

Landscape of emerging and re-emerging infectious diseases in China: impact of ecology, climate, and behavior

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Abstract For the past several decades, the infectious disease profile in China has been shifting with rapid developments in social and economic aspects, environment, quality of food, water, housing, and public health infrastructure. Notably, 5 notifiable infectious diseases have been almost eradicated, and the incidence of 18 additional notifiable infectious diseases has been significantly reduced. Unexpectedly, the incidence of over 10 notifiable infectious diseases, including HIV, brucellosis, syphilis, and dengue fever, has been increasing. Nevertheless, frequent infectious disease outbreaks/events have been reported almost every year, and imported infectious diseases have increased since 2015. New pathogens and over 100 new genotypes or serotypes of known pathogens have been identified. Some infectious diseases seem to be exacerbated by various factors, including rapid urbanization, large numbers of migrant workers, changes in climate, ecology, and policies, such as returning farmland to forests. This review summarizes the current experiences and lessons from China in managing emerging and re-emerging infectious diseases, especially the effects of ecology, climate, and behavior, which should have merits in helping other countries to control and prevent infectious diseases.

Keywords infectious disease profile; emerging infectious diseases; influence factor

Introduction

Over the last few decades, China has benefited from an unprecedented economic boom with its gross domestic product per capita growing from \$193 in 1980 to \$8866 in 2016. Learning hard lessons from the severe acute respiratory syndrome (SARS) outbreak in 2003, the central government has been investing heavily on disease control and prevention and has devoted efforts to minimizing the damage of infectious diseases. As a result, remarkable improvements have been achieved in public health infrastructure with new laboratory facilities, upgrades of

the surveillance system nationwide, and increase in the number of highly qualified public health professionals [1]. Indeed, the incidence of some infectious diseases has declined considerably. However, some other infectious diseases have rebounded or even increased in some regions. An unanswered question remains: how well the current disease prevention and management system works in response to future challenges on emerging and re-emerging infectious diseases, which may be exacerbated by rapid urbanization, high numbers of population movement, such as migrant workers, ecological effects of global climate change, and policies, such as returning farmland to forests [2].

In this article, we extensively reviewed the current situation of infectious diseases in China and comprehensively analyzed the prevention and response strategies. As a country with such a huge population and economy size,

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as well as high geographical and climatological diversities, China has gained lessons and experiences that should have implications for global infectious disease control and prevention.

Trends of infectious diseases in China

The overall profile of infectious diseases shifts substantially

The association between poverty and infectious disease is evident. Disease transmission is usually associated with various factors, including poor water, sanitation, food, and vectors. Low income generally means poor nutritional status, low quality of water and food, and numerous mosquitoes and flies. China has achieved great development in economy, hygiene, and public health since the SARS outbreak [3]. Thus, the increase, not decrease, in the overall incidence of a total of 39 notifiable infectious diseases from 3 906 566 cases (7248 deaths) in 2004 to 6 944 240 cases (18 237 deaths) in 2016 is difficult to understand (Fig. 1 and Fig. 2). These released numbers were public data accessible from the new web-based reporting system for notifiable infectious diseases established in 2004 [4], and this system is so far the largest infectious disease surveillance tool equipped with modern

information technology [5] and covering the largest populations in the world.

Some notifiable infectious diseases were eradicated or nearly eradicated

Five notifiable infectious diseases were eradicated or nearly eradicated, including polio, filariasis, SARS, plague, and diphtheria. Aside from the polio outbreak in 2011 caused by imported cases [6], no domestic case has been reported over the past decades. No SARS case has been reported since the closure of the Xinyuan Animal Market in Guangzhou City of Guangdong in 2004; the same is the case for visceral filariasis for the past five years. Only three cases of diphtheria have been reported since 2004. On average, only one case of plague is annually diagnosed for the past six years, and few patients all admitted a history of touching marmot, one of the major animal reservoir of *Yersinia pestis*, the pathogen of plague [7]. If hunting, trading, processing, or eating marmot is completely “eradicated,” the plague would most probably be “eradicated” in China. Nevertheless, vigilance in China is still high for plague, considering that its notoriety has killed over 10 million Chinese in the past and that it is still one of the only two Class A infectious diseases on the notification list; furthermore, approximately 10 000 cases were reported in the 1950s [8].

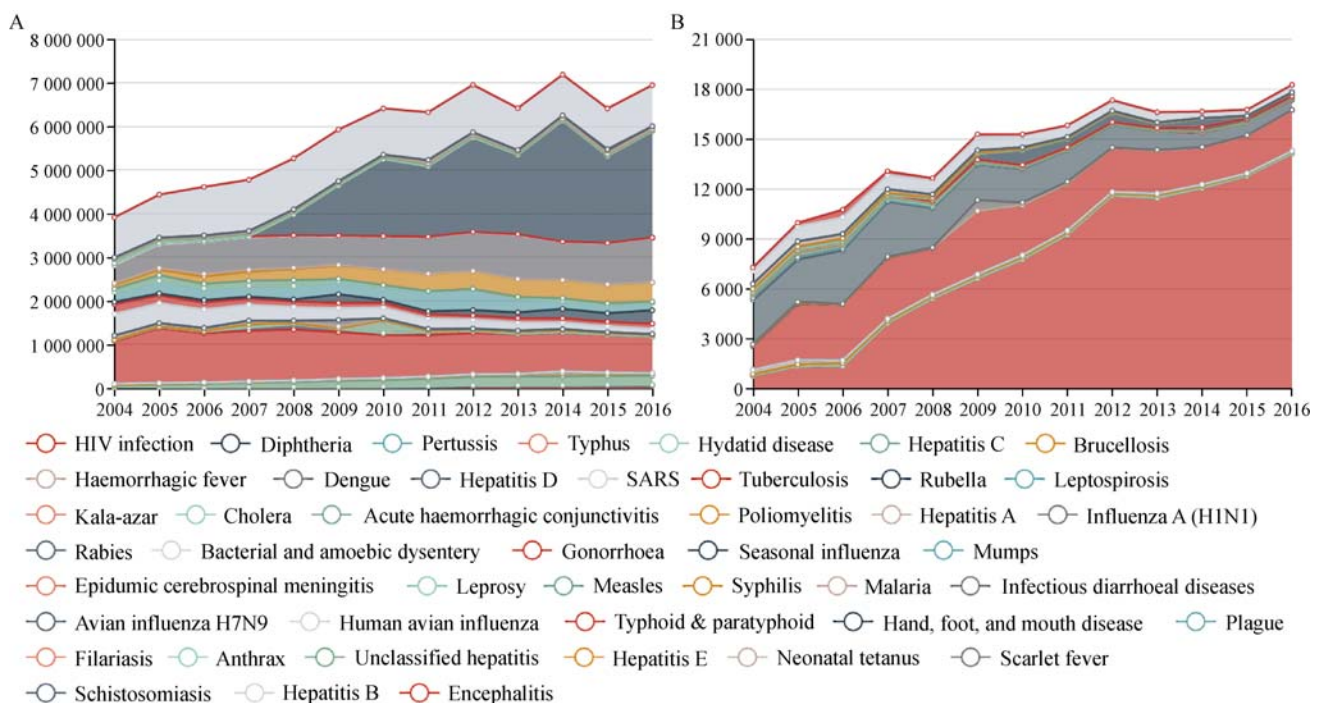


Fig. 1 Stacked graph for incidence (A) and case-fatality ratios (B) of notifiable infectious diseases in China.

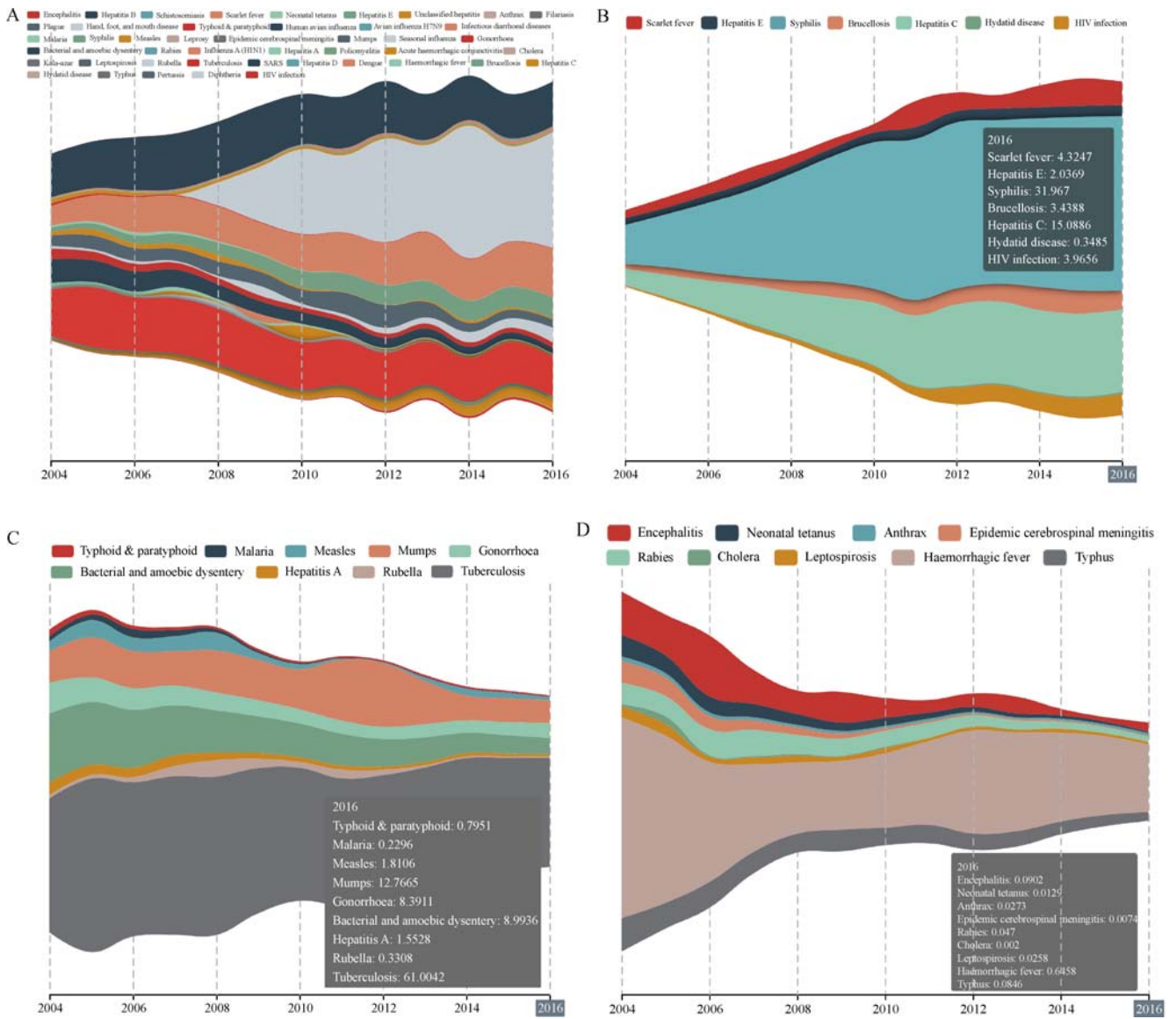


Fig. 2 Trends in the incidence of notifiable infectious diseases in China. (A) Trends in the incidence of 39 notifiable infectious diseases. (B) Increase in the incidence of 7 notifiable infectious diseases. (C) Decline trend in 9 notifiable infectious diseases with relatively high incidence (over 0.2296/100 000). (D) Decline trends in 9 notifiable infectious diseases with relatively low incidence (less than 0.002/100 000).

The incidence of some notifiable infectious diseases was reduced

A reducing trend was observed for 18 notifiable infectious diseases, including cholera, hepatitis A, bacterial dysentery, amoebic dysentery, typhoid, paratyphoid, gonorrhoea, pertussis, epidemic cerebrospinal meningitis, hemorrhagic fever, rabies, leptospirosis, anthrax, typhus, encephalitis, malaria, tuberculosis, and tetanus (Fig. 2C and 2D). These diseases might be considered as susceptible to current control and prevention strategies. However, the numbers of tuberculosis and gonorrhoea cases are still very high, and therefore should be further monitored. In a sense, they are economy- and hygiene-susceptible infectious diseases.

Their public health significance will be reduced when the quality of food, water, and housing for humans is improved.

The eradication status and decreasing trend of some infectious diseases have been largely attributable to the extensive vaccination coverage during the past decades, such as vaccines for polio, diphtheria, measles, hepatitis B virus (HBV), pertussis, and hepatitis A virus [9,10]. China provides a large amount of resources to the immunization system. For example, from 2009 to 2011, the central government invested 2 billion Chinese Yuan for the catch-up immunization of HBV for children under 15 years of age across the country. A network system was established to monitor the adverse events following immunization.

Since 2008, vaccines for the expanded program on immunization (EPI) have expanded to cover 15 types of vaccine-preventable diseases with follow-up epidemiological studies to evaluate the efficacy of the vaccination [11].

