Etiological, epidemiological, and clinical features of diarrhea in China

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Summary

Background: Acute diarrhea is a serious cause of mortality and morbidity in China.

Methods: National-based prospective surveillance of all-age diarrheal patients were conducted in 217 sentinel hospitals of 31 provinces in Chinese mainland between 2009–2018. Twenty-three pathogens were detected and compared regarding demographic, epidemiological characteristics, and ecological determinants.

Findings: 152 792 eligible patients were enrolled for etiological tests. Rotavirus A and norovirus were two leading viral pathogens detected in 20·40% and 12·47% of the patients, followed by adenovirus (3·33%) and astrovirus (2·77%). Diarrheagenic *Escherichia coli* and nontyphoidal *Salmonella* were two leading bacterial pathogens detected in 6·71% and 4·41% of the patients, followed by *Shigella* (2·44%) and *V. parahaemolyticus* (2·08%). Patients aged <5 years had higher overall detection rate of viral pathogens, while bacterial pathogens were more common in patients aged 18–45 years. Joinpoint analysis showed the full picture of age-specific detection rate for individual pathogens. The daily mean temperature had significantly affected most of detected viruses and bacteria, but with different directions of effects. The proportion of children and elderly significantly affected viral infection to a greater extent, while the population density affected bacterial infection more. The presence of respiratory symptoms, neurological, and gastrointestinal symptoms varied significantly by bacterial or viral single infection, which could be applied in the differential diagnosis.

Interpretation: The current findings fill crucial gaps in our knowledge of how the enteropathogens change in diarrheal patients, which allows enhanced identification of predominant diarrheal pathogens candidates for diagnosis in clinical practice and targeted prevention control.

Introduction

Diarrhea remains one of the major causes of disease burden worldwide, despite significant progress in sanitation status and public health awareness.[1-3] Nearly 4·4 billion cases and 1·6 million deaths (ranking eighth as common cause of life loss) due to diarrhea occur worldwide,[1] causing substantial medical and healthcare costs and a high economic impact on society. Evidence shows that diarrheal disease is a major contributor to pediatrics morbidity and mortality, especially in developing countries.[4] More than 0·5 million of diarrheal deaths occurred among children younger than 5 years globally in 2017, 88% of which occurred in south Asia and sub-Saharan Africa.[5] The etiology of acute diarrhea differs between regions depending on economic development, local climate, and geography. Better understanding of the epidemiology, etiology and seasonality of acute diarrhea would be valuable for planning and adopting targeted preventive measures and antimicrobial therapy.

China is one of the 15 countries with high-incidence of diarrhea.[6] Although there are numerous studies that investigated the gastrointestinal pathogens in acute diarrhea,[7-9] the previous studies were subject to major limitations such as small specimen size, limited coverage area, surveillance duration, tested pathogens and catchment population. In addition, pooled data analysis was hindered by inconsistent detection assay among studies. Here based on a national surveillance network for the patients with acute diarrhea, we made the first try to identify the etiological, epidemiological and clinical features of acute diarrhea in all-age population for a prolonged duration in China. It is anticipated that long-term continuous collection of surveillance data will be reasonably representative of the patients to a wide range, and would be valuable for planning and adopting targeted preventive measures and therapy.

Methods

The active surveillance system

Between January 2009 and December 2018, an active surveillance on patients with acute diarrhea was administered in 217 sentinel hospitals and 95 reference

laboratories in all 31 provinces (autonomous regions or municipalities) in Chinese mainland which was managed by Chinese Center for Diseases Control and Prevention (China CDC) (appendix p 5). The sentinel sites were chosen after careful consideration of surveillance and laboratory testing capacities and representation of geographical locations (appendix p 2). All participating hospitals and laboratories used a surveillance protocol that included guidelines for patient enrollment, specimen collection, laboratory testing, data management and other related standard operating procedures (SOP) that were developed by China CDC.[10] A case of diarrhea was defined as the presence ≥3 passages of watery, loose, mucus-, or bloody-stools within a 24-h period. Patients referred from other hospitals or patients not initially diagnosed in sentinel hospitals or patients with non-infectious disease were excluded from this study.[7]

Specimen collection and laboratory tests

For all participating patients, stool specimens were collected immediately after they were admitted into the hospital and before therapy was administered. For virological and parasitological testing, stool was collected in sterilized containers without preservatives and tested as soon as possible, and if not, were stored at -80 °C until tested. For bacteriological testing, stool specimen was collected using 5 sterilized cotton swabs and immediately plated onto culture medium, and if not, were placed in Cary Blair Medium at 4 °C for transporting to the laboratory.

Seven viral pathogens were tested from the stool specimens. Rotavirus A antigen was detected by enzyme-linked immunosorbent assay (ELISA), and G and P genotyping was performed by reverse transcription-polymerase chain reaction (RT-PCR). Detection of norovirus, adenovirus, astrovirus and sapovirus, rotavirus B and rotavirus C was performed by polymerase chain reaction (PCR) or RT-PCR. Thirteen bacterial pathogens were tested by performing isolation with or without enrichment procedures at the first step. For *Yersinia enterocolitica* (*Y. enterocolitica*), *Yersinia pseudotuberculosis* (*Y. pseudotuberculosis*), diarrheagenic *Escherichia coli* (DEC), *Campylobacter jejuni* (*C. jejuni*) and *Campylobacter coli* (*C. coli*), the isolation was

subsequently tested by PCR, and for nontyphoidal *Salmonella* (NTS), *Vibrio parahaemolyticus* (*V. parahaemolyticus*), *Vibrio cholerae* (*V. cholerae*), *Vibrio fluvialis* (*V. fluvialis*), *Vibrio mimicus* (*V. mimicus*), *Aeromonas hydrophila* (*A. hydrophila*), *Plesiomonas shigelloides* (*P. shigelloides*) and *Shigella*, the isolation was subsequently tested by biochemical and serological assays. Altogether three parasites, including *Entamoeba histolytica* (*E. histolytica*), *Giardia lamblia* (*G. lamblia*) and *Cryptosporidium* were tested by direct microscopy, commercial immunoassay, and PCR as guided (appendix p 6). The surveillance and laboratory test protocol was reviewed and approved by the ethical review committees of China CDC.

