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Consensus and Practice Guideline

Expert consensus on One Health for establishing an enhanced and integrated surveillance system for key infectious diseases



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ABSTRACT

China has been continuously improving its monitoring methods and strategies to address key infectious diseases (KIDs). After the severe acute respiratory syndrome epidemic in 2003, China established a comprehensive reporting system for infectious diseases (IDs) and public health emergencies. The relatively lagging warning thresholds, limited warning information, and outdated warning technology are insufficient to meet the needs of comprehensive monitoring for modern KIDs. Strengthening early monitoring and warning capabilities to enhance the public health system has become a top priority, with increasing demand for early warning thresholds, information, and techniques, thanks to constant innovation and development in molecular biology, bioinformatics, artificial intelligence, and other identification and analysis technologies. A panel of 31 experts has recommended a fourth-generation comprehensive surveillance system targeting KIDs (41 notifiable diseases and emerging IDs). The aim of this surveillance system is to systematically monitor the epidemiology and causal pathogens of KIDs in hosts such as humans, animals, and vectors, along with associated environmental pathogens. By integrating factors influencing epidemic spread and risk assessment, the surveillance system can serve to detect, predict, and provide early warnings for the occurrence, development, variation, and spread of known or novel KIDs. Moreover, we recommend comprehensive ID monitoring based on the fourth-generation surveillance system, along with a data-integrated monitoring and early warning platform and a consortium pathogen detection technology system. This series of considerations is based on systematic and comprehensive monitoring across multiple sectors, dimensions, factors, and pathogens that is supported by data integration and connectivity. This expert consensus will provides an opportunity for collaboration in various fields and relies on interdisciplinary application to enhance comprehensive monitoring, prediction, and early warning capabilities for the next generation of ID surveillance. This expert consensus will serve as a reference for ID prevention and control as well as other related activities.

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Abbreviations: KIDs, key infectious disease; IDs, infectious diseases; SARS, severe acute respiratory syndrome; COVID-19, Coronavirus disease 2019. * Corresponding authors.

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1. Introduction

Since the 1950s, dozens of newly emerging and major infectious diseases (IDs) have been discovered worldwide [1], and the threat of IDs to humans has been increasing, manifested by notorious and fatal viral infections caused by influenza virus, severe acute respiratory syndrome (SARS) coronavirus, and the novel coronavirus SARS-CoV-2 [2]. As reported in a review by Huang et al. [3], as early as the mid-20th century, the United States first systematically put forward the principles of disease surveillance and emphasized its importance in the practice of disease prevention and control. With promotion by the World Health Organization (WHO), the concept of infectious disease monitoring as the "cornerstone of warning about and controlling epidemics" has become widely accepted [4].

Since the establishment of the People's Republic, China has been continuously improving its ID monitoring and reporting system. Following the SARS outbreaks in 2003, two new systems have been established nationwide. The first is the network direct reporting system for IDs and sudden public health events [5]. The second system is the automatic early warning information system for IDs. These systems have fulfilled their intended purpose and played an critical role in safeguarding the population and maintaining social stability [6,7]. However, with the evolution of society and increasing public demand for better health, the established warning checkpoints (lagging behind), warning information relay (monotonous), and warning technologies (not sufficiently advanced) are no longer suitable for monitoring, analyzing, judging, and comprehensive warning with regard to key infectious diseases (KIDs) [8]. To ensure strong technical support to provide quality health care services and sound biosafety both domestically and throughout countries participating in China's Belt and Road Initiative, up-to-date monitoring and early warning concepts and pathogen detection technologies are urgently needed so that China's overall ID monitoring system can be optimized [9,10].

2. Epidemic situation of key infectious diseases (KIDs)

IDs are diseases caused by various pathogens that can be transmitted among people or among animals or that can spread between people and animals (i.e., zoonotic IDs) [11]. IDs that receive the most attention differ among countries and regions owing to diverse geographical locations, natural conditions, living habits, cultural customs, and other factors. In this expert consensus, we define major IDs as 41 legally notifiable IDs that pose serious threats to human health in China, as well as newly emerging IDs.

2.1. Overview of modern infectious diseases (IDs)

Some early Chinese characters among the Yin Ruins oracle bones have different definitions of IDs such as "jie" "nüe" and "gu" [11]. Besides some well-known ID events (Roman smallpox epidemic in 164 AD, the bubonic plague in medieval Europe, and the global cholera epidemic in the early 19th and late 20th centuries), other major IDs (all viral) that have seriously affected human health in the last century include: 1) influenza virus infections, including the 1918 "Spanish flu" (global excess deaths exceeded 40 million), the 1957 H2N2 Asian flu (100-200 million deaths), and the 1968 H3N2 Hong Kong flu and the 2009 H1N1 flu (50–100 million deaths) [12]; 2) coronavirus infections, including SARS in 2003; Middle East respiratory syndrome (MERS) in 2012; and the SARS-CoV-2 (Coronavirus disease 2019, COVID-19) pandemic beginning in 2019, with over 760 million infections and 6.9 million deaths to date [13]; 3) vector-borne diseases including dengue fever, chikungunya, Zika virus disease, and West Nile fever, as well as diseases caused by novel Bunyaviridae; 4) Ebola hemorrhagic fever, Marburg hemorrhagic fever. In 2019 (excluding the impact of COVID-19), 60% of the global disease burden was caused by IDs. Among people aged 0-24 years, it is estimated that 30 million years of healthy life will be lost owing to disability each year, corresponding to a total disease burden of 288.4 million disability-adjusted life-years (57.3% of the total ID burden across all ages) [14].