Considerable progress has been made in reducing the incidence of measles with implementation of the National EPI, which includes routine vaccination, follow-up supplement immunity activities (SIAs), catch-up SIAs, and school-based vaccination. Similarly, China has maintained polio-free status [12], which is largely attributed to efforts on expanding vaccination. For those < 5 years old in China benefiting from mass vaccination, the prevalence rate of hepatitis B surface antigen (HBsAg) has decreased from 9.67% in 1992 to 0.96% in 2006, and the morbidity rate of hepatitis A also decreased by 96.7% (from 55/100 000 in 1990 to 1.8/100 000 in 2012) [13].

The incidence of some notifiable infectious diseases increased

By contrast, an increasing trend was observed for 11 notifiable infectious diseases, including human immunodeficiency virus (HIV), brucellosis, hepatitis C, hepatitis E, syphilis, scarlet fever, dengue, influenza, infectious diarrhea, hydatid disease, leishmaniasis, and schistosomiasis (Fig. 2B). Among them, HIV and syphilis are closely associated with personal behavior. Brucellosis is associated with large-scale farming and trading of goats. Dengue is associated with climate changes, population migrants, the ecology of mosquito vectors, etc. These diseases will be discussed below in more detail.

Five new notifiable infectious diseases were added to the reporting list after 2004, including hand, foot, and mouth disease (HFMD) [14], human infection of avian influenza virus, human infection of H7N9 influenza virus, H1N1 influenza, and hepatitis E. Nine years after its addition to the list, HFMD has contributed over 18 million cases to the national surveillance system [15].

Frequently reported outbreaks of infectious diseases

In contrast to the progress mentioned above, some major infectious disease outbreaks/events were significantly increased, resulting in almost one outbreak or event per year since 2003. Before that time, only 12 infectious disease outbreaks/events were reported for the whole 23-year period (1979–2002). The causative pathogens responsible for the 12 outbreaks during 1979–2002 varied from hepatitis A (1979) [16], *Y. enterocolitica* (1981) [17], rotaviruses causing adult diarrhea (1982–1983) [18], virus causing hemorrhagic fever with renal syndrome (1980) [17,19], *Borrelia burgdorferi* (1986) [20], hepatitis C (1986–1988) [21], HIV (1983) [22], *Campylobacter jejuni* (1986) [23], *Legionella pneumophila* (1992) [24], *Vibrio*

cholera O139 (1993) [25], *Streptococcus suis* ST7 (1998) [26], and *Escherichia coli* O157:H7 1999 (first isolated in 1986) [27]. However, in the following 13 years (2003–2016), a total of 26 infectious disease outbreaks/events, which was more than doubled, was reported. These 26 events involved humans with the following viral or bacterial infections: severe SARS [28], avian influenza virus H5N1 (2005–2006), *Neisseria meningitidis* serotype C sequence type complex T4821(2003–2005) [29], *S. suis* ST7 (2005) [30], avian influenza H5N1 [31], HGA (2006) [32], influenza H1N1 (2009) [33], New *Bunyavirus* (2009) [34–36], avian influenza H7N9 (2013) [37], dengue fever (2013) [38], West Nile virus (2014) [39], Zika virus (2015) [40], yellow fever (2016) [41], Rift Valley fever (2016) [42], Middle East respiratory syndrome (MERS) (2015) [43], poliomyelitis (Xinjiang) (2011) [6], *Anaplasma capra* (2014) [44], *Shigella flexneri* Xv (2003) [45], Tahyna virus (2006) [46], *Babesia venatorum* (2014) [47], *Rickettsia sibirica* BJ-90 (2012) [48], *R. tarasevichiae* (2012) [49], *R. raoultii* (2012) [50], *Borrelia valaisiana* (2010) [51], *Anaplasma ovis-like* (2014) [44], *Wolbachia* (2012) [52], adenovirus serotype 50 (2010) [53], and Creutzfeldt–Jakob disease [54].

The newly emerged pathogens causing outbreaks in China and discovered or identified for the first time in history include SARS, new *Bunyavirus*, Wenzhou virus, and *Anaplasma ovis-like*. Incredibly, the same new *Bunyavirus* appeared in the literature with three different names, i.e., Huaiyangshan fever virus [55], Thrombocytopenia syndrome virus [35], and Henan fever virus [36].

A total of 130 new pathogens, including the three pathogens identified for the first time in China, ranging from newly discovered pathogens, newly recognized pathogens, new sequence types, new genotypes, and new serotypes of known pathogens (Fig. 3), have been identified in the past 30 years (Supplementary Table 1: Chronological table of EIDs and R-EIDs in China). However, the true nature of the increasing trend of disease incidence remains to be investigated. On the one hand, these diseases might really be on the rise. On the other hand, the trend might be a reflection of possibilities that more people were simply coming to clinics for tests or diagnosis, the assays are far sensitive nowadays than old times, or the surveillance system for historical reasons as earlier data collection may suffer from incompleteness (missing data). The national surveillance system built in 2005 is supposed to be more complete with far less missing data.

Emerging infectious diseases

Emerging new genotypes and serotypes of well-known pathogens

More than 100 new genotypes and serotypes of known pathogens have been identified in the last two decades that

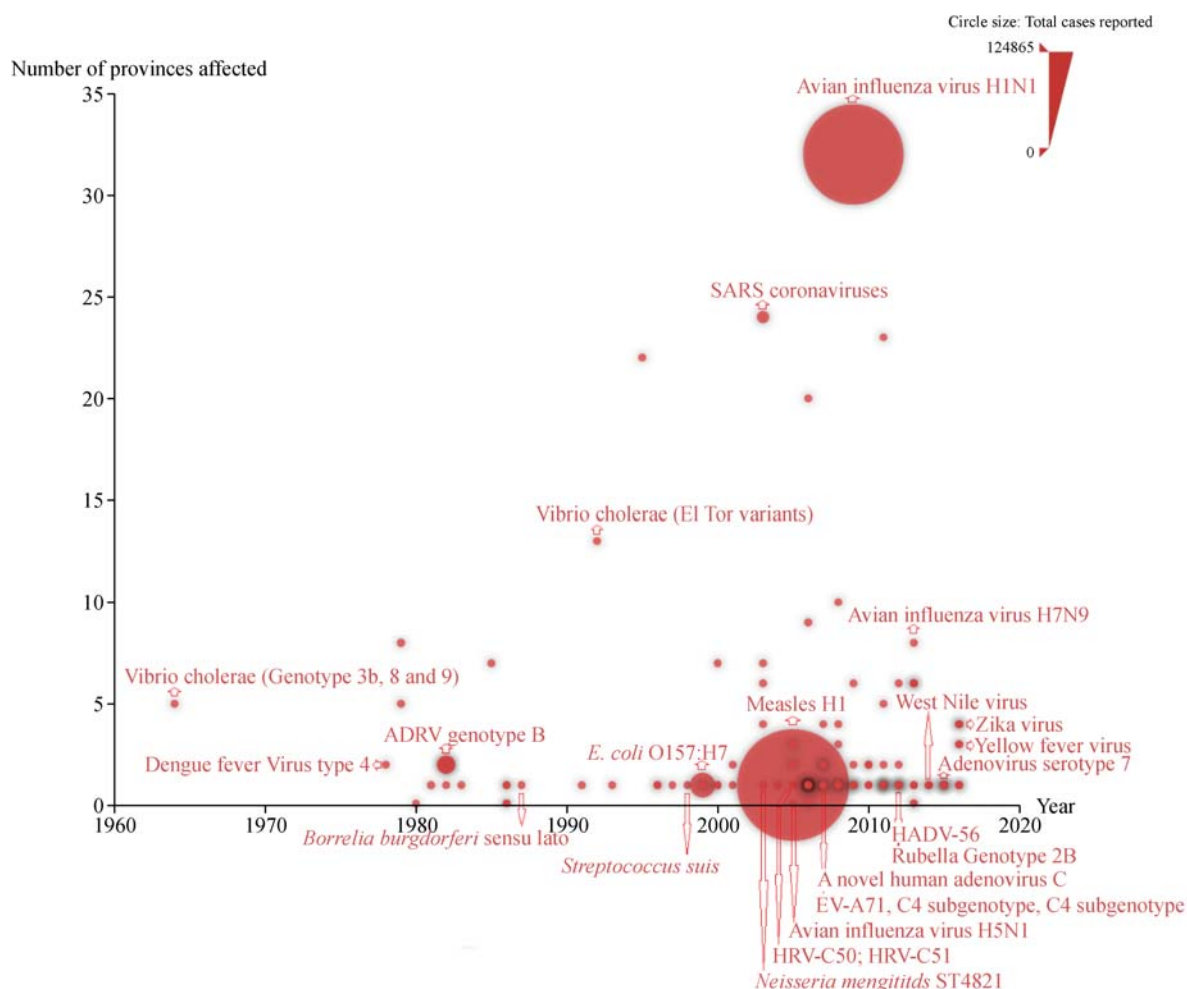


Fig. 3 EIDs and R-EIDs in China in chronological order.

were responsible for larger outbreaks in human, including *S. suis* ST7, *N. meningitidis* clonal complex 4821, human enteroviruses EV-A71 genotype C4a, *E. coli* O157:H7 clone ST96, *S. flexneri* clone ST91.

EV-A71 genotype C4a emerged and spread in China

Human enteroviruses (EV) can cause a range of clinical manifestations. EV-A71 is one of the main pathogens of HFMD with possible serious and potentially fatal neurological complications, which is already considered as the most significant neurotropic enterovirus second to poliovirus. EV-A71 is currently classified into seven genotypes (genotypes A to G), and genotypes B and C can be further divided into subgenotypes B0 to B7 and C1 to C6. Most of these subgenotypes are co-circulating worldwide; C4b and C4a were first isolated from Shenzhen City of Guangdong in 1998 and from Linyi City of Shandong in 2007, respectively.

Further phylogenetic analysis indicated that C4a first

emerged in 2003 and became predominant since 2007 (Fig. 4). Another subgenotype, C4b, although dominating and circulating in China from 1998 to 2006, rarely caused any severe or fatal cases. Upon switching from C4b to C4a since 2007, the number of severe and fatal cases increased significantly. The first two laboratory confirmed outbreaks of HFMD caused by C4a, which occurred in Linyi City of Shandong in 2007 and in Fuyang City of Anhui in 2008 (1 March to 9 May), resulting in 6049 cases with 353 severe cases and 22 deaths. Since May 2, 2008, HFMD had been designated as a class “C” notifiable disease, meaning that all clinical and laboratory diagnosed cases were required to be reported through the web-based national disease surveillance and information management system. After reclassification, over 10 million cases of HFMD were annually reported in China from 2009 to 2016. Surveillance data revealed that EV-A71 was associated with large HFMD outbreaks between 2008 and 2016, causing 50.8%–82.3% of the severe cases and 87.2%–95.5% of the fatal cases (Fig. 4). Results of the pathogen spectrum,