Statistical analysis

Individual data about demography, clinical manifestations, laboratory testing results, medication use, and outcomes were collected by reviewing medical records and the data were entered into a standardized database by trained clinicians. All the data were uploaded to the online management system structured by the China CDC, sorted to remove redundant data, and checked for incomplete data. The detection rate of any specific pathogen was calculated by dividing the number of positive specimens by the total number tested for that pathogen. Descriptive statistics were performed for all variables. The pathogen interactions at the individual host level were tested by multivariable binary logistic regression. Holm's method was applied to control the probability of one or more false discoveries arising. The associations between daily positive detection and six meteorological indicators (including daily average temperature, daily average relative humidity, daily sunshine duration, daily precipitation, daily average wind speed, and daily average air pressure) and four sociological factors (GDP per capita, population density, proportion of children, and proportion of the elderly) were explored by using a negative binomial regression at the sentinel city level. The incidence rate ratio (IRR) and 95% confidence intervals (CIs) were estimated using the maximum likelihood method. Statistical analysis was performed using R statistical software (version 3.5.3), SAS software version 9.4 and Joinpoint Trend Analysis Software (version 4.7.0.0) (Statistical Research and

Applications Branch, National Cancer Institute, USA) (appendix p 2, 3). All statistical tests were two-sided and $p<0·05$ were statistically significant.

Role of the funding source

The funder of the study had no role in the study design, data collection, data analysis, data interpretation, writing of the report, or the decision to publish. The corresponding authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

From January 2009 to December 2018, 157 883 diarrhea patients were recruited, from whom 5091 patients were excluded due to incomplete data or not initially diagnosed in the sentinel hospitals, thus 152 792 patients were used for the final analysis (appendix p 7). The demographic and epidemiological characteristics of the studied patients were shown in appendix p 9. Of these, 58·96% (90 093/152 792) were male, 55·63% were aged <18 years and 11·02% were the elderly aged ≥60 years. On average, 15 536 (IQR: 9592–18 065) patients from 127 (IQR: 91–149) hospitals were analyzed annually (appendix p 8).

Detection of viral pathogens

There were 33·61% (28 811/85 731) patients who had at least one positive viral pathogen detected. The highest detection rate (20·40%, 15 155/74 307) was to rotavirus A, followed by norovirus (12·47%, 9707/77 855), adenovirus (3·33%, 2669/80 054), and astrovirus (2·77%, 2201/79 529) (figure 1, appendix p 10, 11). This represented the same ranking as that obtained from the all-viruses-tested specimens (appendix p 12, 13).

Across the study period, rotavirus A remained as the most frequently detected virus (appendix p 14), however, the positivity declined from an annual median of 39·59% in the first year to 14·61% in the last year, showing a significantly decreasing trend with average annual percentage changes (AAPC) of -12·4% ($p<0·0001$)

(appendix p 15). A biennial pattern emerged, with alternating years of low and high rotavirus activity. Sapovirus showed obviously increasing trend with AAPC of 6·6% (p<0·0001). For rotavirus A positive specimens, 50·17% (7604/15 155) were successfully genotyped, with the most prevalent genotype as G9P[8] (14·69%), followed by G3P[8] (8·56%) and G1P[8] (6·83%) (appendix p 16). GII was the most common genotype of norovirus 90·85% (8426/9275) (appendix p 10, 11).

Based on the seven age groups classification, 46·73% (6874/14 710) of the children aged 6–11 months had at least one positive viral detection, dropping to 27·85% in 5–17 years' adolescents, 21·55% in 18–45 years, 21·86% in 46–59 years and 19·82% in the elderly ≥60 years. All viruses were detected with the highest frequency in children <5 years old, except for norovirus, the highest frequency was seen at 18–59 years adults (p<0·05) (figure 1, appendix p 10, 11). The joinpoint regression analysis disclosed similar trend for rotavirus A and B, adenovirus, norovirus, all showing one descending turnaround point at 2 to 3 years old, although norovirus alone had an additional turnaround point at 5 years old marking an obvious increase rate. The stabilized or decreased turnpoints were shown at around 21 years old for all these viruses (figure 2). Rotavirus, adenovirus, and sapovirus were detected with slightly higher rates in male (all p<0·05), with the difference for rotavirus mostly resulted from age groups <5 years (appendix p 17).

Detection of bacterial pathogens

There were 16·82% (16 841/100 129) of patients who were positive for at least one bacterial pathogen. DEC had the highest detection rate (6·71%, 6191/92 238), followed by NTS (4·41%, 4366/99 114), *Shigella* (2·44%, 2331/95 593), and *V. parahaemolyticus* (2·08%, 1981/95 155) (figure 1, appendix p 10, 11). Of the DEC positive specimens, *Enteroaggregative E. coli* was the most frequently detected (28·51%), followed by *Enteropathogenic E. coli* (25·36%), *Enterotoxigenic E. coli* (24·07%), *Enteroinvasive E. col*i (6·59%), and *Enterohaemorrhagic E. coli* (3·02%).