Among the major IDs, the risk of transmission and outbreaks of new, unknown pathogens is increasing. An emerging ID refers to a newly or re-emerging disease caused by a novel pathogen, an ID caused by a new drugresistant pathogen, or an existing ID associated with a communicable pathogen that is discovered owing to the development of diagnostic techniques [15]. Studies have shown that although humans have recognized more than 2000 viral and bacterial IDs, 99.8% of pathogens remain to be identified. It is estimated that there are 631,000 to 827,000 zoonotic pathogens that are not yet known [16,17]. In the past half century, some new IDs discovered globally include Legionnaires' disease caused by Legionella pneumophila, a new type of enteritis caused by Campylobacter jejuni, a novel hemorrhagic colitis caused by Escherichia coli O157:H7, and several respiratory syndromes caused by novel coronaviruses (SARS, MERS, and SARS-CoV-2) [18]. Considering changes in the environment and human lifestyles and behavior, the ability of pathogens to transmit across hosts and across regions has increased [19,20]; therefore, the potential risk of new pathogens spreading among humans has increased accordingly. Increasingly more unknown pathogens carried by animals (e.g., bats) will likely be discovered in the future, and serious and acute outbreaks of IDs similar to SARS, MERS, and COVID-19 are likely to continue to occur [21,22].

2.2. Challenges in the prevention and control of IDs

ID pathogens, especially respiratory pathogens, have a wide range and rapid transmission and are therefore prone to causing national, transnational, intercontinental, and even global epidemics (i.e., pandemics). These pathogens not only severely threaten the health and lives of people worldwide but also cause problems such as exhausting human and material (especially medical) resources, exerting humanitarian harm, seriously hindering economic and social development, and even destabilizing society. ID prevention and control requires continuous vigilance against known major IDs while actively seeking to identify new ID pathogens and avoid or limit their potential spread. Despite considerable progress in biological diagnosis, vaccine development, epidemic surveillance, and community prevention and control, modern societies still face enormous challenges regarding new IDs, with limitations in terms of early detection, monitoring and early warning, diagnosis and treatment, and vaccine and drug development [23]. The main reasons for these limitations are outlined below.

First, ID pathogens are widely distributed and diverse with respect to their sources and types; therefore, these can be unknown pathogens or new subtypes and variants of known pathogens with cryptic pathogenic characteristics and the possibility of continuous evolution and being highly epidemic. Second, factors that affect the spread of IDs are hugely complex and variable on a case-bycase basis. The spread of IDs is influenced by natural factors such as geography and climate, as well as social factors such as population mobility, lifestyle, socioeconomic level, religion, and culture. The rapid development of transportation and high mobility of people in modern society have reduced the impact of geographical barriers on the spread of IDs, making it extremely difficult to achieve ideal results with a single control measure. Third, the likelihood of human exposure to previously inaccessible pathogens (existing in places such as glaciers, polar regions, and deep oceans) or new variants of previously prevalent pathogens has increased, also owing to climate change, urbanization, industrialization and pollution, and antibiotic overuse. Fourth, the possibility of non-human host pathogens spilling over to humans has increased. Studies have shown that there have been 16 newly discovered or imported pathogens in China over the past 20 years, including SARS-CoV (2003), Streptococcus suis (2005), fever with thrombocytopenia syndrome virus (2006), enterovirus 71 (2008), influenza A (H1N1) virus (2009), chikungunya virus (2010), wild strains of poliovirus (2011), Try panosoma (2014), MERS coronavirus (2015), highly pathogenic avian influenza virus A (H5N1 in 2005, H7N9 and H10N8 in 2013), moderately pathogenic avian influenza virus A (H5N6 in 2014, H7N4 in 2018, H10N3 in 2021), Zika virus, yellow fever virus (2016), and SARS-CoV-2 (2019) [15]. Among them,

12 viruses were transmitted to humans from non-human hosts, accounting for up to 75%. Fifth, the clinical characteristics of population infection are hugely complex and diverse. Owing to factors such as individual susceptibility and varying pathogenicity, there are often differences in the infection spectrum of different pathogens. For instance, SARS is mainly caused by dominant infections whereas multiple studies during the early stages of the COVID-19 pandemic show a relatively high proportion of asymptomatic infections [24]. IDs with a high proportion of latent infections have hidden transmission and are therefore very difficult to control in a timely manner.

3. Infectious disease (ID) surveillance

3.1. History of ID surveillance

ID surveillance refers to the epidemiological, serological, pathological, and clinical symptomatic investigations as well as investigation of other relevant influencing factors, conducted in specific environments and populations with the aim to predict the occurrence, development, and prevalence of certain IDs. Surveillance methods are divided into two types: active monitoring (such as sentinel surveillance and special surveys) and passive monitoring (such as case reporting and data collection). According to its historical development, ID surveillance can also be divided sequentially into first, second, and third-generation surveillance.

First-generation surveillance was based on epidemiological surveillance at the epidemic site. Limited by the available technology and equipment to detect pathogens, first-generation surveillance only focused on reporting and research of infected individuals, with a focus on the prevention and control of IDs at the epidemic site. Secondgeneration surveillance was based on biological identification and analysis of pathogens. With the development of molecular biology, the ID pathogenic biology monitoring network gradually expanded and improved. In 1996, the WHO established a network of 60 countries and 140 technical partners for ID laboratory surveillance. During the period of 2000-2005, this network launched more than 70 global ID outbreak emergency response projects, providing strong technical support for global epidemic surveillance at that time. Third-generation surveillance added extra factors [25], such as health-related behaviors that affect the spread of IDs and high-risk behaviors in special populations (e.g., multiple sexual partners and intravenous drug use). The results of monitoring and analysis of factors influencing high-risk behaviors have gradually become the basis for developing intervention measures for special populations. This monitoring mode has shifted the frontline of surveillance, highlighting the role of epidemic surveillance and risk assessment.