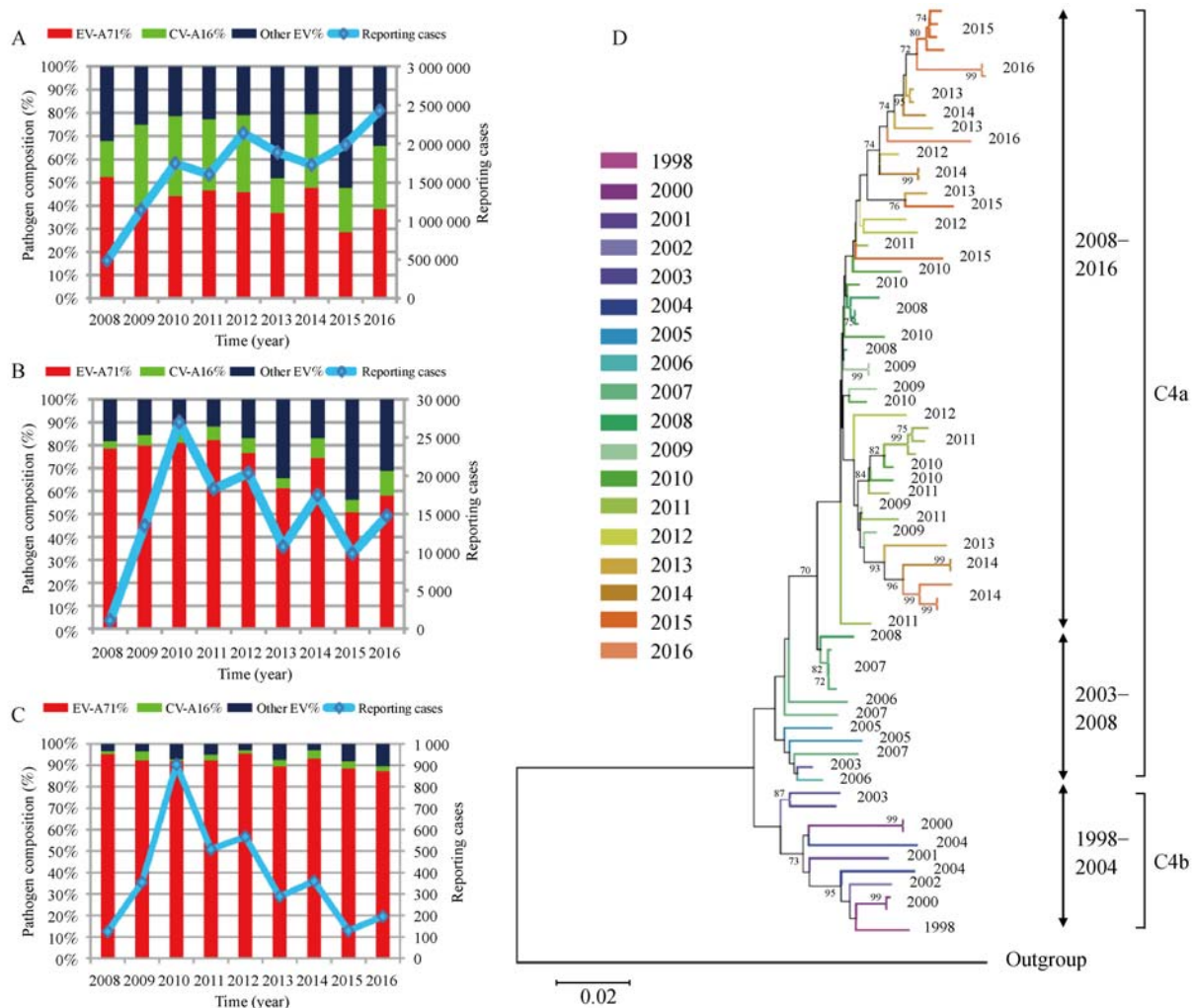


Fig. 4 Emerged EV-A71 genotype C4a and its public health significance in China. (A–D) Number of reported cases of HFMD and proportions of enterovirus serotypes in laboratory-confirmed HFMD cases by clinical severity in 2008–2016. (A) Based on mild cases; (B) Based on severe cases; (C) Based on fatal cases; (D) Emerging of EV-A71 C4a based on phylogenetic analysis of VP1 sequences.

epidemiology, and clinical manifestations of HFMD indicated that C4a has higher neurovirulence and transmissibility than C4b. Moreover, C4a had a wider spread worldwide, causing outbreaks in Vietnam, Cambodia, Denmark, and some other places.

N. meningitidis hyper-invasive clonal complex 4821

The meningococcal diseases caused by *N. meningitidis* serogroup A used to be a big problem in China. The incidence declined below 0.2/100 000 in populations after the introduction of the national vaccination program in the 1990s. Outbreaks caused by serogroup C were initially reported in Anhui in 2003, which soon spread over to 25 other provinces across the country. During the period from 2003 to 2005, the serogroup C clone CC4821 infected

more than 100 cases and caused dozens of deaths in Anhui. Most patients in the outbreaks were adolescent middle school students. By multilocus sequence typing (MLST), CC4821 was identified as the causal agent, which is a new member of the hyper-invasive clonal complexes worldwide [29]. CC8, CC11, CC32, and CC41/44 were also members of the major clonal complexes within serogroup C, circulating in Northern America, Latin America, and Europe [29]. In 2004 and 2005, over 2000 cases were reported annually nationwide. Therefore, the bivalent meningococcal A plus C (MenAC) polysaccharide vaccine was included in the EPI in 2007. After 10 years of immunization with this vaccine, capsule-switching was noticed. Serogroup B of CC4821 increased significantly, resulting in invasive meningococcal cases, especially among infants [56].

S. suis ST7 emerged and spread in China

As a variant of *S. suis* ST1, ST7 has increased virulence [30]. ST7 emerged for the first time in 1996–1997, causing the 1998 outbreak with 25 human infections, then diverged into additional 5 clades, causing the 2005 outbreak [57]. Notably, ST7 is only isolated in China so far without any report from other countries. Unlike ST1, ST7 strains can stimulate host cells to produce massive amounts of pro-inflammatory cytokines, leading to Streptococcal toxic-shock-like syndrome and deaths [58].

E. coli O157:H7 clone ST96 outbreak

MLST of 15 housekeeping genes revealed that the 1999 outbreaks in Jiangsu and Anhui were caused by ST96, a unique clone of *E. coli* O157:H7. Analysis following the complete genome sequencing of one of the outbreak isolates showed that the strain Xuzhou21 of ST96 is phylogenetically and closely related to Sakai (Japan 1996 outbreak isolate), and EDL933 (US outbreak isolate) is the most recent common ancestor of both strains. While both can stimulate peripheral blood mononuclear cells to produce significantly more IL-6 and IL-8 than EDL933, Xuzhou21 and Sakai induced similar levels of IL-6, and the former induced the highest level of IL-8. With mitomycin C induction, Shiga toxin 2 production of EDL933, Sakai, and Xuzhou21 were 4.5, 32.7, and 68.6 times more than that without induction. Conversely, Xuzhou21 produces 2 and 15 times more Shiga toxin 2 than Sakai and EDL933 upon mitomycin C induction. Among these three representative strains, Xuzhou21 is the most pro-inflammatory and most toxic. Moreover, Xuzhou21 carries a *Salmonella* plasmid, which EDL933, Sakai, and many other isolates lack [59].

S. flexneri epidemic clone ST91 and new serotypes Xv, 4a, Yv, and 1d

Under our surveillance, a new serotype of *S. flexneri* Xv, first appeared in 2001, became the most prevalent serotype (replacing serotype 2a) in Henan in 2003 and were the dominant serotype by 2007 in 7 of the 10 other provinces. Several other newly identified serotypes (4a, Yv, and 1d) carry plasmid or phage. ST91 (many serotypes) was identified as a new clone by MLST. Analysis of 655 isolates with pulsed-field gel electrophoresis (PFGE) revealed they had 154 pulse types with 57 serotype switching events. These results suggest that *S. flexneri* epidemics in China have been caused by a single epidemic clone, ST91, with frequent serotype switching away from serotypes to which the human population was previously exposed and had developed immunity [45]. Whole-genome sequencing of 59 isolates of 14 serotypes indicated that ST91 arose around 1993 by acquiring multidrug

resistance and had spread across China within a decade. These findings further suggest that multidrug resistance is the key selective pressure for the emergence of the *S. flexneri* epidemic clone and that *Shigella* epidemics in China were caused by a combination of local expansion and inter-regional spread of serotype Xv [60]. The data together underscore challenges to the current vaccine development and control strategies for shigellosis [45].

New serotypes of human adenovirus

Over 30 novel types of human adenovirus (HAdV) and several variants have been recently identified worldwide based on the analysis of the complete genome sequences. Some of the novel HAdVs have stronger virulence and transmission capacity, leading to large-scale human infections (<http://hadv.wg.gmu.edu/>). One of the new types, HAdV-55, was first isolated from a senior high school in Shaanxi in 2006 [61] and later on widely spread into seven metropolitan cities/provinces (Beijing, Tianjin, Shandong, Jiangsu, Tibet, Chongqing, and Guangdong), causing respiratory infection or community-acquired pneumonia. It had caused two large outbreaks of acute respiratory tract infections among military trainees in Shanxi (339 cases with 1 death) and Hebei (601 cases) successively in 2011 and 2012, firmly establishing itself as one of the major etiological agents for pneumonia in Chinese mainland [62].

Another new serotype, HAdV-56, was found to be the causative agent for a large scale of outbreak of epidemic keratoconjunctivitis, with 451 cases in the Dalian City in 2012 [63]. The HAdV-14p1 seems more associated with kids, being isolated from a baby with pneumonia in Beijing and causing an outbreak of febrile respiratory illness in a primary and a middle school in Gansu in 2011, which was the first school-based HAdV-14p1 outbreak in the world [61]. After its silence for 21 years in China, HAdV-7d re-emerged and was associated with an outbreak in Guangdong in 2011. Recent severe acute respiratory infections among children in Shanghai and Beijing were suspected to be caused by some possibly hybrid virus within HAdV-C [64], making HAdV a new challenge to disease surveillance, control, and prevention.

Outbreaks caused by new pathogens discovered in China

A few new pathogens were discovered in China since the government heavily invested in the field of infectious diseases.

New *Bunyavirus*

In April 2009, physicians of the Union Hospital of Tongji Medical College, Wuhan City learned that 8 out of 49

patients (16.3%) died from an unknown disease featured with high fever, leucopenia, thrombocytopenia, and elevated liver transaminase levels. All patients were from the Huaiyangshan mountain area of Hubei and Henan provinces (central China), and some recalled a history of tick bites. Given that the clinical features of the above patients resembled those of human granulocytic anaplasmosis (HGA) caused by *Anaplasma phagocytophilum* which was first isolated from the neighboring province of Anhui in 2006, they were clinically diagnosed initially as suspected HGA in 2010. Patient samples were subsequently sent to National Institute for Communicable Diseases Control and Prevention, China CDC, and they were tested negative for *A. phagocytophilum* by PCR and immunologic methods, definitely excluding *A. phagocytophilum* as the causal agent. Further efforts trying to isolate the etiologic agent by culturing samples with DH82 cells led to the discovery of a novel *Bunyavirus*, and some of the results were published in March 2011. Since all the patients were from the Huaiyangshan mountain area, the disease was proposed as Huaiyangshan hemorrhagic fever, and the causative agent was named as *Huaiyangshan virus* (HYSV) [34].

Compared with the survivors, the blood samples collected at admission from all the patients who died of the above outbreak had higher levels of viral RNA load, serum liver transaminases, acute phase proteins (phospholipase A, fibrinogen, and hepcidin), cytokines (IL-6, IL-10, and interferon- γ), and chemokines (IL-8, monocyte chemotactic protein 1, macrophage inflammatory protein 1b) plus more pronounced coagulation disturbances. Notably, viral RNA load was highly correlated with the level of these host molecules, and it gradually declined over 3–4 weeks after illness onset, with gradual resolution of symptoms and laboratory abnormalities. Viral RNA was also detectable in the throat, urine, and fecal specimens of a substantial proportion of patients, including all fatal cases assayed. Therefore, the host immune responses to the HYSV infection and viral replication very likely played an important role in determining the severity and clinical outcome of the patients [55]. As several groups were involved in the investigation, the agent was also reported in the literature as severe fever thrombocytopenia syndrome virus [35] and Henan fever virus [36].

Of the five species of ticks carrying the novel tick-borne *Bunyavirus* *Huaiyangshan viruses*, *Haemaphysalis longicornis* was the most abundant in endemic regions and is considered to be the major vector [65]. Its usual hosts (cattle, goats, dogs, rats, and chickens) tested positive for *Huaiyangshan virus* RNA and had high seroprevalence. The distribution of *H. longicornis* and the migratory routes of four wild fowls across China, South Korea, and Japan had a good match. Thus, a tick and a migratory bird model for the transmission of the *Huaiyangshan virus* was

proposed. The *H. longicornis* ticks presumably play a key role in transmitting the virus, probably via a free international ride between China, Korea, and Japan on migratory birds [65].

Anaplasma capra

A novel *Anaplasma* species (*Anaplasma capra*) was detected with PCR and sequencing in Heilongjiang in 2014 by screening blood samples from 477 patients with a history of tick bite and 28 (6%) of them tested positive. Three strains were subsequently isolated from three individuals. Phylogenetic analysis of the three strains suggested that they were distinct from all known *Anaplasma* species. These PCR positive patients presented a series of non-specific febrile manifestations, including fever in 23 patients (82%), headache in 14 patients (50%), malaise in 13 patients (46%), dizziness in 9 patients (32%), gastrointestinal symptoms in 8 patients (29%), myalgia in 4 patients (14%), and chills in 4 patients (14%). Some had observable physical findings, including rash or eschar in 10 patients (36%), lymphadenopathy in 8 patients (29%), and stiff neck in 3 patients (11%). Five severe patients were eventually hospitalized. Among the 17 patients examined, 6 (35%) had high levels of hepatic aminotransferases in the serum. *A. capra* has also been detected in ticks from Liaoning [66]. Therefore, people living in or traveling to endemic regions in Northern China should take precautions to avoid tick bite to minimize the possibility of infection [44].

Wenzhou virus

Wenzhou virus (WENV) was isolated from rodents and shrews in 2013 in Wenzhou City, Zhejiang Province, a locality where hemorrhagic fever diseases are endemic in humans. Phylogenetic analysis revealed that all WENV strains harbored by both rodents and Asian house shrews formed a distinct lineage most closely related to Old World arenaviruses [67]. The public health effect of Wenzhou virus on China remain unknown. However, a genetic variant of the Wenzhou virus was detected in Cambodian rodents and caused human infection. The identification of human Wenzhou virus infection represents the first detection of human mammarenavirus infection in Asia [68]. Human infection with Wenzhou virus, or a closely related virus, occurs widely throughout Cambodia and may possibly result in disease in some cases. The association of these viruses with widely distributed mammals of diverse species, commonly found in human dwellings and in peridomestic habitats, illustrates the potential for widespread zoonotic transmission and adds to the known etiologies of infectious diseases for this region [65].