Across the study years, four bacterial pathogens showed significantly increasing trends of detection, with extraordinary high AAPC for *C. coli* and *C. jejuni* (17·5%

and 14·5% respectively) (figure S5, appendix p 15). In contrast, *Shigella*, *V. cholerae* and *A. hydrophila* showed significantly decreasing rates of detection, with AAPC of -26·5%, -26·0% and -14·2%, respectively.

The bacterial detection rate differed among age groups, the children <6 months had the lowest detection rate for at least one bacterial pathogen (7·92%), increased to the highest rate in 18–45 years (20·27%), and decreased thereafter (figure 1, appendix p 10, 11). For each detected bacterium, the age specific pattern differed. The joinpoint regression analysis disclosed similar trend for NTS, *Shigella*, *C. jejuni* and *Y. enterocolitica*, which were more frequently detected in children, with similar turnaround point seen at 2 to 5 years old marking a decreased APC (figure 2). DEC, *V. parahaemolyticus*, *P. shigelloides* and *V. cholerae* were more frequently detected in young adults aged from 19–28 years, with both *P. shigelloides* and *V. cholerae* showing obvious descending turnaround points at 19–24 years old, and a second stabilized point at around 27 years old (figure 2). Sex specific difference was only observed for DEC and *V. parahaemolyticus*, with higher detection rates observed in female than in male.

Detection of parasitical pathogens

There were 1·95% (253/12 988) of patients who were positive for at least one parasitical pathogen (appendix p 10, 11). *E. histolytica* was the most frequently detected (1·05%, 125/11 861), followed by *G. lamblia* (0·78%, 97/12 433) and *Cryptosporidium* (0·27%, 34/12 625). *E. histolytica* and *G. lamblia* showed significantly decreasing trends of detection across the study years, with average APC of-37·4% (-49·5 to -22·5), -30·5% (-40·7 to -18·5) (appendix p 15). *Cryptosporidium* was detected with higher rates in male (p<0·05). *E. histolytica* and *G. lamblia* were detected with higher frequencies in the adult, attaining the highest rate in 46–59 years for *E. histolytica* and 18–45 years old for *G. lamblia* (p<0·0001) (appendix p 10, 11).

Bacterial and viral co-infection pattern

Viral coinfection rate of 3·03% (1779/58 620), bacterial coinfection rate of 0·90% (536/59 384), and parasitical coinfection rate of 0·03% (3/11 167) were observed

(figure 3). Children had higher viral coinfection rate, with the highest level seen in subgroup of <6 month children ($p<0·0001$), while adults of 18–45 years old had the highest bacterial coinfection rate ($p<0·0001$). The ranking of coinfection types also differed across age groups. For those with all-viruses tested patients, we observed positive correlations between norovirus-adenovirus, norovirus-astrovirus, adenovirus-astrovirus, adenovirus-sapovirus, astrovirus-sapovirus, all with OR>1 and $p<0·05$ adjusted by Holm's method. We observed negative correlations between rotavirus-norovirus, rotavirus-adenovirus, rotavirus-sapovirus, norovirus-sapovirus at the individual level, all with OR<1 with p-values<0·05 (appendix p 18).

Among 25 239 patients tested for all seven viruses and 13 bacteria, at least one pathogen was detected in 37·34% (9423/25 239), including 23·04% (5816/25 239) viral single infection, 11·66% (2942/25 239) bacterial single infection and 2·63% viral-bacterial coinfection (665/25 239) (appendix p 18). Coinfection with ≥2 pathogens primarily occurred among rotavirus A, norovirus, adenovirus, sapovirus, astrovirus, DEC, and NTS (appendix p 18).

Of 44 494 patients with positive detection, 30·15% reported vomiting, 13·68% reported fever, 7·08% reported respiratory symptoms, 2·31% reported dehydration, and 0·46% reported neurological symptoms. Most of them differed between patients with viral single infection and bacterial single infection, i.e., more vomiting, respiratory symptoms and neurological symptoms in the former, while more fever in the latter (All $p<0·01$). This intergroup differences of syndrome and clinical signs were consistently observed for children and adults (appendix p 19).

The spatial-temporal pattern

The geographic diversity of detection and the seasonal patterns for each pathogen were demonstrated for seven ecological regions (figure 4). The effect on the spatial and the seasonal pattern was explored at the sentinel city level by using four sociological and six meteorological factors (appendix p 20, 21). The daily mean temperature had significantly affected most of the detected viruses and bacteria, but with different directions of effects. Consistent with these effects, the viral infection

exhibited a winter-spring seasonality that spanned from December–January and ending in April–May, while the bacterial infection exhibited a Summer–Autumn seasonality that spanned from May to October with peaks in summer (figure 4). At the city level, the proportion of children and the elderly significantly affected viral infection to a greater extent, while the population density significantly affected bacterial infection more (appendix p 20, 21). According to the direction and magnitude of the effect from the evaluated factors that were exerted on each pathogen, two viral clusters and two bacterial clusters can be inferred with similar impacting factors. Norovirus, sapovirus, astrovirus and adenovirus constituted Cluster I, with the detection rates of former three positively associated with lower temperature, and detection rates of latter two negatively associated with higher wind speed (appendix p 20, 21 and figure 4E). Rotavirus A, B and C constituted Cluster II, all were positively associated with lower sunshine hour, wind speed, and higher proportion of children. DEC, *Shigella*, NTS and *A. hydrophila* constituted Cluster III, all were associated with higher temperature, while *Shigella* and *A. hydrophila* additionally associated with lower GDP per capita (figure 4C and appendix p 20, 21). *C. jejuni* and *C. coli* constituted Cluster IV, both positively associated with high population density (figure 4F).