Since humans, animals, vectors, and pathogens all exist within the Earth's ecosystem and interact with each other,

humans face the challenge of IDs (described in Chapter 2.2). In addition, with the development and application of new technologies such as bioinformatics, big data, artificial intelligence (AI), and mathematical models, a new generation of monitoring is conceivable, inevitable, and necessary.

3.2. The importance of ID surveillance

Over years of continuous practice and data accumulation, ID surveillance has gradually become the core aspect of public health development in nearly every country. Its importance is manifested in the following aspects. First, the aim of researching IDs is to understand their natural history, providing a basis for disease diagnosis and treatment. Second, in studying public health emergencies, the prevalence of diseases in the population is analyzed to identify epidemic trends and provide a scientific basis for formulating prevention and control measures. Third, comprehensively analyzing the sources of pathogens and factors that contribute to the spread of IDs is based on multifactorial and multidimensional surveillance data to ensure timely warning of a potential epidemic and national public health security. In terms of approaches, in addition to monitoring traditional ID-related factors (infectious pathogens, vector biology, and animal hosts), ID surveillance has been extended but not limited to studying syndromes of clinical infection, investigating environment related to vector animals, and legally and appropriately collecting data related to the Internet, telecommunications, and spatiotemporal human flows [26,27].

3.3. Major problems in ID surveillance

Since the SARS outbreak in 2003, China's health emergency preparedness has been consistently enhanced by continuously improving the health emergency legal framework and optimizing systems for contingency plans and emergency response, as well as monitoring and early warning assessment. However, numerous formidable challenges remain in terms of early monitoring and warning of major IDs in general, and dealing with unknown IDs in particular.

3.3.1. Monitoring of diseases is overly focused on a single aspect

Different IDs have their own monitoring plans, aimed at detecting only a single pathogen and its associated impact factors, which leads to inefficient resource use.

3.3.2. Monitoring content is fragmented

Existing case reporting and sentinel surveillance are suitable for IDs caused by known pathogens (such as H1N1, SARS-CoV-2, H7N9, H5N1, and EV71). Novel IDs possess characteristics of unpredictability and being unexpected and hidden, with no known existing detection methods. During the early stages of transmission, IDs usually appear sporadically and locally in a specific human population. Therefore, it is both feasible and necessary to analyze and identify potential risk sources through monitoring of symptoms or syndromes in the early detection of weak signals.

3.3.3. Monitoring scope is one-dimensional

Currently, there is no systematic and overall coordination or joint monitoring of humans, animals, and vectors by multiple organizations. For example, health and epidemic prevention institutions only monitor outpatients with infection-related symptoms in medical institutions. Border officials only conduct health declarations and symptom-based sampling and monitoring of inbound individuals. Additionally, animal epidemic prevention authorities only monitor a small number of animals (livestock, poultry and birds) at any given time.

3.3.4. Monitoring technology is disconnected

Commonly used pathogen detection methods mostly comprise single-system detection of a single pathogen. In recent years, multiplex PCR assays have been developed that can detect more than 20 pathogens simultaneously. However, the instruments and reagents needed for these tests are expensive and have low throughput, making them unsuitable for large-scale monitoring. With continuous innovation in next-generation sequencing (NGS) technology, bioinformatics analysis technology for pathogen identification has developed rapidly. Targeted NGS (tNGS) can simultaneously detect more than 200 pathogens in one session and has the advantages of good specificity, sensitivity, anti-interference, high throughput, and excellent cost effectiveness, making it suitable for large-scale multi-pathogen screening and monitoring. Additionally, machine learning and AI technologies have become highly valuable in the field of data integration and mining. Now, the urgent question for all contemporary public health personnel to consider, discuss, and act upon is how to apply these modern analytical techniques safely and effectively in ID monitoring, early warning, assessment, disposal, diagnosis, follow-up, and other related work.

3.3.5. Monitoring data are separated

Owing to differences in collection, processing, and storage formats, data from different monitoring agencies/organizations or systems usually lead to fragmentation, which will exacerbate problems of data management and sharing, thereby limiting data exchange and comprehensive analysis.

4. Pathogen detection for IDs

Pathogen detection methods have witnessed unprecedented recent development. Pathogen detection has evolved from traditional morphological, molecular biological, and immunological approaches to the application of advanced techniques such as amplicon sequencing and metagenomic sequencing [28]. However, for highly variable pathogens, existing pathogen detection methods struggle to precisely identify all subtypes and variants [29]. The sensitivity and specificity of individual diagnostic assays continue to challenge professionals in the field. Additionally, resource constraints may pose challenges to conducting diagnostic experiments that require complex instrumentation, particularly in resource-limited regions.