Infectious diseases caused by overlooked pathogens

Severe infection of *Rickettsia sibirica* BJ-90

Unlike patients infected with *R. sibirica* and *R. heilongjiangensis* in the same region, BJ-90, a new variant of *R. sibirica* without precedent of human infection [69], caused a patient to become severely ill with multi-organ dysfunction in 2012 [50]. Coincidentally, BJ-90 was first isolated in 1990 from a *Dermacentor sinicus* tick in the campus where our China CDC laboratories are located. It has also been detected in *D. silvarum* in Russia.

First human infection of *Wolbachia*

Probably the most abundant intracellular bacteria ever described, *Wolbachia* inhabits in many species of terrestrial arthropods and some species of filarial nematodes. However, human infection of *Wolbachia* has not been reported until 2015. A 50-year-old man, without any history of arthropod bite or animal exposure, was initially suspected of having influenza virus infection, with symptoms including intermittent fever, headache, and myalgias. He was diagnosed with *Wolbachia* infection verified by sequencing [70].

Infectious diseases caused by vector-borne pathogens

Various biological factors, including changes in the dynamics of disease vector (tick) and host population, can affect the transmission and dissemination of tick-borne zoonotic diseases. Changes in land use were also shown to affect the emergence of tick-borne zoonotic diseases by altering the interaction patterns between pathogens, wild/domestic hosts (e.g. ticks), and humans. Since the mid-1990s, the Chinese central government has initiated the Greening Program to restore forests and grasslands from former agricultural lands. Reforestation and grass replanting with high-quality vegetative cover could have increased the abundance and diversity of ticks and animal hosts, which favored the re-establishment of pre-existing tick vector enzootic cycles in these areas. In the past three decades, China has experienced the most rapid urbanization in its history. This rapid urbanization was accompanied with widespread rural-to-urban migration of the human population, intensive long-distance trade, and explosive short-term travel for shopping, thereby increasing health risks, including air pollution, occupational and traffic hazards, and so on. All these changes in human activity, together with increased contact between human beings and their pets and nature, have probably contributed to the increasing exposure to ticks, as seen in other developed countries. Increase in winter temperatures is known to cause the northward extension and increase the abundance of *Ixodes ricinus*, which subsequently raises the

risk of tick-borne disease dissemination.

Since the beginning of the 1980s, 33 emerging tick-borne agents have been identified across the country, including 8 species of spotted fever group *rickettsiae*, 7 species in the family *Anaplasmataceae*, 6 genospecies in the complex *Borrelia burgdorferi* sensu lato, 11 species of *Babesia*, and the virus causing severe fever with thrombocytopenia syndrome. A total of 15 out of the 33 emerging tick-borne agents have been known to cause human disease. The non-specific clinical manifestations caused by tick-borne pathogens present a major diagnostic challenge to physicians who are unfamiliar with many tick-borne diseases if patients present non-specific symptoms in the early stages of illness (Fig. 5) [71].

Human granulocytic anaplasmosis (HGA) identified in 2006

A cluster of ten cases of HGA via nosocomial transmission was identified in Anhui in 2006 and the index patient of this outbreak had a history of tick biting [32]. Later, 94 cases of HGA have been reported from several provincial or megacity regions, including 41 in Shandong, 33 in Beijing, 6 in Tianjin, 1 in Anhui, and 4 to 5 each in Henan, Hubei, and Inner Mongolia [71].

Re-emerging infectious diseases

Some re-emerging infectious diseases, including dengue illness and brucellosis, have attracted increasing attention in recent years.

Dengue illness was common in the 1940s. In the newly established People's Republic of China, no outbreak of dengue-like illness during the period of 1950–1977 was reported. Dengue fever reappeared in 1978 in Foshan of Guangdong [72]. Since then, dengue occurred in a few provinces in Southern China, although at a relatively low rate. Suddenly in 2014, Guangdong experienced a large outbreak with 45 224 cases [73].

Brucellosis in two foreigners was recorded in Shanghai in 1905 [74]. A total of 621 404 brucellosis cases were reported during 1955–2016. Most patients were farmers, veterinarians, or workers involved in livestock husbandry, transportation, and trade. Increasing and decreasing trends were observed in the incidence of brucellosis for the past 60 years. Two incidence peaks appeared: one from 1957 to 1963 and another from 1969 to 1971. After that, the incidence reduced dramatically from 1979 to 1993 until 329 cases re-emerged across the country. However, the incidence has increased from 1995 through 2016 with a peak with 56 989 cases in a single year [74]. The brucellosis incidence remains to exhibit an increasing trend for the coming years. The number of countries with brucellosis increased more than 20-fold, from 87 in 1993 to 2209 in 2016 [74], which is probably related to the increasing farming of goats and sheep. The number of

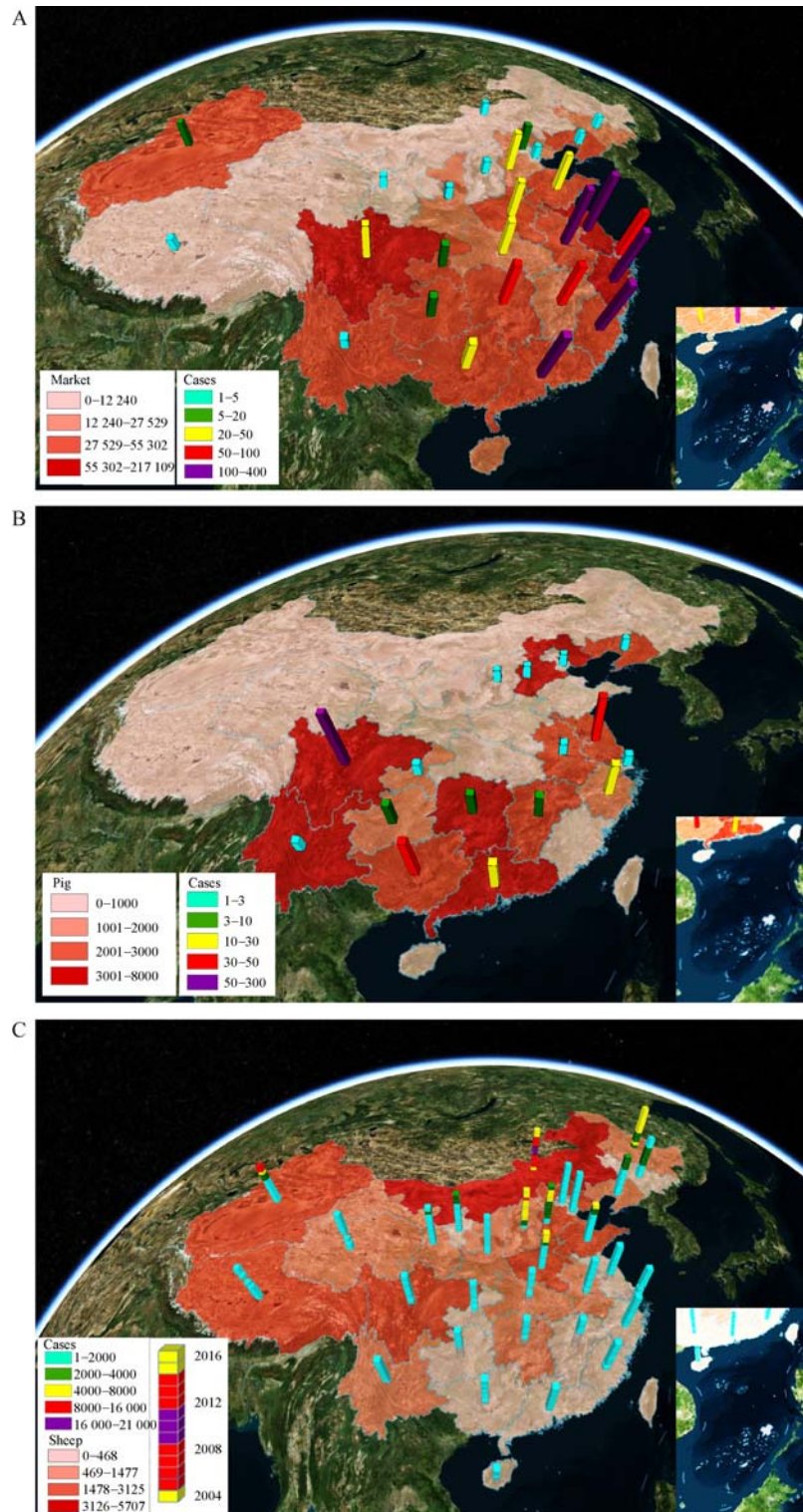


Fig. 6 Infectious diseases associated with malpractice in meat animal production in China. (A) Geographic distribution of H7N9 cases and the number of live poultry markets (LPM). The background represents the number of LPM. The 3D bars are for the collective cases of H7N9 from 2013 to 2017 for individual provinces. (B) Geographic distribution of human infection of *S. suis* cases and density of swine. The background represents the annual number of pig slaughtered. The 3D bars are for the total numbers of human infections from the literature. (C) Geographic distribution of case number of brucellosis and density of sheep slaughtered. The background represents the provincial average number of slaughtered sheep from 2004 to 2016. The 3D stacked box is the number of cases of brucellosis per year from 2004 to 2016.

infectious diseases.

The large-scale meat animal production and backyard farming in China have developed rapidly in the past two decades, which have been linked to the emergence and the spread of zoonotic pathogens. The close contact and onsite slaughtering of live poultry in market resulted in transmission of pathogens to human, causing large human infection outbreaks [2]. Five huge outbreaks or epidemics reported were associated with large-scale food animal production, including SARS, *E.coli* O157:H7 [59], *S. suis* ST7 [30], avian influenza H5N1 and H7N9 [37], and brucellosis [74]. Our surveillance system and management of infectious diseases are facing unprecedented new challenges from the current model of animal farming, trading, and consuming practice.

SARS outbreak and closing of live animal markets

Consuming civets in winter was popular in Guangdong because people believed in a myth that it is good for health. The demand for civets gradually increasing along with the booming economy in the region was the main cause for the presence of large scale civet farming industry. Civets supplied by farmers from 12 provinces, including Guangdong, were frequently transferred in open-framed trucks to a large live animal market in Guangzhou City. The transfers on the road and mixing of multiple species of wild animals or poultry during the transportation process and at the market created a dynamic micro-environment favoring cross-species transmission of pathogens among animals or from animals to humans. We strongly believe that this is the pathway of the emergence of SARS. As a control measure dealing with the re-emergence of SARS in Guangdong, massive numbers of palm civets were culled in January 2004 soon after the presence of SARS coronavirus was detected in animals of the market and in restaurants at the same time. Prior to culling, SARS virus was identified in 91 palm civets and 15 raccoon dogs from the animal market but tested negative for 1107 palm civets directly sampled from 25 farms across the 12 provinces where the market animals were traded [76]. All civets in the market supposed for delivery to restaurants were tested positive for SARS virus and therefore culled. Dinners were infected after consuming civets at a restaurant without quarantine [77]. As a kind of proof of our hypothesis that the civet supply chain is associated with SARS, no SARS case was reported since January 2004 when the animal market was forcedly closed and civet trading was banned [2].

Human infection of avian influenza virus and live poultry markets

The role of live poultry for transmission of AIV was evident when AIV H5N1, the first avian influenza virus,

was detected positive in samples of live poultry market (LPM) in Guangzhou City in 2006, and associated with human infection [78]. LPMs served as an important ecosystem for the circulation and evolution of AIVs. During the long-distance transportation of live poultry to large wholesale markets or distribution centers, different avian influenza viruses had the opportunity to mix up and share their genetic materials, a way to generate novel variant(s). Then the asymptomatic live poultry transported across the country increased the possibility for the rapid and nationwide dissemination of AIVs, resulting in extensive human exposure. In Southern China, buying live poultry from LPMs is very popular because the lifestyle there prefers consumption of live poultry. Since AIV was associated with human infection and LPM was associated with AIV transmission (Fig. 6A), closing the LPM was the right thing to do but understandably met resistance. Approximately a week after closing the LPM, the H7N9 outbreaks were effectively stopped in the endemic areas, and no H7N9 case was reported for quite a while [79,80].

Outbreak of E.coli O157:H7 1999

The outbreak of *E. coli* O157:H7 in Jiangsu and Anhui in 1999 infected approximately 20 000 people, causing hospitalization of 194 patients with acute kidney failure and resulting in 177 deaths. This is the largest outbreak caused by *E. coli* O157:H7 reported in world history. The pathogen was isolated from 8.3% to 16.9% meat animals raised in the backyards of farmers in Jiangsu, including cattle, pigs, goats, and chickens. Bohr goats, introduced into this region in the 1990s aiming to boost the local economy, were considered as the main reservoir of the causal agent because a unique clone of *E. coli* O157:H7 (discussed below) isolated from patients and Bohr goats showed identical PFGE pattern. Nine years after the introduction of Bohr goats (1999), this clone started to appear in animals and patients in China, suggesting its possible association with the original batch of seed goats [59,81,82].