The seasonal patterns also showed regional heterogeneous across China. For example, rotavirus was strongly seasonal in the temperate areas with latitude above 40°, where epidemics peaked during the winter. In contrast its seasonality was less pronounced in the subtropical and tropical regions, characterized by multiple peaks in the regions with latitude below 40°. The seasonality of norovirus shows obvious bimodal pattern, and in a similar patter as rotavirus, the peaking time in areas with latitude below 30° or between 30°–40° was shown earlier than that regions with latitude above 40° (appendix p 22).

Discussion

In this study of a longitudinal surveillance spanning 10 years in China, we provided updated results on the viral, bacterial and parasitical etiologies in patients with acute diarrhea which differed in terms of patients' demography, epidemic season, and socioeconomic level.

Age effect on the pathogen detection was comprehensively explored. Generally, there was a trend for patient with younger age, especially <5 years old to be infected with increased rates and higher variety of viral pathogens, while adults of 18−45 years were more likely to be infected with bacterial pathogens. Within children group, the peaking detection level for each virus varied. By performing joinpoint analysis, we could infer the detection rate of rotavirus, norovirus, and adenovirus peaking at the age of 2−3 years old and began to decrease thereafter. For norovirus, a second peaking point at 16 years old was observed, marking the significant turnpoint at which the trend switched. Three years old and 16 years old are the threshold when children enter the kindergarten and the high school, respectively in China, possibly leading to the establishment of the host protective immunity and the ensuing decreased infection after this age scope. It's noteworthy that the leading viral pathogen switched from rotavirus among children to norovirus among adults, with the high detection level maintained in all-age adult. This was partially due to the continuous mutation and recombination of norovirus, generating novel strains with high potential of causing outbreak events and sporadic cases.[11]

In contrast with viral infection, a divergent turnpoints of age were presented for the detection of bacterial pathogens. NTS, *Shigella*, *C. jejuni* and *Y. enterocolitica* displayed a Children-Pattern, with detection turnpoint seen at 2−5 years, while DEC, *V. parahaemolyticus*, *P. shigelloides* and *V. cholerae* displayed an Adult-Pattern, with turnpoints seen at 19 to 28 years. Consistent with previous findings, the elderly patients (≥60 years) were the least likely to get infected with infectious diarrhea.[12] This diversity of age distribution might reflect a natural change in host immunity and dietary habit that related to age. These findings provided unprecedented information

as to the point at which the implementing prevention strategies should be stressed.

Through a long-lasting observation, we found a slowly decreased detection of rotavirus across the study years, probably owing to the rotavirus vaccine interventions that had been advocated after the year of 2000.[13] Rotavirus vaccine was not mandatory in China, but higher LLR vaccination coverage might indeed decrease the incidence risk among children younger than 4 years according to the city-level ecological study.[14] In many countries with universal vaccination for rotavirus, the childhood deaths of rotavirus has decreased significantly.[15] The current findings supported the potential benefit of including rotavirus vaccine into the schedule of immunization of infants in China. The biennial circulation patterns of rotavirus might be caused by an increase in the number of young, unexposed persons during years of low circulation, which leads to a larger number of susceptible persons acquiring and transmitting the infection in the following year. Decreased detection of several bacterial pathogens across the study years is likely due to the improved hygiene of food/water supplying in recent years, especially in rural areas.[16] On the other hand, increasing antibiotic usage have contributed to antibiotic resistance in recent years[17], which may be related to increased detection of several bacterial pathogens.

We examined the viral pathogen interactions at the individual scale by using results from patients who had all-viruses tested. The detection of rotavirus was negatively correlated with all the other enteroviruses, which might be explained by the viruses interactive antagonize within the host by competing for receptors and resources.[18] In addition, studies showed that rotavirus replication is susceptible to interference by other enteric viruses in the gut.[19] Norovirus was positively correlated with adenovirus and astrovirus, possibly owing to their shared transmission routes or susceptible population. The bacteria-bacteria and bacteria-virus interactions were not examined owing to low bacterial detection rate. The elaboration of such interactions may have economic implications, if the circulation of one pathogen enhances or diminishes the infection incidence of another, through impacts on the healthcare burden, public health planning, and the clinical management of diarrhea disease.

The simultaneous detection of a wide range of pathogens offer the opportunity of making discrimination analysis between bacterial and viral diarrhea, which according to our data, could be attained by using age, presence of fever and vomiting. These findings if real, are encouraging that a preliminary diagnosis could be made before the laboratory diagnosis could be performed.