4.1. Traditional detection methods

4.1.1. Morphological examination

Morphological examination is the basis for the classification and identification of bacteria and other microorganisms, providing a reference for subsequent related biochemical reactions and serological identification. Morphological examination can be used to quickly detect the presence of bacteria and the approximate bacterial quantity in a specimen, as well as preliminarily determine its genus and species based on the morphology, structure, and staining characteristics of bacteria, which has certain reference value for timely selection of the appropriate antibiotics to treat disease. The advantage of morphological detection is its simplicity and speed via the direct observation of microorganisms with the help of instruments. However, the disadvantages of this approach include the strong influence of the examiner's level of experience, making this method prone to incorrect assessment (some pathogens are atypical and therefore difficult to distinguish) and unsuitable for the clinical examination of viruses. Morphological examination also has low sensitivity, requiring a certain concentration of bacteria in the sample.

4.1.2. Cultivation technology

Cultivation methods are widely used in the isolation of bacterial and viral pathogens. Cultivation refers to the isolation of pathogens in clinical specimens or other samples such that colonies are formed by the propagation of a single bacterium on an artificial culture medium, or viral cultivation/amplification in feeding cells (mainly animal inoculation, chicken embryo inoculation, and cell culture). The advantages of cultivation technology are that this method can be used to selectively obtain pure cultures of a pathogen, which is a prerequisite for subsequent biochemical identification and whole-genome sequencing. However, detection methods that depend on cultivation are cumbersome, time-consuming, and require several days or more to obtain results, which limits their application in clinical emergencies and sudden outbreaks. Moreover, some pathogens are difficult to cultivate or cannot be cultivated at present.

4.2. Molecular biological detection

Molecular biology technology is often used for the detection of nucleic acids in pathogens. The advantages of nucleic acid detection techniques include: simplicity and speed (results obtained in a few hours); high sensitivity (detects a small quantity of nucleic acids); good specificity (accurately distinguishes different types of pathogen); and unlimited by growth conditions (in contrast to bacterial and viral cultivation techniques). The disadvantages include: high requirements for the assay environment, personnel, instruments, and reagents, and a high cost. Moreover, molecular biology techniques can only be used to determine the presence or absence but not the viability of any pathogens in a sample; for example, the intermittent and unstable release of low-level SARS-CoV-2 RNA in recovering/recovered patients may lead to recurrent positive results rather than indicating re-infection. These techniques may also cause false positives owing to the contamination of PCR products when handling samples in large quantities and/or with high concentrations of nucleic acids.

4.3. Immunological detection

Immunological detection methods are used to diagnose disease by analyzing the response of the human immune system to specific pathogens. This approach has been widely used in clinical diagnosis, drug development, and vaccine research. Capitalizing on the principle of antigen-antibody binding, the advantages of immunological detection methods include high specificity and stability, short detection time and simple operation, and quantification at the microgram level with high sensitivity using enzyme-linked immunosorbent assay and radioimmunoassay methods. Owing to occasional antigenantibody cross-reactions, the disadvantages of immunological detection methods include: false positives, such as detecting antibodies that may cross-agglutinate with nontarget pathogen antigens; and a relatively long detection window period, with poor timeliness in the early detection of pathogens.

5. The concept of One Health in the prevention and control of IDs

5.1. The One Health concept

The concept of One Health (also known as integrated health or holistic health) was first proposed in 2004 at the "One World, One Health" symposium organized by the Wildlife Conservation Society. The American Veterinary Medical Association established the One Health Initiative task force and passed the One Health resolution in 2007, defining it as "a new strategy based on human, animal, and environmental health care, discussing multidisciplinary and cross-regional collaboration and communication, promoting the health of humans and animals, and maintaining and improving the ecological environment." One Health is a multidisciplinary and crossdisciplinary concept that aims to reduce human and animal health risks as a whole, with comprehensive environmental, ecological, social, and economic factors in mind. The essential goal is to integrate human and animal disease surveillance and early pathogen detection; identify new ID pathogens in a timely manner as well as their occurrence, development, evolution, and transmission patterns; and promote and maintain the overall common health of humans, animals, and the environment [30].

5.2. Regional public health governance

The COVID-19 pandemic and the suboptimal response to it in countries worldwide serve as a stark reminder that the health of the environment, animals, and humans is one inseparable entity, and that no single department, discipline, or region can solve the complex public health issues of emerging IDs. Thus, holistic and comprehensive public health governance is needed, and different health issues require different departmental cooperation models, dialogue platforms, and information-sharing networks to effectively address various challenges in the real world.

In 2022, the Food/Agriculture Organization and the Environment Program of the United Nations, the WHO, and the World Organization for Animal Health together launched a 5-year One Health Joint Action Plan (2022–2026) [31]. The action plan will use a comprehensive and systematic strategy to identify health interconnections among humans, animals, plants, and the environment, coinciding with the new era of a whole-society public health governance policy system. The risks addressed by this action plan include but are not limited to outbreaks of zoonotic diseases, tropical and vector-borne diseases, food safety, and antibiotic resistance as well as animal, plant, and ecosystem health.