MLST analysis of strains found that the 1999 outbreak in Jiangsu and Anhui was caused by a unique clone of *E. coli* O157:H7, ST96. Results from whole genome sequence phylogenetic analysis of an outbreak isolate, Xuzhou21, showed that the strain is phylogenetically closely related to the Japan 1996 outbreak isolate Sakai, both of which share the most recent common ancestor with the US outbreak isolate EDL933. The levels of IL-6 and IL-8 from peripheral blood mononuclear cells infected with Xuzhou21 or Sakai were significantly higher than those infected with EDL933. The level of IL-8 induced by Xuzhou21 was significantly higher than that caused by Sakai, whereas similar levels of IL-6 were triggered by

these isolates. The expression level of Shiga toxin 2 in Xuzhou21 induced by mitomycin C was 68.6 times that of under non-inducing conditions, which is twice that of Sakai (32.7 times more than without induction) and 15 times higher than EDL933 (4.5 times). Furthermore, Xuzhou21 carries a *Salmonella* plasmid, which is not present in EDL933, Sakai, and many other isolates [59], and the biological role of the plasmid is under study.

Multiple parallel pig-to-human transmission of S. suis ST7

In 2005, China reported the largest human infection outbreak of *S. suis* ST7 (diverged further into five clades), resulting in 215 patients with 39 deaths in Sichuan. Retrospective genome analysis revealed that *S. suis* already had 41 lineages by the end of 2004, and it rapidly expanded to 68 genome types through single base mutations when the outbreak occurred in June 2005. The large-scale supply of possible *S. suis* carrier piglets was distributed into a large geographical area with no identified transmission link. People were concomitantly infected in those geographic sites. This outbreak was a collective multiple pig-to-human transmissions in parallel, a newly recognized transmission model for infectious diseases, although common for other zoonotic diseases in China [57].

Approximately half of the meat pigs in the world are raised in China. The exponential expansion of pig breeding was believed to be in proportion with the exponential expansion of the *S. suis* population size. Like many other countries in Asia, China imports advanced breeds of pigs from European countries, such as the UK and Denmark, which may have facilitated the spread of *S. suis*. The pathogen spread further in China through wide adoption of indoor rearing of meat pigs. During 1996–2005, Sichuan significantly increased swine production from 52.76 million to 87.64 million (Fig. 6B). The industrialized piglet breeding companies (PBC) provided farmers with piglets possibly carrying the pathogen, and the farmers raised in their backyards under poor hygienic conditions, and practice like that contributed to the expansion of *S. suis*. Moreover, pigs slaughtered at home without hygiene inspection apparently increased risks for human *S. suis* infection. All factors together eventually led to the mounting of the *S. suis* human infection crisis in China. Accordingly, strategies, such as supply of healthy pathogen-free piglets, improving backyard hygiene for raising animals (pigs in particular), and regular pathogen monitoring at the PBC level should be effective in preventing most of the infection/outbreak.

Increasing trend of hepatitis E

The biggest verified acute hepatitis epidemic in the recorded Chinese history, leading to 119 280 cases with

707 deaths, was caused by genotype 1 hepatitis E virus (HEV) in Xinjiang Uighur Autonomous Region during 1986–1988 [83]. Among the four major mammalian genotypes, genotype 1 dominated in the 1980s and early 1990s, followed by genotype 4 since 2000 [84]. Genotype 3 was first identified in 2006 from pigs in Shanghai suburb [85] and gradually spread to Northern China. From 2003 and onwards, HEV cases were in the up-trend, and more than a quarter million HEV cases for the last few years were reported annually. The genotype 3 and 4 distribution in human overlaps with that in pigs [86], and this finding may provide scientific evidence explaining the increasing human incidence of HEV over a decade [84].

Effects of climate change on vector-borne diseases

The first dengue outbreak was reported in Guangdong in 1978 and originated from imported cases from southeast Asian countries [87]. Since then, the disease has been gradually spreading from south coast region to the inland (Fig. 7), specifically to Hainan, Guangxi, Fujian, and Zhejiang, mainly because of the increasing population movement. An unexpected dengue outbreak with 39 707 cases, the largest for the past 30 years, occurred in 2014 in Guangdong, and such outbreak was probably related to global climate change and increasing motility of the international population.

Dengue fever has already become a major threat to public health. Imported dengue cases frequently ignite local dengue outbreak. People back home from the dengue epidemic area were the most probable source for the importation of dengue fever in recent years. Pearson correlation analysis of the 10-year period data (2005–2015) revealed a positive association between the numbers of imported dengue cases and the numbers of tourists to southeast Asia ($r = 0.912$, $P < 0.01$), and migrant workers traveled abroad ($r = 0.691$, $P < 0.05$).

Dengue epidemics are known to be associated with climate factors, including ambient temperature, humidity, and rainfall. Both temperature and rainfall affect the dengue fever incidence most likely through affecting the mosquito density. Results of the analysis of the 2014 dengue outbreak in Guangzhou indicated that one month's lag in the mean and minimum temperature with a threshold of 18.25 °C was positively associated with the dengue incidence; specifically, 1 °C increase in previous month's minimum or mean temperature increased dengue fever incidence by 52.8% or 51.8%, respectively [38]. Since the vector population (mosquitos) for dengue fever will expand in more areas, and the intensity and scope of the dengue fever epidemic will increase accordingly along with changes in various climate components. Apparently, more preventive measures should be formulated to curb this trend.

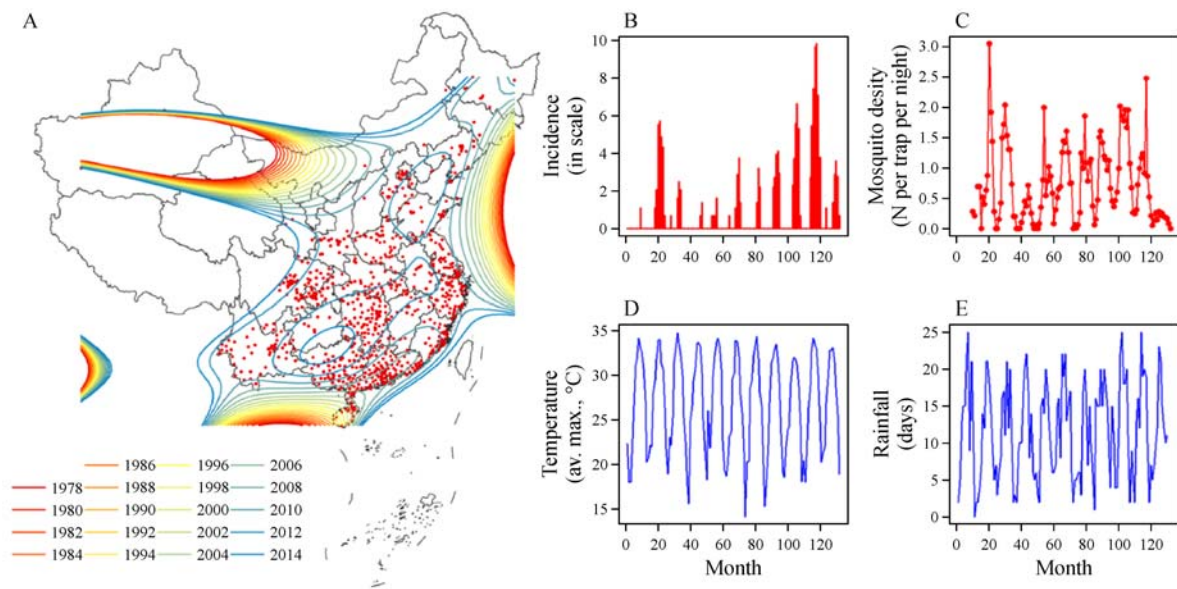


Fig. 7 Spatial spread process of dengue from South-west boundary region to inland China. Dengue outbreak and local climate variables were generated from the monthly scale data in Guangzhou from Jan. 2005 to Dec. 2015. (A) Contours were drawn based on the trend surface, which showed the predicted dengue invasive year. The slope of the trend surface represents the reciprocal spread speed of dengue from the year 1978 to 2016. Red points indicate the location of counties with cases of dengue infection. Based on the spatial spreading pattern of trend surface analysis, the dengue extends from the coastal region into the inner land of China, which may link with the global climate change. (B) Monthly time series of dengue incidence in Guangzhou. (C) Monthly time series of population density of the adult dengue vector *A. albopictus*. (D) Monthly time series of average maximum temperature in Guangzhou. (E) Monthly time series of number of days with rainfall in Guangzhou.

Effects of behaviors on infectious diseases

Effects of international tourism on imported infectious diseases

In the past few decades, a number of infectious diseases, such as yellow fever (YF) [88], Zika virus infection [89], Middle East respiratory system (MERS) [90], malaria [91], Rift valley fever (RVF) [42], and dengue fever [92], have been imported to China because of the increase in global population migration caused by tourism, large-volume exchanges of labor services and products, and global climate changes.

To show the pressing pressure on our surveillance system from the imported infectious diseases, the cases imported during 2015–2016 were taken as examples. On May 29, 2015 an imported MERS case involving a Korean businessman was confirmed in Huizhou, Guangdong [90], who decided not to report his health history to the Chinese custom upon his entry that had close contact with a confirmed MERS case during his stay in South Korea. On February 9, 2016 the first imported Zika virus infection appeared in Jiangxi. Since then, 25 Zika cases have been reported to be associated with importation from Venezuela (17), Samoa (3), Surinam (2), Guatemala (2), and Ecuador (1). Of these cases, 15, 4, and 3 cases emerged in

Guangdong [93], Zhejiang, and Beijing, respectively, and one case each in Jiangxi, Henan, and Jiangsu. The first imported case of YF was documented on March 13, 2016; afterward, a total of 11 similar cases have been imported into China. All the YF cases were involved in business or migrant labor services with Angola. Majority of the patients (10/11) had a history of mosquito bites. On July 23, 2016 a migrant worker infected with RVF in Angola returned to China for treatment. In summary, all of these imported cases are related to the population movement from other countries to China mainly because of globalization. Our surveillance and management of infectious diseases must timely evolve to meet this new pattern of challenge.

Although we had impressive progress in the control of malaria in the past, the imported malaria cases increased dramatically from 22.7% in 2005 to 98.8% in 2015. To counter against this threat, the Chinese government launched the national malaria elimination campaign in 2010 to reduce malaria cases across the country. This campaign has successfully reduced the number of domestic cases. As a result of the campaign, more than 90% of the malaria cases were imported from Africa and Southeast Asian countries. Touring, accommodating, or staying in a malaria-endemic area are the major risks concerning the imported malaria cases. Similar to the status of dengue

fever, the number of imported malaria cases from Africa is positively associated with the numbers of tourists in Africa ($r = 0.938$, $P < 0.01$), as indicated by Pearson correlation analysis of relevant data from 2005 to 2015.

Infectious diseases associated with social behavior

The infectious disease spectrum in China has shifted in the past decades. The contributing factors and presentation statures of infectious diseases have been considerably changed and mainly associated with changes in social behavior, personal behavior, large-scale production and development, lifestyle, environment, and ecology. Therefore, we proposed the term “behavioral and ecological infectious diseases” to emphasize the significance of those contributing factors. Compared with the 20-year period (1982–2002), the frequency of emerging infectious disease outbreak in China was remarkably increased (one or two per year) for the past 14 years (from the SARS epidemic in 2003 and onward), which is quite contrary to our assumption. As the economy and living condition of China have improved rapidly, the major human factors that contributed to the increase in emerging infectious diseases are attributed to flaws in meat production system and practice (especially in markets dealing with live poultry, possibly carrying deadly pathogens) and personal behavior, such as unsafe sex, (inter)national transportation, or travel. People are becoming increasingly aware that changing the social or personal behavior associated with the occurrence of infectious diseases for the better can help disease control and prevention. An example of this notion is that the timely shutdown of the potentially dangerous live poultry market had an immediate effect on controlling the outbreaks of avian influenza H7N9, H5N1, and others.

Diseases associated with personal sexual behavior

Tremendous efforts have been exercised to control HIV and other sexually transmitted disease (STD) infections in China over decades. However, the incidence of HIV and syphilis has been increasing according to our surveillance data (Figs. 1 and 2). In the meantime, the seemingly stable status of gonorrhea might be the result of passive reporting practice (Figs. 1 and 2). Economic growth and globalization greatly affect the re-emergence of sex service. A huge migrant population of male workers alone without spouses/partners around have created an increasing demand for sex service. Some of the young people are tempted to experience sex at earlier ages and before marriage, which also changes the sexual practice pattern. Recent findings showed that males who aged over 60 years but are still sexually active are vulnerable to STD [94]. With these factors, preventing the spread of STD, especially syphilis [4], is difficult.