For the first time, by analyzing an exceptionally aggregated nationwide data among regions with wide meteorological and socio-economical variation, we can estimate their influence on the prevalence of enteropathogens. In agreement with previous studies,[20, 21] we found most of the viral infections increased as temperature and humidity decreased and vice versa. These associations could be supported by laboratory findings indicating that lower temperature and humidity increase the survival of viral enteropathogens in environment.[22] We found high wind speed, precipitation and sunshine hour could reduce most of the viral detection. Considering that infectious virus persists not only on surface but also in aerosolization of virus-laden dust particles,[23] it's logical to deduce that viral survival in air can be reduced by these factors, thus resulting in the decreased detection. These findings are also in agreement with previous modelling results that rotavirus transmission is enhanced when aerosols are able to linger in slow moving air and inhibited by stronger winds that transport particles away from susceptible individuals.[24]

Our study suggests that temperature affects epidemic level of bacteria, but this effect is less robust than those from population density and GDP, supporting that crowded conditions and lower living standard might favor the infection. These findings strengthened the existing evidence that the patients living in developing areas were more susceptible to *Shigella* and other bacterial diarrhea, primarily due to poor access to health care, safe water, and sanitation, and low-income or marginalized populations.[25,26]

For the first time, we show differences in etiological structure among regions in China, disclosing marginal spatial variation in seasonal activity and dynamics. The climatic and socioeconomic factors that underlie these regional differences were

disclosed, based on which, we presented pathogen clustering at the population scale in a novel way. This information could assist knowing of the timing of pathogen activity at both national and subnational levels, which is important to healthcare providers and health officials who use this data to guide diagnostic testing, conduct disease surveillance and response to outbreaks.

There are some limitations in this study. Not all the listed pathogens were detected in all recruited patients, however, with the patients that received different panel of testing pathogens highly comparable, we are confident that the pathogen spectrum was not biased from the real situation. The sentinel hospitals that were set at the Western China was less than those in the densely populated regions, as there was a lower than average population size in this region. This limitation hindered a full understanding of the dynamic pattern of the diarrhea pathogens in this region. Moreover, there were 68·26% of the patients who were negative for all of the 23 currently detected pathogens, who might be infected with organisms not included in our diagnostic algorithms. In recent years, a growing list of emerging pathogens, especially viral pathogens were found to cause diarrhea, owing to the breakthroughs in the metagenomics field, such as Saffold cardiovirus,[27] coronaviruses,[28] picobirnaviruses[29] and MW polyomavirus[30] that have been proposed as ‘‘new’’ viral etiologic agents of diarrhea. The new-generation sequencing techniques, though not yet adapted for widespread use in the pathogen surveillance, should be strengthened for their application to identify novel pathogens to close the diagnostic gap.

In summary, our data provided an unprecedented and comprehensive understanding of etiologic diagnosis of diarrhea, as well as their demographic, seasonal and geographic patterns, which allows an enhanced identification of predominant diarrheal pathogens candidates for diagnosis in clinical practice and targeted prevention control from the public health perspectives at both national and subnational levels.

Contributors

LPW, ZJL, WZY, HQJ, GFG, LQF and WL conceived, designed and supervised the

study. XW, LSS, XR, YFW, SHL, CHZ, MJG, XAZ, JL, SWZ, ZGY, XC, ZSY, LM, XHW, YLL, ALC, SJL, and YLZ collected data. SXZ, QBL, LSS, XR, HYZ, XAZ, MYL, and YLZ cleaned data. SXZ, QBL, HYZ, LSS and YLZ analyzed the data supervised by LPW, LQF and WL. WL, SXZ, LPW, ZJL and LQF wrote the drafts of the manuscript. LPW, WL, LQF, ZJL, XW, WBX, YC, JGW, ZHY, MFL and LYH interpreted the findings. ZJL, LPW, LQF and WL commented on and revised drafts of the manuscript. All authors read and approved the final report.

Declaration of interests

We declare no competing interests.

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Research in context

Evidence before this study

In Aug 2020, we did a search of PubMed for all papers published from Jan 1, 2009 to Aug 20, 2020, using search terms "viral/virus/viruses" or "bacterial/bacteria/bacterium" or "parasitical/parasite/parasites" and "diarrheal" or "diarrhea" or "diarrhoea" and "China". Among the 3044 papers from the preliminary screening, 265 papers have reported the etiological detection in human with or without the clinical and epidemiological investigation of diarrhea infections in China during 2009–2020 after excluding diarrhea infections in other species including swine, canine, and domestic pets. 113 papers reported single pathogen detection (30 papers on rotavirus, 29 on norovirus, 10 on NTS, 9 on DEC, 8 on adenovirus, 6 on *V. parahaemolyticus*, 5 on *Cryptosporidium*, 4 on *Shigella*, 4 on astrovirus, 3 on *E. histolytica*, 2 on sapovirus, 2 on *C. jejuni*, 1 on *Y. enterocolitica*). There were 152 papers reporting multiple diarrheal pathogens detection, which included 32 papers on detection of viral and bacterial pathogens, 72 papers on viral pathogens, 38 on bacterial pathogens, 2 on parasitical pathogens. Only 8 papers reported simultaneous detection of viral, bacterial, and parasitical pathogens, however with limited study period (1–2 years period), within one province and among specific age group (mostly focusing on children under 5 years of age).

To identify the meteorological or climatic factors that might affect the incidence of diarrhea, we did additional search of PubMed for all papers from Jan 1, 2009 to Aug 20, 2020, using search terms "viral/virus/viruses" or "bacterial/bacteria/bacterium" or "parasitical/parasite/parasites" and "diarrhea" or "diarrhoea" or "diarrheal" and "meteorological" or "meteorology" or "climate" or "climatic", or "weather" that were performed in any country/regions. Among the 791 papers from the preliminary screening, 34 papers have reported the meteorological or climatic factors that affect the diarrheal disease with determined pathogens. Most of papers reported the analysis either based on single pathogen detection or in a single region. Only three papers investigated the meteorological impacts on multiple pathogens causing diarrhea, and none of them was performed on nationwide.