5.3. Prevention and control of IDs from a population perspective

Application of the One Health concept is of utmost importance to plan, design, and develop ID monitoring and warning, prevention and control strategies, tactics, measures, and action plans, as well as to establish a prevention and control system that is well organized, effectively guaranteed, orderly, efficient, coordinated, integrated, and responsive. For known KIDs with clear characteristics such as epidemic transmission patterns, detection findings, and clinical diagnosis and treatment, the priority is primary prevention, reinforced by secondary prevention. Considering the current epidemics of KIDs and their influencing factors, it is urgent to consider the issue of population prevention from five dimensions. The first is to shift the time window forward, i.e., start the monitoring and prevention and control layout when a certain ID occurs in another region, before it reaches the local area. Second, geographical checkpoints should be moved forward by establishing specific ID monitoring points in key countries and regions, either independently or cooperatively, to better predict and analyze the prevalence and import risks of new IDs. Third, the monitoring content must be updated. To detect weak signals of new IDs in the early stage, a system is needed to continuously monitor and report symptoms, syndromes, and indicators of a new pathogen via biological laboratories, further supplemented by monitoring certain major epidemic source animals and vectors. Fourth, the checkpoints for target (pathogen) monitoring, prevention, and control should be moved to the frontlines of animal and vector control, and relevant departments should be combined to carry out animal disease prevention work. Fifth, state-of-theart detection methods and technologies should be used. It is a prerequisite to flexibly use NGS (e.g., tNGS) and bioinformatics technologies to identify pathogens, especially new pathogens. Additionally, safe, efficient, and long-lasting vaccine development and vaccination are the best choices for combating IDs. Rapid and effective development of technologies targeting emerging IDs is not only a crucial challenge but also a key pathway in the battle against IDs.

5.4. Prevention and control of pathogen/ID transmission from animals

Most new IDs originate from wildlife species, which carry a wide range of pathogens (parasites, bacteria, viruses, fungi, rickettsia). Among them, viruses are most common, especially influenza viruses, dengue virus, Ebola virus, SARS-CoV-2, and other RNA viruses. RNA viruses have a simple structure and rapid mutation, making them highly likely to spread to humans via intermediate hosts [32]. Wild animals can serve as reservoirs for livestock diseases, and activities involving livestock (domestication, breeding, migration, trade, transport) create opportunities for cross-species transmission of pathogens, increasing the risk of new diseases occurring and spreading. The emergence and application of new technologies in aqua-agriculture (animal husbandry and fisheries), large-scale aquaculture, and invasion by foreign species (e.g., Aedes albopictus) caused by climate change can all lead to the reconstruction of food webs. The profound impact on the cross-species transmission of pathogens has changed the probability of zoonotic diseases occurring. For disease prevention in humans and animals, greater attention must be directed toward animal health and resource investment; establishing scientifically based animal protection, breeding, quarantine management, and disease and pathogen monitoring systems; increasing the development and use of therapeutic drugs and vaccines for key animal IDs (especially zoonotic diseases); early detection of new, recurrent, or foreign zoonotic pathogens; and controlling the spread of animal diseases. Supporting protection and maintenance of the health of animal ecosystems is also of great practical importance for protecting human health.

5.5. Prevention and control of pathogen transmission from vectors

Pathogens can spread to humans through vectors, causing disease outbreaks and epidemics. The population dynamics caused by interspecies struggles between animals and vectors can affect the number, evolutionary speed, diversity, and pathogenicity of disease vectors, thereby affecting the risk of disease transmission. Vector monitoring, control, and ecological regulation can help control the transmission of certain IDs among humans, as exemplified by successful cases in the prevention and control of Japanese encephalitis virus and Italian West Nile virus, achieved through monitoring and comprehensive management of vector organisms such as mosquitoes, based on the concept of One Health. While monitoring the pathogens that cause KID, it is also necessary to establish a sound monitoring and warning system for intermediate hosts, such as vector organisms [33], to detect their pathogen-carrying status and ecological changes in a timely manner, analyze and predict the transmission mode of pathogens, and implement control measures accordingly. Additionally, the management of vector habitats must be improved and vector reproduction and pathogen transmission reduced. Reasonably safe and effective chemical agents should be used to prevent and control vector organisms, and proper attention should be given to protecting the environment, the ecological balance of vector organisms, and human health during such use.

6. Recommendations for building a comprehensive monitoring system for KIDs

To improve China's comprehensive ID monitoring system, it is advisable to adopt a One Health approach, which involves systematic and comprehensive monitoring of various pathogens across multiple dimensions. This endeavor should comprise collaborative efforts from multiple departments, supported by data sharing and interconnectivity. By fostering cooperation in multiple fields and interdisciplinary applications, these measures will substantially enhance the overall predictive and early warning capabilities of China's ID monitoring system. The following recommendations are proposed to improve the monitoring system in the new era.

6.1. The concept of fourth-generation surveillance

Fourth-generation surveillance refers to a comprehensive monitoring system based on the One Health concept, with objectives that include early discovery, prediction, and warning of the occurrence, development, variation, and prevalence of KIDs by systematically monitoring pathogens in major epidemic reservoir hosts including humans, animals (such as livestock, poultry, and birds), and vector organisms, as well as relevant environmental factors (such as meteorology, population flow, behavioral factors, and ecological changes in animals and vector organisms), and risk assessment elements (such as symptoms/syndromes, population migration indexes, Internet buzzword searches, and public opinion analyses). This system can comprehensively analyze various types of data and information such as distributions, transmission modes, population flows, and public opinion with respect to pathogens, to more accurately understand ID transmission trends and risks and provide a scientific basis for formulating effective prevention and control measures for IDs [34].

6.2. Re-establishment of a comprehensive monitoring and management system for IDs

6.2.1. Organizational infrastructure for comprehensive ID monitoring

The government designates a lead department to form a comprehensive monitoring working group for IDs. All related departments (such as health, border control, market supervision, port authority, urban management, ecological environment, agriculture, industry, information technology, and government statistics) collaborate and cooperate in accordance with their respective expertise, responsibilities, and management functions to carry out comprehensive monitoring of epidemic source hosts, relevant environmental epidemiology, and KID pathogens, as well as the collection, reporting, analysis, and evaluation of relevant risk factors and information. Based on the description above, the specific recommended management framework can be found in Fig. 1.