AIDS (HIV) in China, in a sense, is a behavior disease.

The association of HIV transmission with traveling to Thailand has been documented [22]. The first wave of HIV infection in China in the 1990s resulted from commercial plasma donors who were infected with HIV and transmitted the virus to their families and others. The uncontrolled blood-for-sale practice exacerbated the spread of HIV [95]. The second wave of HIV infection was associated with drug abuse. As one of the major underground transfer base for drugs from the “Golden Triangle” and “Gold Crescent” areas in Asia, China has become an increasingly important drug-consuming market with approximately a million documented drug users. Injection drug users have contributed to 42% of HIV/AIDS cases reported so far. Therefore, strengthening government leadership at both central and local levels, scaling up methadone substitution and needle exchange programs, has been a success. Sexual transmission has emerged as the primary mode of HIV transmission in China, with heterosexual transmission through commercial sex as one of the main modes. Infections among men who had sex with other men and transgender individuals are increasing, indicating that more effective strategies are urgently needed to deal with this tough problem. HIV vaccine development is far behind the need of the market, and healthy behavior may be an effective mechanism to stop the epidemic.

Syphilis, one of the top five reported communicable diseases in many major municipalities and provinces, is a sexually transmitted infection caused by the spirochete bacterium. The syphilis incidence rate increased more than 4-fold [96] from 7.1 /100 000 in 2004 to 32.0/100 000 in 2016 (Fig. 2A and Fig. 2B). The rapid spread of syphilis is probably attributable to a combination of biological and social factors.

With limited studies on gonorrhea, comparing it with other STDs is difficult. A study in Guangdong has found that the distribution of gonorrhea cases is weakly associated with that of syphilis [97].

Perspectives on new pathogens of the future

The majority of human emerging infectious diseases are zoonotic. The specific species that will be the likely host(s) for the next human pathogen to cause a large-scale outbreak and the pathogen that can cross species boundaries to pose threat to human health should be predicted and verified. The total number of viruses that infect a given species and the proportion that is likely to be zoonotic are predictable, and these parameters are possible to assess if a newly discovered mammalian virus can infect people [98]. Therefore, the priority for future surveillance should be on the taxa and on the regions with the largest estimated number of missing viruses and missing

zoonoses.

Through RNA sequencing of 70 arthropod species in China, Li *et al.* discovered 112 novel viruses that appear to be ancestral for much of the documented genetic diversity of negative-sense RNA viruses. These arthropods contain viruses that fall basal to major virus groups, including vertebrate-specific arenaviruses, filoviruses, hantaviruses, influenza viruses, lyssaviruses, and paramyxoviruses [99]. Shi *et al.* profiled the transcriptomes of over 220 invertebrate species sampled across nine animal phyla in China and reported the discovery of 1445 RNA viruses, including some that are sufficiently divergent to comprise new families. These data demonstrated that the RNA virosphere is considerably more diverse phylogenetically and genomically than that depicted by current classification schemes [100]. Although the total bacterial species harbored by wild animals remains unknown, the number of bacteria yet to be discovered in the world is estimated to be considerably higher than that of viruses.

Using the new methodology named metataxonomics, researchers can integrate the high-throughput sequencing of almost all full-length small subunit rRNA (16S rRNA) gene amplicons in tandem with the operational phylogenetic unit analysis strategy. Nine vultures from three species in Qinghai-Tibet Plateau harbor 314 OTUs, including 102 known species, in which 50 have yet to be described and 161 unknown new lineages of unculturable representatives have yet to be identified. Forty-five species have been reported to be responsible for human outbreaks or infections. *Clostridium perfringens* is the most abundant in all vultures, and this species accounts for 30.8% of the total reads. Therefore, vultures and other animals can be a reservoir for the soil-related *C. perfringens* and other pathogens [101]. The possible public health significance of those unknown pathogens residing in the virosphere and microbiome of wild animals warrants extensive evaluation.

The assumption that infectious diseases will diminish with improvement in economy, quality of water, food, housing, and nutritional status is incorrect and even misleading. China has achieved great development in economy, and the government has invested heavily in managing infectious diseases after SARS. However, the incidence of overall notifiable infectious diseases was not even reduced but in the rising trend. Other important infectious diseases that are prevalent in developed countries but are not even under our surveillance may also be associated with climate and socioeconomic factors. In other words, the profile of notifiable infectious diseases is shifting as the Chinese economy grows. Approximately half of the notifiable infectious diseases have been reduced significantly, and a few of them have been eradicated or almost eradicated. This result is a success of our tremendous efforts on infectious disease control and prevention. However, the infectious disease profiles change with rapid urbanization, high numbers of migrant

workers, changing climate, ecology and returning farmland to forests, and social and personal behaviors. Some infectious diseases have rebounded and even increased in some areas. Frequently imported infectious diseases have become a common issue for the first time in China since 2015. The incidence of over 10 notifiable infectious diseases has been increasing. Many new pathogens, genotypes, and serotypes of known pathogens have been discovered. Therefore, current strategies based on conventional knowledge are not scientific enough to respond to future challenges and must therefore be re-evaluated and optimized. When deadly pathogens are blamed, we should have an enhanced understanding of the repercussions of development models, society, behavior, ecology, and environment.

Conclusions

In summary, this review suggests that the landscape of emerging and re-emerging infectious diseases in China is closely associated with changes in ecological factors, climate, and social and human behaviors. The experiences we gained and lessons learned in the past few decades should have important implications for some developing countries to prevent and control infectious diseases.

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Compliance with ethics guidelines

Qiyong Liu, Wenbo Xu, Shan Lu, Jiafu Jiang, Jieping Zhou, Zhujun Shao, Xiaobo Liu, Lei Xu, Yanwen Xiong, Han Zheng, Sun Jin, Hai Jiang, Wuchun Cao, and Jianguo Xu declare that they have no financial conflicts of interest. This manuscript is a review article and does not involve a research protocol requiring approval by a relevant institutional review board or ethics committee.

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References

1. Tong MX, Hansen A, Hanson-Easey S, Cameron S, Xiang J, Liu Q, Sun Y, Weinstein P, Han GS, Williams C, Bi P. Infectious diseases, urbanization and climate change: challenges in future

- China. *Int J Environ Res Public Health* 2015; 12(9): 11025–11036
2. Xu JG. Behavioral and ecological infectious diseases: from SARS to H7N9 avian influenza outbreak in China. *Chin J Epidemiol (Zhonghua Liu Xing Bing Xue Za Zhi)* 2013; 34(5): 417–418 (in Chinese)
 3. Lu J, Milinovich GJ, Hu W. A brief historical overview of emerging infectious disease response in China and the need for a One Health approach in future responses. *One Health* 2016; 2: 99–102
 4. Yang S, Wu J, Ding C, Cui Y, Zhou Y, Li Y, Deng M, Wang C, Xu K, Ren J, Ruan B, Li L. Epidemiological features of and changes in incidence of infectious diseases in China in the first decade after the SARS outbreak: an observational trend study. *Lancet Infect Dis* 2017; 17(7): 716–725
 5. Yang W, Li Z, Lan Y, Wang J, Ma J, Jin L, Sun Q, Lv W, Lai S, Liao Y, Hu W. A nationwide web-based automated system for early outbreak detection and rapid response in China. *Western Pac Surveill Response J* 2011; 2(1): 10–15
 6. Luo HM, Zhang Y, Wang XQ, Yu WZ, Wen N, Yan DM, Wang HQ, Wushouer F, Wang HB, Xu AQ, Zheng JS, Li DX, Cui H, Wang JP, Zhu SL, Feng ZJ, Cui FQ, Ning J, Hao LX, Fan CX, Ning GJ, Yu HJ, Wang SW, Liu DW, Wang DY, Fu JP, Gou AL, Zhang GM, Huang GH, Chen YS, Mi SS, Liu YM, Yin DP, Zhu H, Fan XC, Li XL, Ji YX, Li KL, Tang HS, Xu WB, Wang Y, Yang WZ. Identification and control of a poliomyelitis outbreak in Xinjiang, China. *N Engl J Med* 2013; 369(21): 1981–1990
 7. Stone R. China. Race to contain plague in quake zone. *Science* 2010; 328(5978): 559
 8. Yu D. Prevention of plague in China in last 50 years. *Chin J Epidemiol (Zhonghua Liu Xing Bing Xue Za Zhi)* 2000; 21(4): 300–303 (in Chinese)
 9. Liang X, Bi S, Yang W, Wang L, Cui G, Cui F, Zhang Y, Liu J, Gong X, Chen Y, Wang F, Zheng H, Wang F, Guo J, Jia Z, Ma J, Wang H, Luo H, Li L, Jin S, Hadler SC, Wang Y. Evaluation of the impact of hepatitis B vaccination among children born during 1992–2005 in China. *J Infect Dis* 2009; 200(1): 39–47
 10. Xiao J, Lin H, Liu T, Zeng W, Li X, Shao X, Tan Q, Xu Y, Xu X, Zheng H, Ma W. Disease burden from hepatitis B virus infection in Guangdong Province, China. *Int J Environ Res Public Health* 2015; 12(11): 14055–14067
 11. Yezhou L. The National Immunization Plan: China. *Australas Med J* 2010; 3(7): 375–379
 12. Luo HM, Zhang Y, Wang XQ, Yu WZ, Wen N, Yan DM, Wang HQ, Wushouer F, Wang HB, Xu AQ, Zheng JS, Li DX, Cui H, Wang JP, Zhu SL, Feng ZJ, Cui FQ, Ning J, Hao LX, Fan CX, Ning GJ, Yu HJ, Wang SW, Liu DW, Wang DY, Fu JP, Gou AL, Zhang GM, Huang GH, Chen YS, Mi SS, Liu YM, Yin DP, Zhu H, Fan XC, Li XL, Ji YX, Li KL, Tang HS, Xu WB, Wang Y, Yang WZ. Identification and control of a poliomyelitis outbreak in Xinjiang, China. *N Engl J Med* 2013; 369(21): 1981–1990
 13. Zhang S, Li RT, Wang Y, Liu Q, Zhou YH, Hu Y. Seroprevalence of hepatitis B surface antigen among pregnant women in Jiangsu, China, 17 years after introduction of hepatitis B vaccine. *Int J Gynaecol Obstet* 2010; 109(3): 194–197
 14. Lin H, Zou H, Wang Q, Liu C, Lang L, Hou X, Li Z. Short-term effect of El Niño-Southern Oscillation on pediatric hand, foot and mouth disease in Shenzhen, China. *PLoS One* 2013; 8(7): e65585
 15. Zhang Y, Zhu Z, Yang W, Ren J, Tan X, Wang Y, Mao N, Xu S, Zhu S, Cui A, Zhang Y, Yan D, Li Q, Dong X, Zhang J, Zhao Y, Wan J, Feng Z, Sun J, Wang S, Li D, Xu W. An emerging recombinant human enterovirus 71 responsible for the 2008 outbreak of hand foot and mouth disease in Fuyang city of China. *Virology* 2010; 7(1): 94
 16. Ding ZS. An outbreak of water-borne infection by viral hepatitis A. *Chin J Epidemiol (Zhonghua Liu Xing Bing Xue Za Zhi)* 1982; 3(2): 80–83 (in Chinese)
 17. Yan YC. Preliminary investigation on the etiology and host animals of epidemic hemorrhagic fever in Honan. *Chin J Epidemiol (Zhonghua Liu Xing Bing Xue Za Zhi)* 1982; 3(4): 197–200 (in Chinese)
 18. Hung T, Chen GM, Wang CG, Yao HL, Fang ZY, Chao TX, Chou ZY, Ye W, Chang XJ, Den SS, *et al.* Waterborne outbreak of rotavirus diarrhoea in adults in China caused by a novel rotavirus. *Lancet* 1984; 1(8387): 1139–1142
 19. Lin H, Zhang Z, Lu L, Li X, Liu Q. Meteorological factors are associated with hemorrhagic fever with renal syndrome in Jiaonan County, China, 2006–2011. *Int J Biometeorol* 2014; 58(6): 1031–1037
 20. Zhang ZF. Investigation of Lyme disease in northeast of China. *Chin J Epidemiol (Zhonghua Liu Xing Bing Xue Za Zhi)* 1989; 10(5): 261–264 (in Chinese)
 21. Wang HY. Investigation of an outbreak of HNANB[E] in Shufu County, Xinjiang. *Chin J Epidemiol (Zhonghua Liu Xing Bing Xue Za Zhi)* 1989; 10(5): 270–273 (in Chinese)
 22. Zeng Y. HIV infection and AIDS in China. *Arch AIDS Res* 1992; 6(1-2): 1–5
 23. Zhang TC. Epidemiologic studies of enteritis caused by *Campylobacter jejuni*. IV. A study of the principal reservoir hosts. *Chin J Epidemiol (Zhonghua Liu Xing Bing Xue Za Zhi)* 1985; 6(1): 26–28 (in Chinese)
 24. Deng C. A report on investigation of an outbreak of Legionnaires' disease in a hotel in Beijing. *Chin J Epidemiol (Zhonghua Liu Xing Bing Xue Za Zhi)* 1993; 14(2): 78–80 (in Chinese)
 25. Qu M, Xu J, Ding Y, Wang R, Liu P, Kan B, Qi G, Liu Y, Gao S. Molecular epidemiology of *Vibrio cholerae* O139 in China: polymorphism of ribotypes and CTX elements. *J Clin Microbiol* 2003; 41(6): 2306–2310
 26. Hu X, Zhu F, Wang H, Chen S, Wang G, Sun J, Hua C, Yang H. Studies on human streptococcal infectious syndrome caused by infected pigs. *Chin J Epidemiol (Zhonghua Liu Xing Bing Xue Za Zhi)* 2000; 34(3): 150–152 (in Chinese)
 27. Xu J, Cheng B, Feng L, Jing H, Yang J, Zhao G, Wang H, Li H. Serological investigations on patients with hemolytic uremic syndromes due to enterohemorrhagic *Escherichia coli* O157:H7 infection. *Chin J Epidemiol (Zhonghua Liu Xing Bing Xue Za Zhi)* 2002; 23(2): 114–118 (in Chinese)
 28. Enserink M. SARS in China. China's missed chance. *Science* 2003; 301(5631): 294–296
 29. Shao Z, Li W, Ren J, Liang X, Xu L, Diao B, Li M, Lu M, Ren H, Cui Z, Zhu B, Dai Z, Zhang L, Chen X, Kan B, Xu J. Identification of a new *Neisseria meningitidis* serogroup C clone from Anhui Province, China. *Lancet* 2006; 367(9508): 419–423
 30. Ye C, Zhu X, Jing H, Du H, Segura M, Zheng H, Kan B, Wang L, Bai X, Zhou Y, Cui Z, Zhang S, Jin D, Sun N, Luo X, Zhang J,