Added value of this study

To the best of our knowledge, this study provided an unprecedented and comprehensive etiological, epidemiological, and clinical investigation on diarrhea patients with determined pathogens. Based on detection of 23 commonly seen diarrheal pathogens from totally 152 792 all-age diarrhea patients that were recruited from 217 sentinel hospitals and 95 reference laboratories of all 31 provinces in mainland of China from Jan 1, 2009 to Dec 31, 2018, we provided viral, bacterial and parasitical etiological structure of acute diarrhea, and further explored their demographical, seasonal, spatial and socioeconomical patterns. The important findings included:

1. Rotavirus A was the leading viral pathogens, followed by norovirus, adenovirus, and astrovirus. DEC was the leading bacterial pathogens detected, followed by NTS, *Shigella*, and *V. parahaemolyticus*. *E. histolytica* was the leading parasitical pathogens detected, followed by *G. lamblia* and *Cryptosporidium*.

2. Age affects pathogen spectrum. Children <5 years old having the highest viral detection rate, with rotavirus A as the leading pathogen. The adult aged 18–45 years had the highest bacterial detection rate, with DEC as the leading one. The join-point regressions demonstrated different turnaround points at specific age or age range that marked increased or decreased detection rate for each of the investigated pathogens.

3. We show differences in etiological structure among regions in China, disclosing marginal spatial variation in seasonal activity and dynamics. The climatic and socioeconomic factors that underlie these regional differences were disclosed.

4. Among all evaluated meteorological factors, daily mean temperature had exerted the most robust effect on viral and bacterial detection. Among all evaluated socioeconomic factors, the proportion of children and the elderly at the city level significantly affected viral infection to a greater extent, while the population density affected bacterial infection more.

5. Multiple clinical features might be used to differentiate viral from bacterial infection.

Implications of all the available evidence

Our findings could serve as a useful instrument for timely identification of predominant diarrheal pathogens candidates for diagnosis and targeted prevention control. By identification of temporal trends and circulation patterns of individual pathogen, the current findings could also serve as a useful instrument for a timely identification and prediction of predominant pathogens occurrence and help guide outbreak investigations. The enhanced understanding on the pathogen coinfection pattern and clinical features enabling the differential diagnosis between viral/bacterial, would help improve clinical management by physicians.

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Figuers Legends

Figure 1. Detection rate of pathogens by sex and age in patients with diarrhea in China, 2009–2018. The lengths of colored bars indicate the detection rate of each pathogen by sex and age groups. The same group was marked by same colors of bars filling. *indicates a significant difference (P-value <0·05 by either Chi square test or Fisher's exact test) found within the group.

Figure 2. The Join-Point regression of the detection rates of each enteropathogen by age of patient. A red point indicates the mean detection rate of patients in terms of age and the colored curves indicates fitted patterns by the red points. Legends give the Annual Percent Change (APC) value of each fitted curve for each virus. *indicates that the APC is significantly different from zero at P <0·05.

Figure 3. Co-detection pattern of enteropathogens in diarrhea patients by age group in the mainland of China, 2009–2018.

(A) The viral co-detection pattern of 58 620 diarrheal patients who had all the seven viral pathogens tested. (B) The bacterial co-detection pattern of 59 384 diarrheal patients who had all the 13 bacterial pathogens tested. (C) The parasitical co-detection pattern of 11 167 diarrheal patients who had all the three parasitical pathogens tested. The proportion of each positive pathogen was noted in % and by length of colored bars. The orange bar indicates viral mono-detection; the blue bar indicates bacterial mono-detection; the red bar indicates parasitical mono-detection; the green bar indicates co-detection. For viruses, co-detection means viral-viral co-detection. For bacteria, co-detection means bacterial-bacterial co-detection. For parasites, co-detection means parasitical-parasitical co-detection.