6.2.2. Guidelines and implementation strategies for comprehensive monitoring of IDs

We recommend establishing standardized and unified workflows before undertaking specific tasks. This involves defining the concepts and monitoring-related terms; determining the scope of work; specifying the work content and processes; analyzing and assessing key points in prediction, early warning, and response measures; and clarifying the responsibilities of relevant departments. Additionally, the lead department should establish a system for coordinating meetings to facilitate collaboration [35].

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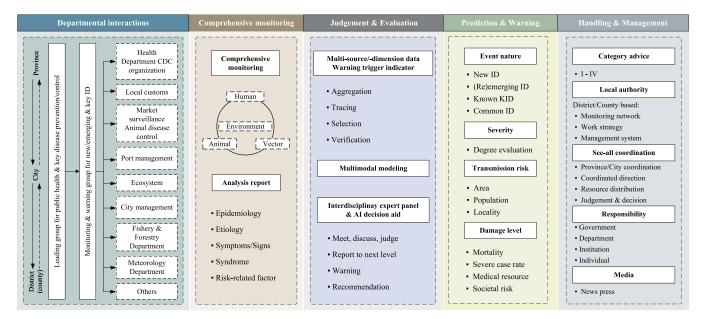


Fig. 1. Integrated surveillance organization and management system for key infectious diseases.

6.2.3. Five working mechanisms for comprehensive surveillance of IDs

First among the working mechanisms in ID surveillance is sample collection and submission. The monitoring samples are collected and transported by a responsible monitoring unit to the designated testing institution for identification and characterization. Samples from patients with severe pneumonia or six major syndromes with unknown causes in various levels and types of medical institutions are collected according to the applicable regulations and sent to regional public health testing laboratories or reference laboratories for comprehensive pathogen analysis. Samples of newly discovered pathogens detected in various levels of biological testing laboratories (including those in third-party testing institutions, sequencing companies, research institutions, and biopharmaceutical enterprises) are sent to the reference laboratory for review within 12 h after detection.

The second working mechanism involves information reporting and sharing. This is done by establishing a unified public health information platform to achieve satisfactory connection, intercommunication, integration, sharing, and analysis of information regarding diagnosis and treatment in medical and health institutions, microbiological laboratory testing, meteorology, population migration/flow, and capture of early weak signals of a KID outbreak as well as monitoring data collected for animal disease, vector, and related risk factors, border entry/exit, and biological products.

The third mechanism comprises monitoring, evaluation, and prediction/warning. The use of multidimensional, multi-source, and big data monitoring information can lead to a substantial increase in data pollution and disruption. To effectively identify, uncover, and define useful weak signals from massive data and prevent excessive unnecessary warnings and responses that waste public resources, the working group needs to: 1) establish an integrated and unified monitoring system to aggregate, screen, confirm, and process the collected information; 2) classify and establish a scientifically structured and standardized warning trigger indicator set based on the characteristics of disease transmission routes; 3) make full use of machine deep learning and AI technology to establish multimodal analysis and prediction warning models; 4) establish an expert panel of a multi-professional, interdisciplinary, and interdepartmental nature, establish a consultation and judgment mechanism, report to responsible/administrative departments and personnel in charge or on call, and propose crisis warnings.

The fourth, decision-making and response mechanisms, should be analyzed. After confirming the potential or definite occurrence of an ID-related public health event, response and management are graded based on the severity of the event or crisis. The departments and personnel responsible for specific tasks, such as command decision-making, resource channeling, medical treatment assignment, on-site handling, logistic support, and investigation and evaluation, are clearly defined and the corresponding working mechanisms established.

The fifth working mechanism involves information release and risk management. To improve the openness and transparency of crisis response work and ensure the public's right to know about and participate in such an event, a mechanism for information dissemination and a risk management strategy for KIDs and other public health events are established. At the first moment of a crisis (upon verification, validation and confirmation), government departments disseminate any health crises-related information to the public through various authorized means such as the media, government announcements, and information networks to stop the spread of rumors and disinformation/misinformation.

6.3. Improvement and optimization of the surveillance system to detect and monitor pathogens

According to the concept of fourth-generation ID monitoring, comprehensive monitoring is carried out for the main epidemic source hosts and environments related to humans and animals. Monitoring is based on the established monitoring networks and aims for improvement by focusing on the following aspects. 1) In terms of monitoring content, expansion occurs from monitoring a single ID pathogen and case reports to monitoring via big data of symptoms/syndromes, as well as monitoring of the climate, environment, behaviors, Internet buzzwords, and spatiotemporal human flows that affect the occurrence and development of IDs [36]. 2) The objects of monitoring are expanded from population monitoring only to monitoring of non-human epidemic hosts and related environments. In terms of pathogens, monitoring is expanded from single and fragmented pathogen monitoring to multiple-pathogen, integrated monitoring using various systems, as well as step-by-step comprehensive monitoring for major known and unknown pathogens. 3) Monitoring departments are shifted from mainly health/disease control institutions to joint monitoring by multiple departments, including customs and border control, agricultural and market supervision departments (such as animal disease prevention and control), and agencies, institutions or departments in charge of urban management, the ecological environment, meteorology, and government statistics, in accordance with their respective specialties, responsibilities, and coordination (Fig. 2).