- Gong Z, Wang X, Wang L, Sun H, Li Z, Sun Q, Liu H, Dong B, Ke C, Yuan H, Wang H, Tian K, Wang Y, Gottschalk M, Xu J. *Streptococcus suis* sequence type 7 outbreak, Sichuan, China. *Emerg Infect Dis* 2006; 12(8): 1203–1208
31. Liu J, Xiao H, Lei F, Zhu Q, Qin K, Zhang XW, Zhang XL, Zhao D, Wang G, Feng Y, Ma J, Liu W, Wang J, Gao GF. Highly pathogenic H5N1 influenza virus infection in migratory birds. *Science* 2005; 309(5738): 1206
 32. Zhang L, Liu Y, Ni D, Li Q, Yu Y, Yu XJ, Wan K, Li D, Liang G, Jiang X, Jing H, Run J, Luan M, Fu X, Zhang J, Yang W, Wang Y, Dumler JS, Feng Z, Ren J, Xu J. Nosocomial transmission of human granulocytic anaplasmosis in China. *JAMA* 2008; 300(19): 2263–2270
 33. Cao B, Li XW, Mao Y, Wang J, Lu HZ, Chen YS, Liang ZA, Liang L, Zhang SJ, Zhang B, Gu L, Lu LH, Wang DY, Wang C; National Influenza A Pandemic (H1N1) 2009 Clinical Investigation Group of China. Clinical features of the initial cases of 2009 pandemic influenza A (H1N1) virus infection in China. *N Engl J Med* 2009; 361(26): 2507–2517
 34. Zhang YZ, Zhou DJ, Xiong Y, Chen XP, He YW, Sun Q, Yu B, Li J, Dai YA, Tian JH, Qin XC, Jin D, Cui Z, Luo XL, Li W, Lu S, Wang W, Peng JS, Guo WP, Li MH, Li ZJ, Zhang S, Chen C, Wang Y, de Jong MD, Xu J. Hemorrhagic fever caused by a novel tick-borne Bunyavirus in Huaiyangshan, China. *Chin J Epidemiol (Zhonghua Liu Xing Bing Xue Za Zhi)* 2011; 32(3): 209–220 (in Chinese)
 35. Yu XJ, Liang MF, Zhang SY, Liu Y, Li JD, Sun YL, Zhang L, Zhang QF, Popov VL, Li C, Qu J, Li Q, Zhang YP, Hai R, Wu W, Wang Q, Zhan FX, Wang XJ, Kan B, Wang SW, Wan KL, Jing HQ, Lu JX, Yin WW, Zhou H, Guan XH, Liu JF, Bi ZQ, Liu GH, Ren J, Wang H, Zhao Z, Song JD, He JR, Wan T, Zhang JS, Fu XP, Sun LN, Dong XP, Feng ZJ, Yang WZ, Hong T, Zhang Y, Walker DH, Wang Y, Li DX. Fever with thrombocytopenia associated with a novel bunyavirus in China. *N Engl J Med* 2011; 364(16): 1523–1532
 36. Xu B, Liu L, Huang X, Ma H, Zhang Y, Du Y, Wang P, Tang X, Wang H, Kang K, Zhang S, Zhao G, Wu W, Yang Y, Chen H, Mu F, Chen W. Metagenomic analysis of fever, thrombocytopenia and leukopenia syndrome (FTLS) in Henan Province, China: discovery of a new bunyavirus. *PLoS Pathog* 2011; 7(11): e1002369
 37. Gao R, Cao B, Hu Y, Feng Z, Wang D, Hu W, Chen J, Jie Z, Qiu H, Xu K, Xu X, Lu H, Zhu W, Gao Z, Xiang N, Shen Y, He Z, Gu Y, Zhang Z, Yang Y, Zhao X, Zhou L, Li X, Zou S, Zhang Y, Li X, Yang L, Guo J, Dong J, Li Q, Dong L, Zhu Y, Bai T, Wang S, Hao P, Yang W, Zhang Y, Han J, Yu H, Li D, Gao GF, Wu G, Wang Y, Yuan Z, Shu Y. Human infection with a novel avian-origin influenza A (H7N9) virus. *N Engl J Med* 2013; 368(20): 1888–1897
 38. Xu L, Stige LC, Chan KS, Zhou J, Yang J, Sang S, Wang M, Yang Z, Yan Z, Jiang T, Lu L, Yue Y, Liu X, Lin H, Xu J, Liu Q, Stenseth NC. Climate variation drives dengue dynamics. *Proc Natl Acad Sci USA* 2017; 114(1): 113–118
 39. Lu Z, Fu SH, Cao L, Tang CJ, Zhang S, Li ZX, Tusong M, Yao XH, Zhang HL, Wang PY, Wumaier M, Yuan XY, Li MH, Zhu CZ, Fu LP, Liang GD. Human infection with West Nile Virus, Xinjiang, China, 2011. *Emerg Infect Dis* 2014; 20(8): 1421–1423
 40. Deng YQ, Zhao H, Li XF, Zhang NN, Liu ZY, Jiang T, Gu DY, Shi L, He JA, Wang HJ, Sun ZZ, Ye Q, Xie DY, Cao WC, Qin CF. Isolation, identification and genomic characterization of the Asian lineage Zika virus imported to China. *Sci China Life Sci* 2016; 59(4): 428–430
 41. Ling Y, Chen J, Huang Q, Hu Y, Zhu A, Ye S, Xu L, Lu H. Yellow fever in a worker returning to China from Angola, March 2016. *Emerg Infect Dis* 2016; 22(7): 1317–1318
 42. Liu W, Sun FJ, Tong YG, Zhang SQ, Cao WC. Rift Valley fever virus imported into China from Angola. *Lancet Infect Dis* 2016; 16(11): 1226
 43. Wu J, Yi L, Zou L, Zhong H, Liang L, Song T, Song Y, Su J, Ke C. Imported case of MERS-CoV infection identified in China, May 2015: detection and lesson learned. *Euro Surveill* 2015; 20(24): 21158
 44. Li H, Zheng YC, Ma L, Jia N, Jiang BG, Jiang RR, Huo QB, Wang YW, Liu HB, Chu YL, Song YD, Yao NN, Sun T, Zeng FY, Dumler JS, Jiang JF, Cao WC. Human infection with a novel tick-borne *Anaplasma* species in China: a surveillance study. *Lancet Infect Dis* 2015; 15(6): 663–670
 45. Ye C, Lan R, Xia S, Zhang J, Sun Q, Zhang S, Jing H, Wang L, Li Z, Zhou Z, Zhao A, Cui Z, Cao J, Jin D, Huang L, Wang Y, Luo X, Bai X, Wang Y, Wang P, Xu Q, Xu J. Emergence of a new multidrug-resistant serotype X variant in an epidemic clone of *Shigella flexneri*. *J Clin Microbiol* 2010; 48(2): 419–426
 46. Lu Z, Lu XJ, Fu SH, Zhang S, Li ZX, Yao XH, Feng YP, Lambert AJ, Ni X, Wang FT, Tong SX, Nasci RS, Feng Y, Dong Q, Zhai YG, Gao XY, Wang HY, Tang Q, Liang GD. Tahyna virus and human infection, China. *Emerg Infect Dis* 2009; 15(2): 306–309
 47. Jiang JF, Zheng YC, Jiang RR, Li H, Huo QB, Jiang BG, Sun Y, Jia N, Wang YW, Ma L, Liu HB, Chu YL, Ni XB, Liu K, Song YD, Yao NN, Wang H, Sun T, Cao WC. Epidemiological, clinical, and laboratory characteristics of 48 cases of “Babesia venatorum” infection in China: a descriptive study. *Lancet Infect Dis* 2015; 15(2): 196–203
 48. Jia N, Jiang JF, Huo QB, Jiang BG, Cao WC. *Rickettsia sibirica* subspecies *sibirica* BJ-90 as a cause of human disease. *N Engl J Med* 2013; 369(12): 1176–1178
 49. Liu W, Li H, Lu QB, Cui N, Yang ZD, Hu JG, Fan YD, Guo CT, Li XK, Wang YW, Liu K, Zhang XA, Yuan L, Zhao PY, Qin SL, Cao WC. Candidatus *Rickettsia tarasevichiae* infection in Eastern Central China: a case series. *Ann Intern Med* 2016; 164(10): 641–648
 50. Jia N, Zheng YC, Ma L, Huo QB, Ni XB, Jiang BG, Chu YL, Jiang RR, Jiang JF, Cao WC. Human infections with *Rickettsia raoultii*, China. *Emerg Infect Dis* 2014; 20(5): 866–868
 51. Ni XB, Jia N, Jiang BG, Sun T, Zheng YC, Huo QB, Liu K, Ma L, Zhao QM, Yang H, Wang X, Jiang JF, Cao WC. Lyme borreliosis caused by diverse genospecies of *Borrelia burgdorferi* sensu lato in northeastern China. *Clin Microbiol Infect* 2014; 20(8): 808–814
 52. Pan H, Li X, Ge D, Wang S, Wu Q, Xie W, Jiao X, Chu D, Liu B, Xu B, Zhang Y. Factors affecting population dynamics of maternally transmitted endosymbionts in *Bemisia tabaci*. *PLoS One* 2012; 7(2): e30760
 53. Walsh MP, Seto J, Jones MS, Chodosh J, Xu W, Seto D. Computational analysis identifies human adenovirus type 55 as a re-emergent acute respiratory disease pathogen. *J Clin Microbiol* 2010; 48(3): 991–993

