg is not recommended.

On July 20, 2021, during the seventh meeting of the Chief Technical Officers of the China National Reviewing Committee of National Food Safety Standards, it was noted that:

1) The total dietary cadmium intake among the Chinese population was found to be near the health guidance value or exceeding the PTMI in specific regions of China. Consequently, there is no justifiable evidence to support increasing the limit in accordance with the CAC recommendation.

2) Currently, no processing methods exist to reduce cadmium levels in rice from 0.4 mg/kg to 0.2 mg/kg or

TABLE 2. The estimated TDI and PTMI by the current study, the EFSA CONTAM Panel, the JECFA and other recent studies.

Phase outcomes for HBVG derivation	$BMDL_5$ (EFSA)	$BMDL_5$ (JECFA)	$BMDL_5$ (current study)	$BMDL_{10}$ (current study)	Thresholds derived by generalized additive model	$BMDL_5$ (Meta-analysis)	$BMDL_{10}$ (Meta-analysis)	$BMDL_{10}$ (Ke's study)
Reference point of urinary cadmium (μg/g Cr)	4 (1)*	5.24 (4.9–5.57)†	2.11 (0.88)*	4.46 (1.86)*	0.85 (0.62–0.98)†	1.70 (0.71)*	1.95 (0.81)*	2.0 (M)§ 1.69 (F)§
TK model								
TDI [μg/(kg b.w.·day)]	0.36	1.2 (0.8–1.8)†	0.55	1.17	0.54 (0.39–0.62)†	0.48	0.52	1.25 (M) 1.06 (F)
PTMI [μg/(kg b.w.·month)]	10.8	25	16.5	35.1	16.2 (11.7–18.6)†	14.4	15.6	37.5 (M) 31.8 (F)
PBTK model								
TDI [μg/(kg b.w.·day)]	–¶	–¶	0.37	0.95	0.36 (0.23–0.41)†	0.30	0.35	1.04 (M) 0.84 (F)
PTMI [μg/(kg b.w.·month)]	–¶	–¶	11.1	28.5	10.8 (6.9–12.3)†	9.0	10.5	31.2 (M) 25.2 (F)

Abbreviations: TDI=tolerable daily intake; PTMI=provisional tolerable monthly intake; EFSA CONTAM Panel=European Food Safety Authority's Panel on Contaminants in the Food Chain; JECFA=Joint FAO/WHO Expert Committee on Food Additives; HBGV=health based guidance value; $BMDL_5$=benchmark dose lower confidence limit at the benchmark response of 5%; $BMDL_{10}$=benchmark dose lower confidence limit at the benchmark response of 10%; Cr=creatinine; TK=toxicokinetic; PBTK=physiologically based toxicokinetic.

* Values in brackets have been adjusted for the uncertainty factor.

§ M: Males; F: Females.

† 95% confidence interval.

¶ Data unavailable.

lower before consumption.

3) The existing literature provides insufficient evidence regarding the risk assessment of cadmium exposure stemming from the consumption of husked rice and rice designated for food processing.

4) Globally, standards for cadmium ML in rice are becoming more stringent, as evidenced by the recommendation from the EFSA.

5) Relaxing the ML standard from 0.2 mg/kg to 0.4 mg/kg without substantial evidence may lead to increased concerns about food safety among consumers.

In conclusion, this study recommends upholding ML of 0.2 mg/kg for cadmium in rice, as established by the GB 2762-2017 guidelines.

Conflicts of interest: No conflicts of interest.

Acknowledgments: Guangdong Provincial CDC, Jiangxi Provincial CDC, Hunan Provincial CDC, Guangxi Provincial CDC, West China School of Public Health, Sichuan University; and also for Shanghai Suburban Adult Cohort and Biobank (SSACB) study.

Funding: Supported by the 13th Five-year National Key Research and Development Program of Food Safety Key Technology Research and Development (2019YFC1605200 and 2017YFC1600500); National Natural Science Foundation (No.81573159); National public welfare industry (health) research project (201302005).

doi: 10.46234/ccdcw2023.094

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Submitted: May 10, 2023; Accepted: May 29, 2023

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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. 5 No. 22 Jun 2, 2023

Responsible Authority

National Health Commission of the People's Republic of China

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