6.4. Building a digital intelligent monitoring and early warning platform for data integration and sharing

A monitoring network is established at three levels: remote risk situational awareness, near-end input risk prevention and control, and local occurrence risk monitoring and transmission risk blocking. Database fundamentals (including data of hospital information systems and laboratory information systems, biological laboratory testing, population and migration, climate and environmental monitoring, border entry/exit, and third-party laboratories) are needed for integration and construction of a regional public health information platform for disease monitoring. Also critical are the standardization and normalization of pathogen monitoring and epidemiological monitoring for the main human-animal-vector diseases, as well as the implementation of systematic monitoring of key populations regarding symptom/syndrome or those of a routine or sentinel nature. Finally, monitoring data of related risk factors (the environment, breeding, processing, sales, and storage of wildlife, livestock, poultry, birds, freshwater or marine aquatic products, as well as climate change, environmental changes, and human behavior patterns) are interconnected and shared for mutual benefit and convenience. The establishment of an ID prediction and early warning analysis model and an AIassisted analysis and decision-making system relies on the data platform to cluster, filter, process, analyze, study, predict, and produce early warnings based on the monitoring data (Fig. 2).

6.5. Establishment of a consortium for the pathogen detection technology system

6.5.1. Establishment of a hierarchical and functionally complementary network of pathogen testing laboratories

Pathogen testing laboratories, either those for reference and regional public health or institutional laboratories (including those in clinics/hospitals and for disease control, animal disease prevention and control, customs, third-party testing, biotechnology research and development, and production) are established according to their level, region, and responsibilities, and are supported with appropriate testing equipment, facilities, human resources, and technical capabilities.

6.5.2. Establishment of a standardized quality control system within pathogen detection technology

Guidelines, procedural documents, and quality control standards are established for KID laboratory testing according to the requirements of laboratory testing quality management, with the aim to achieve homogeneous regional testing quality and reciprocal acceptance of the generated results. The biosafety regulatory department sets up a management system to standardize responsibilities with respect to pathogen detection, discovery, reporting, and sample disposal for various levels and types of biological testing laboratory and includes them in monitoring reports of newly discovered pathogens, biosafety, and laboratory testing supervision in the respective regions.

6.5.3. Establishment of a systematic and testing technology platform consortium

Laboratories at all levels must set up appropriate testing technology platforms to meet their responsibilities and practical needs. These platforms include bioinformatic/analytic technology-based techniques, ranging from conventional culturomics, molecular biology, and pathogen etiology to advanced sequencing technologies (e.g., tNGS, and metagenomic next-generation sequencing (mNGS)); AI technology between local data analysis and processing to cloud computing; pathogen identiffication technology from basic single-pathogen identifi-

			Note:	Lea	iding	0	Fechniq	ue suppo	rt 🖌	_	ordinat	ion —	- Less	connec	ted				
			Hosts of outbreak source									Environment					Others		
Monitoring Subjects		Outpatient Fever/infection clinic outpatient pediatric clinic Patients belong to 6	syndromes Symptomatic people after entry	People in endemic area	People with a risky job	Wild animal	livestock	Non-hun	han host	Pet	Vector	Wild animal reservior	Migrating bird reservior	Bird market	poultry breeding and processing plants	Sewage	Meteorology	Hot word search index	Population migration
Montoring departments	Health Local custom Agri-market Ecoenvironment Meteorology Industry and IT	✓ ✓ 	● ✓ – – –			▲ 		▲ ✓ –			✓✓✓✓✓✓		▲ 	▲ 		• - - - -			
methods	Case report Symptom Syndrome Sentinel Special survey	<pre>> > ></pre>	> > > I >	>>>>>	>>>>>	> >	> >	> >		> >	> >	> >	> >	> >	> >	> >	> >	> >	
Sentinel onitoring	Inter-epidemic Epidemic							/half yea						•					
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Monitorin	 Cloud calculation center Public health data center Resource bank Managing system 																		
Trigger signal		Laborat CDC Signals: Case rep Trend c Related Inter-sp New pa	Analysis port: cle changes: l cases: s becies tra	Medic s of info ear epide sympto already nsmissio	ormation emiolog oms/syno existing on: nev	utions collecter ical surve drome of in anima v pathoge	d from ey/anal some l als but j en from	ysis repo kind/typ previous non-hu	ealth pl ort of no e of info ly non- man ou	atforms ewly en ectious pathoge tbreak l	People , institu nerging disease enic to l nost & o	/key info of unkn human a detected	ort, ind ectious of own can nd now from cl	People of the second se	uman cas				
Trigger	Station/dock	Medical institution		School	l	Commu health ce		Farmers	s market	(Air) por	t	Wild an reserv			gration rder		ry & bird b rocessing p	
		Health department	District City Province Nation	Local	CDC		Event in repor			Signal nalysis			gate/ve fy	Si r	ample verifi esample & u	cation/ ipload		On-site anageme	nt

Fig. 2. Digital and smart alerting platform in the integrated surveillance system for key infectious diseases.