54. Shi Q, Zhou W, Chen C, Gao C, Xiao K, Wang J, Zhang BY, Wang Y, Zhang F, Dong XP. Quality evaluation for the surveillance system of human prion diseases in China based on the data from 2010 to 2016. *Prion* 2016; 10(6): 484–491
55. Zhang YZ, He YW, Dai YA, Xiong Y, Zheng H, Zhou DJ, Li J, Sun Q, Luo XL, Cheng YL, Qin XC, Tian JH, Chen XP, Yu B, Jin D, Guo WP, Li W, Wang W, Peng JS, Zhang GB, Zhang S, Chen XM, Wang Y, Li MH, Li Z, Lu S, Ye C, de Jong MD, Xu J. Hemorrhagic fever caused by a novel Bunyavirus in China: pathogenesis and correlates of fatal outcome. *Clin Infect Dis* 2012; 54(4): 527–533
56. Zhu B, Xu Z, Du P, Xu L, Sun X, Gao Y, Shao Z. Sequence type 4821 clonal complex serogroup B *Neisseria meningitidis* in China, 1978–2013. *Emerg Infect Dis* 2015; 21(6): 925–932
57. Du P, Zheng H, Zhou J, Lan R, Ye C, Jing H, Jin D, Cui Z, Bai X, Liang J, Liu J, Xu L, Zhang W, Chen C, Xu J. Detection of multiple parallel transmission outbreak of *Streptococcus suis* human infection by use of genome epidemiology, China, 2005. *Emerg Infect Dis* 2017; 23(2): 204–211
58. Ye C, Zheng H, Zhang J, Jing H, Wang L, Xiong Y, Wang W, Zhou Z, Sun Q, Luo X, Du H, Gottschalk M, Xu J. Clinical, experimental, and genomic differences between intermediately pathogenic, highly pathogenic, and epidemic *Streptococcus suis*. *J Infect Dis* 2009; 199(1): 97–107
59. Xiong Y, Wang P, Lan R, Ye C, Wang H, Ren J, Jing H, Wang Y, Zhou Z, Bai X, Cui Z, Luo X, Zhao A, Wang Y, Zhang S, Sun H, Wang L, Xu J. A novel *Escherichia coli* O157:H7 clone causing a major hemolytic uremic syndrome outbreak in China. *PLoS One* 2012; 7(4): e36144
60. Zhang N, Lan R, Sun Q, Wang J, Wang Y, Zhang J, Yu D, Hu W, Hu S, Dai H, Du P, Wang H, Xu J. Genomic portrait of the evolution and epidemic spread of a recently emerged multidrug-resistant *Shigella flexneri* clone in China. *J Clin Microbiol* 2014; 52(4): 1119–1126
61. Lu QB, Tong YG, Wo Y, Wang HY, Liu EM, Gray GC, Liu W, Cao WC. Epidemiology of human adenovirus and molecular characterization of human adenovirus 55 in China, 2009–2012. *Influenza Other Respir Viruses* 2014; 8(3): 302–308
62. Chen M, Zhu Z, Huang F, Liu D, Zhang T, Ying D, Wu J, Xu W. Adenoviruses associated with acute respiratory diseases reported in Beijing from 2011 to 2013. *PLoS One* 2015; 10(3): e0121375
63. Huang G, Yao W, Yu W, Mao L, Sun H, Yao W, Tian J, Wang L, Bo Z, Zhu Z, Zhang Y, Zhao Z, Xu W. Outbreak of epidemic keratoconjunctivitis caused by human adenovirus type 56, China, 2012. *PLoS One* 2014; 9(10): e110781
64. Mei YF, Skog J, Lindman K, Wadell G. Comparative analysis of the genome organization of human adenovirus 11, a member of the human adenovirus species B, and the commonly used human adenovirus 5 vector, a member of species C. *J Gen Virol* 2003; 84(8): 2061–2071
65. Zhang YZ, Xu J. The emergence and cross species transmission of newly discovered tick-borne *Bunyavirus* in China. *Curr Opin Virol* 2016; 16: 126–131
66. Dong X, Chen XP, Liu N, Dumler SJ, Zhang YZ. Co-circulation of multiple species of Rickettsiales bacteria in one single species of hard ticks in Shenyang, China. *Ticks Tick Borne Dis* 2014; 5(6): 727–733
67. Li K, Lin XD, Wang W, Shi M, Guo WP, Zhang XH, Xing JG, He JR, Wang K, Li MH, Cao JH, Jiang ML, Holmes EC, Zhang YZ. Isolation and characterization of a novel arenavirus harbored by rodents and shrews in Zhejiang Province, China. *Virology* 2015; 476: 37–42
68. Blasdel KR, Duong V, Eloitt M, Chretien F, Ly S, Hul V, Deubel V, Morand S, Buchy P. Evidence of human infection by a new mammarenavirus endemic to Southeastern Asia. *eLife* 2016; 5: e1313519
69. Zhang JZ, Fan MY, Bi DZ, Cui WF, Han YF. Genotypic identification of three new strains of spotted fever group rickettsiae isolated in China. *Acta Virol* 1996; 40(4): 215–219
70. Chen XP, Dong YJ, Guo WP, Wang W, Li MH, Xu J, Dumler JS, Zhang YZ. Detection of *Wolbachia* genes in a patient with non-Hodgkin's lymphoma. *Clin Microbiol Infect* 2015; 21(2): 182 e181–184
71. Fang LQ, Liu K, Li XL, Liang S, Yang Y, Yao HW, Sun RX, Sun Y, Chen WJ, Zuo SQ, Ma MJ, Li H, Jiang JF, Liu W, Yang XF, Gray GC, Krause PJ, Cao WC. Emerging tick-borne infections in mainland China: an increasing public health threat. *Lancet Infect Dis* 2015; 15(12): 1467–1479
72. Lu L, Lin H, Tian L, Yang W, Sun J, Liu Q. Time series analysis of dengue fever and weather in Guangzhou, China. *BMC Public Health* 2009; 9(1): 395
73. Lin H, Liu T, Song T, Lin L, Xiao J, Lin J, He J, Zhong H, Hu W, Deng A, Peng Z, Ma W, Zhang Y. Community involvement in Dengue outbreak control: an integrated rigorous intervention strategy. *PLoS Negl Trop Dis* 2016; 10(8): e0004919
74. Lai S, Zhou H, Xiong W, Gilbert M, Huang Z, Yu J, Yin W, Wang L, Chen Q, Li Y, Mu D, Zeng L, Ren X, Geng M, Zhang Z, Cui B, Li T, Wang D, Li Z, Wardrop NA, Tatem AJ, Yu H. Changing epidemiology of human brucellosis, China, 1955–2014. *Emerg Infect Dis* 2017; 23(2): 184–194
75. Pappas G, Papadimitriou P, Akritidis N, Christou L, Tsianos EV. The new global map of human brucellosis. *Lancet Infect Dis* 2006; 6(2): 91–99
76. Kan B, Wang M, Jing H, Xu H, Jiang X, Yan M, Liang W, Zheng H, Wan K, Liu Q, Cui B, Xu Y, Zhang E, Wang H, Ye J, Li G, Li M, Cui Z, Qi X, Chen K, Du L, Gao K, Zhao YT, Zou XZ, Feng YJ, Gao YF, Hai R, Yu D, Guan Y, Xu J. Molecular evolution analysis and geographic investigation of severe acute respiratory syndrome coronavirus-like virus in palm civets at an animal market and on farms. *J Virol* 2005; 79(18): 11892–11900
77. Wang M, Yan M, Xu H, Liang W, Kan B, Zheng B, Chen H, Zheng H, Xu Y, Zhang E, Wang H, Ye J, Li G, Li M, Cui Z, Liu YF, Guo RT, Liu XN, Zhan LH, Zhou DH, Zhao A, Hai R, Yu D, Guan Y, Xu J. SARS-CoV infection in a restaurant from palm civet. *Emerg Infect Dis* 2005; 11(12): 1860–1865
78. Wang M, Di B, Zhou DH, Zheng BJ, Jing H, Lin YP, Liu YF, Wu XW, Qin PZ, Wang YL, Jian LY, Li XZ, Xu JX, Lu EJ, Li TG, Xu J. Food markets with live birds as source of avian influenza. *Emerg Infect Dis* 2006; 12(11): 1773–1775
79. Xu J, Lu S, Wang H, Chen C. Reducing exposure to avian influenza H7N9. *Lancet* 2013; 381(9880): 1815–1816
80. Yu H, Wu JT, Cowling BJ, Liao Q, Fang VJ, Zhou S, Wu P, Zhou H, Lau EH, Guo D, Ni MY, Peng Z, Feng L, Jiang H, Luo H, Li Q, Feng Z, Wang Y, Yang W, Leung GM. Effect of closure of live

- poultry markets on poultry-to-person transmission of avian influenza A H7N9 virus: an ecological study. *Lancet* 2014; 383(9916): 541–548
81. Pang B, Jing H, Zheng H, Sun H, Zhao A, Xu J. Molecular typing of Shiga-toxin producing *Escherichia coli* O157:H7 isolated in China with pulsed field gel electrophoresis. *Chin J Epidemiol (Zhonghua Liu Xing Bing Xue Za Zhi)* 2002; 23(2): 123–126 (in Chinese)
 82. Meng Q, Xiong Y, Lan R, Ye C, Wang T, Qi T, Wang Y, Wang H, Bai X, Bai X, Ji S, Jin D, Yuan X, Zhao A, Sun H, Jing H, Xu J. SNP genotyping of enterohemorrhagic *Escherichia coli* O157:H7 isolates from China and genomic identity of the 1999 Xuzhou outbreak. *Infect Genet Evol* 2013; 16: 275–281
 83. Xia N, Zhang J, Li S, Ge S, Wu T, Zheng Z, Wu W, Shi W. Advances in research on HEV. *J Xiamen Univ (Natural Science Edition) (Xiamen Da Xue Xue Bao (Zi Ran Ke Xue Ban))* 2011; 50(2): 431–436 (in Chinese)
 84. Zhang W, He Y, Wang H, Shen Q, Cui L, Wang X, Shao S, Hua X. Hepatitis E virus genotype diversity in eastern China. *Emerg Infect Dis* 2010; 16(10): 1630–1632
 85. Ning H, Niu Z, Yu R, Zhang P, Dong S, Li Z. Identification of genotype 3 hepatitis E virus in fecal samples from a pig farm located in a Shanghai suburb. *Vet Microbiol* 2007; 121(1-2): 125–130
 86. Liu P, Li L, Wang L, Bu Q, Fu H, Han J, Zhu Y, Lu F, Zhuang H. Phylogenetic analysis of 626 hepatitis E virus (HEV) isolates from humans and animals in China (1986–2011) showing genotype diversity and zoonotic transmission. *Infect Genet Evol* 2012; 12(2): 428–434
 87. Kyle JL, Harris E. Global spread and persistence of dengue. *Annu Rev Microbiol* 2008; 62(1): 71–92
 88. Wang L, Zhou P, Fu X, Zheng Y, Huang S, Fang B, Zhang G, Jia K, Li S. Yellow fever virus: Increasing imported cases in China. *J Infect* 2016; 73(4): 377–380
 89. Xiang B, Gao P, Kang Y, Ren T. Importation of Zika Virus in China: a significant risk in southern China. *J Infect* 2017; 74(3): 328–330
 90. Song T, Kang M, Zhang Y, Liang L, Lin H. Elements of successful management of an imported Middle East respiratory syndrome case in Guangdong, China. *Western Pac Surveill Response J* 2015; 6(4): 33–34
 91. Lin H, Lu L, Tian L, Zhou S, Wu H, Bi Y, Ho SC, Liu Q. Spatial and temporal distribution of falciparum malaria in China. *Malar J* 2009; 8(1): 130
 92. Sang S, Chen B, Wu H, Yang Z, Di B, Wang L, Tao X, Liu X, Liu Q. Dengue is still an imported disease in China: a case study in Guangzhou. *Infect Genet Evol* 2015; 32:178–190
 93. Li X, Liu T, Lin L, Song T, Du X, Lin H, Xiao J, He J, Liu L, Zhu G, Zeng W, Guo L, Cao Z, Ma W, Zhang Y. Application of the analytic hierarchy approach to the risk assessment of Zika virus disease transmission in Guangdong Province, China. *BMC Infect Dis* 2017; 17(1): 65
 94. Liu AY, Zang WJ, Yuan LL, Chai YL, Wang S. Latent syphilis among inpatients in an urban area of China. *Glob J Health Sci* 2014; 7(3): 249–253
 95. Wu Z, Rou K, Detels R. Prevalence of HIV infection among former commercial plasma donors in rural eastern China. *Health Policy Plan* 2001; 16(1): 41–46
 96. Chen ZQ, Zhang GC, Gong XD, Lin C, Gao X, Liang GJ, Yue XL, Chen XS, Cohen MS. Syphilis in China: results of a national surveillance programme. *Lancet* 2007; 369(9556): 132–138
 97. Tan NX, Messina JP, Yang LG, Yang B, Emch M, Chen XS, Cohen MS, Tucker JD. A spatial analysis of county-level variation in syphilis and gonorrhoea in Guangdong Province, China. *PLoS One* 2011; 6(5): e19648
 98. Olival KJ, Hosseini PR, Zambrana-Torrel C, Ross N, Bogich TL, Daszak P. Host and viral traits predict zoonotic spillover from mammals. *Nature* 2017; 546(7660): 646–650
 99. Li CX, Shi M, Tian JH, Lin XD, Kang YJ, Chen LJ, Qin XC, Xu J, Holmes EC, Zhang YZ. Unprecedented genomic diversity of RNA viruses in arthropods reveals the ancestry of negative-sense RNA viruses. *eLife* 2015; 4:e05378
 100. Shi M, Lin XD, Tian JH, Chen LJ, Chen X, Li CX, Qin XC, Li J, Cao JP, Eden JS, Buchmann J, Wang W, Xu J, Holmes EC, Zhang YZ. Redefining the invertebrate RNA virosphere. *Nature* 2016; 540(7634): 539–543
 101. Meng X, Lu S, Yang J, Jin D, Wang X, Bai X, Wen Y, Wang Y, Niu L, Ye C, Rosselló-Móra R, Xu J. Metatranscriptomics reveal vultures as a reservoir for *Clostridium perfringens*. *Emerg Microbes Infect* 2017; 6(2): e9