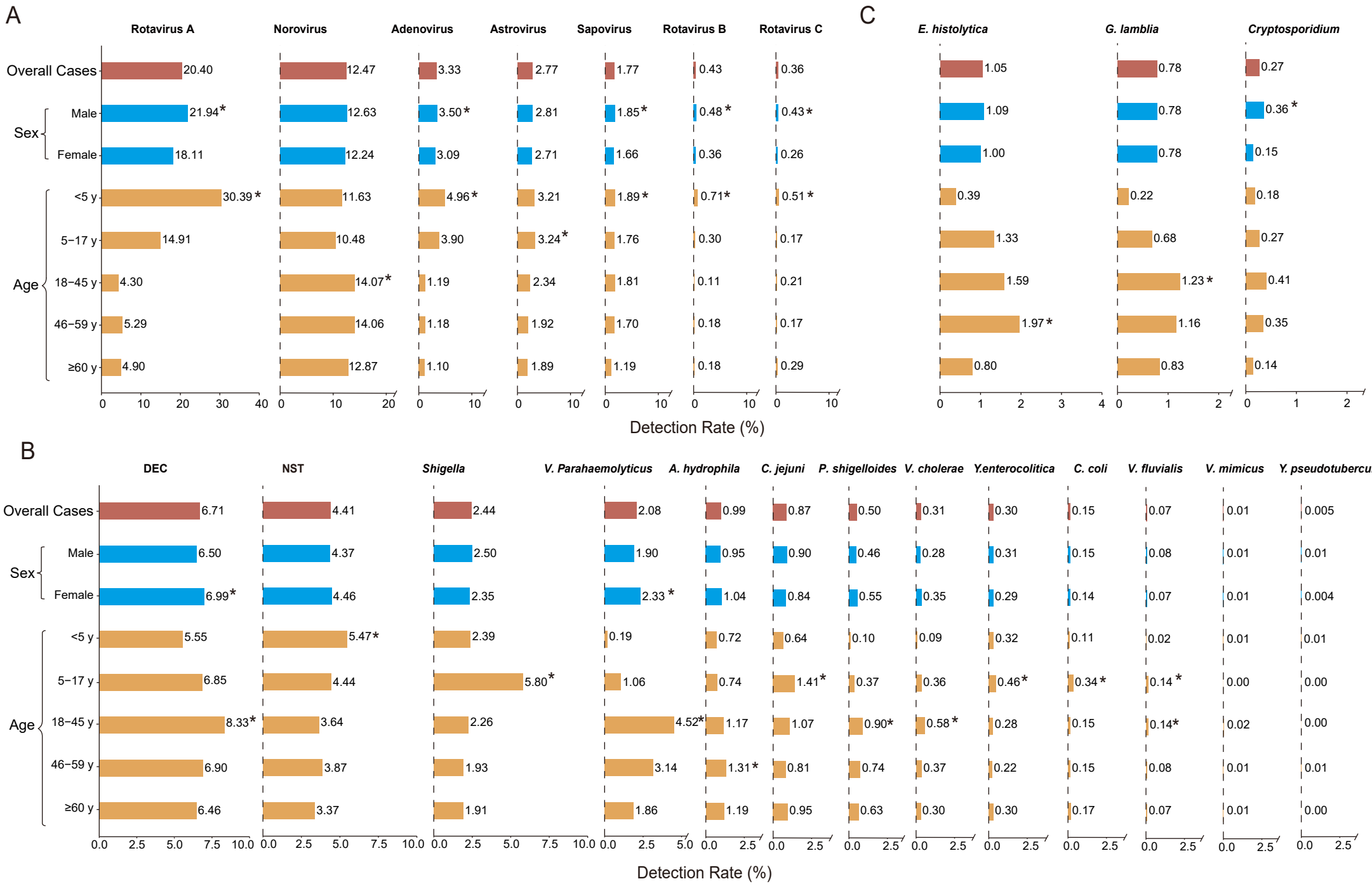
Figure 4. Spatial and temporal pattern of four clusters of enteropathogens in patients with diarrhea in the mainland of China during 2009–20**18.** Thirteen of the

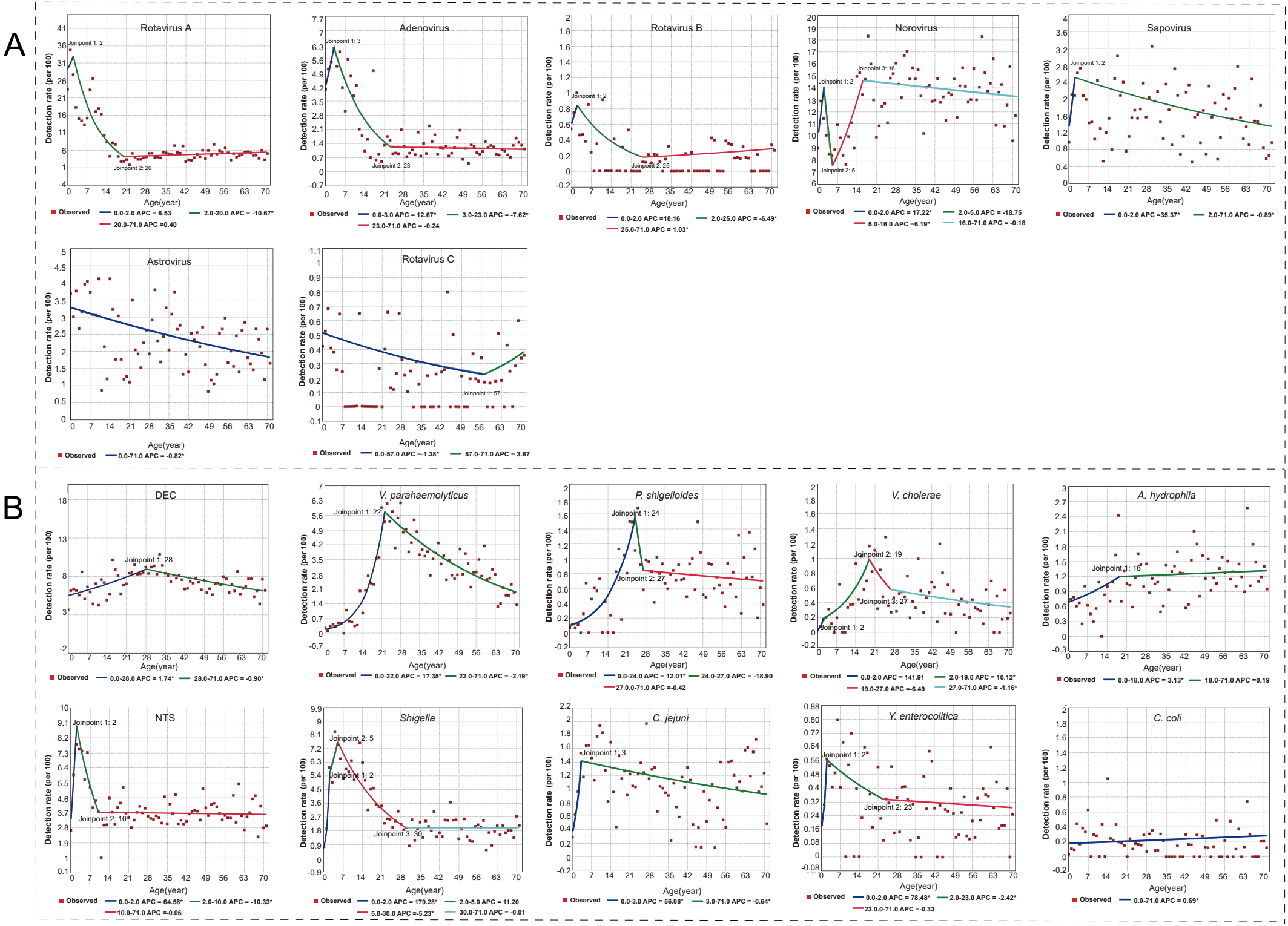
tested enteropathogens were formed into four clusters (Panels A–D).