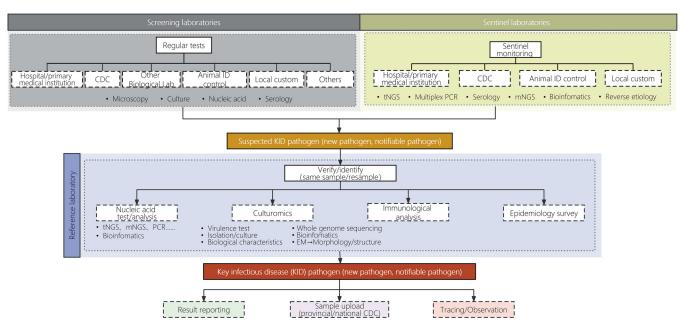


Fig. 3. Consortium of pathogen detection technologies based on the fourth-generation integrated surveillance system.

cation to fast, advanced, high-throughput, and simultaneous identification of multiple pathogens; surveillance based on pathogen isolation from on-site and laboratory monitoring to population monitoring data and genome data; and from rapid detection of known IDs to identification of unknown new ID pathogens. The advantages of tNGS technology include high throughput, speed, convenience, and cost-effectiveness, and its importance and role in monitoring KID pathogens and assisting with clinical diagnosis are increasingly apparent. For sentinel monitoring of known KID pathogens, high-throughput, rapid, and simultaneous multi-agent (>200 pathogens) tNGS detection technology is a plus. For unknown pathogens, analytic techniques such as mNGS, bioinformatics, culturomics, serology, and electron microscopy are needed (Fig. 3).

6.6. Joint innovation in ID surveillance and biomedical industry development

ID monitoring involves multiple and varying procedures, such as collection/transport/storage/processing and pathogen detection of samples; data analysis and processing; case treatment; follow-up management; quarantine and isolation; individual and group risk assessment; and disinfection and protective equipment [37,38]. For different IDs, it is necessary to develop various fast, specific, sensitive, convenient detection technologies with a gradient high-low throughput capacity, as well as detection instruments and specific vaccines [31]. This requires joint innovation practices among stakeholders (biopharmaceutical enterprises, health care and research institutions, big data companies) to maximize their respective technological advantages. ID monitoring also requires interdisciplinary cooperation [39]. For example, in terms of epidemic analysis and prediction, it is crucial to combine knowledge and technology from multiple disciplines such as epidemiology, statistics, computer science, and AI [31,40] to better solve various challenges in ID monitoring. In terms of joint innovation, governments can provide financial support, diversified investment, policy guidance, and coordinated resources to promote innovation in local biopharmaceutical industries and testing equipment development industries [41], and cooperation between and among academia and industries can accelerate the transformation and industrialization of scientific and technological achievements.

7. Key issues requiring further investigation

To expand China's overall monitoring capacity for major IDs, practical experience is needed in ID prevention and control to build a smart, intelligent, and better network for ID surveillance; train teams of talent with indepth knowledge in the field, technology and management; and increase science research spending for applied sciences in the medical field. These steps will comprehensively enhance the capacity to monitor, analyze, forecast, and predict IDs to achieve the goal of One Health. Three urgent issues currently must be addressed, as follows.

7.1. Top-level design of an integrated and updated monitoring system with streamlined processes and unlimited use/sharing of data with the same standards

All levels of the health sector must implement three measures to strengthen the top-level design of the ID monitoring and warning system, draw a working blueprint, refine operational procedures, unify standards for use, and make the system efficient and effective. One measure is to focus on integration of medical and preventive measures within the health system and formulate data standards and sample transportation requirements for comprehensive monitoring of IDs in medical institutions. The ensuing results will be a part of the annual performance evaluation. The second measure is to implement the requirements of the National Health China Strategy to build a monitoring and early warning system, formulate data interconnection standards for relevant departments, and achieve data sharing. The third measure involves strengthening industry supervision and the construction of data-sharing mechanisms and implementing the interconnection and exchange of relevant industry monitoring data. The fourth measure is to ensure comprehensive data security throughout the entire data life cycle. Focusing on each stage is important, including data collection, transmission, storage, processing, exchange, and disposal, to ensure coherency and consistency in data security strategies and processes.

7.2. Building a big data platform for integrated monitoring of IDs and strengthening technologies for comprehensive analysis, early warning, and forecasting

Based on the premise of network and data security, it is necessary to build a comprehensive monitoring big data platform for ID surveillance to gather monitoring data, which will hasten the establishment of a warning signal trigger system for new IDs. To further control the "key" to understanding the microbial world, training personnel to become high-potential and interdisciplinary professionals with versatile abilities is important, to integrate and mine the massive amount of life science data using bioinformatics analysis and AI technology.

7.3. Sustainable commitment to promote research in applied sciences for public health

It is necessary to optimize the infrastructure for epidemic prevention and control in times with or without an outbreak, to tackle difficult issues in public health science and research, and to concentrate efforts on integrating core technologies. Several win-win cases exemplify the successful translation of advanced technologies developed in basic research to on-site use; examples include the use of highly sensitive tNGS in identifying pathogens and the joint use of fully automated rapid database construction and high-throughput sequencing, as well as immunological assays in simultaneously detecting multiple pathogens. Relying on the cooperation and sharing mechanisms between the China CDC and basic science research institutions to jointly expand and deepen regional and international cooperation will benefit the translation and practical application of scientific and technological achievements, which in turn will help the public health sector contribute to a healthier China [42].

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Author contributions

Y.P.C. and Z.Z contributed to interpretation of the data, drafting the paper, and approving the final version. Y.L.S, L.L.R, M.K, D.F.K, X.L.S, Q.Y.L, Z.G.C, Y.H.L, R.L.Z, P.X.L, Y.L, T.T.L, N.X.C, H.W.X, C.D, J.Y, L.W, R.Q.L, W.H.C, X.Y.L, Q.H.L, G.L, X.D.Z, J.H.Y, T.Q.W, Y.C.G, J.H.L, and X.Z contributed to investigation and interpretation of the data. T.J.F contributed to conceptualization and approving the final version.

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Declaration of competing interest

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

Data available statement

Not applicable.

Ethics statement

Not applicable.

Informed consent

Not applicable.

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