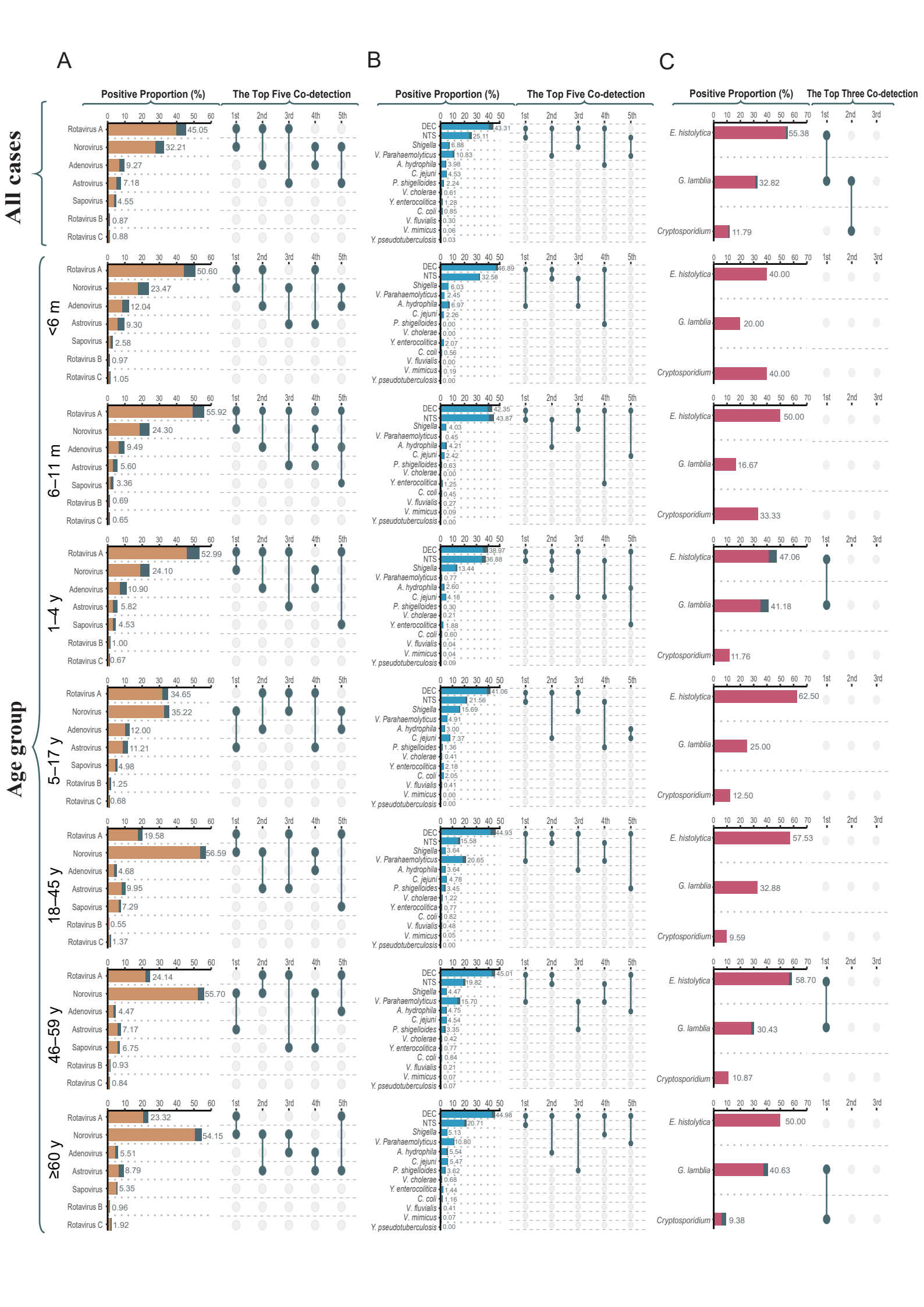
The seasonality was presented with a radar diagram based on monthly detection rate from 2009 to 2018. The circumference is divided into 12 months in a clockwise direction, and the radius from inside to outside represents a particular year from 2009 to 2018. Seven ecological regions were marked (I, Northeast China district; II, North China district; III, Inner Mongolia-Xinjiang district; IV, Qinghai-Tibet district; V, Southwest China district; VI, Central China district; VII, South China district). Within each ecological region, the detection rate was noted and reflected by the background color.

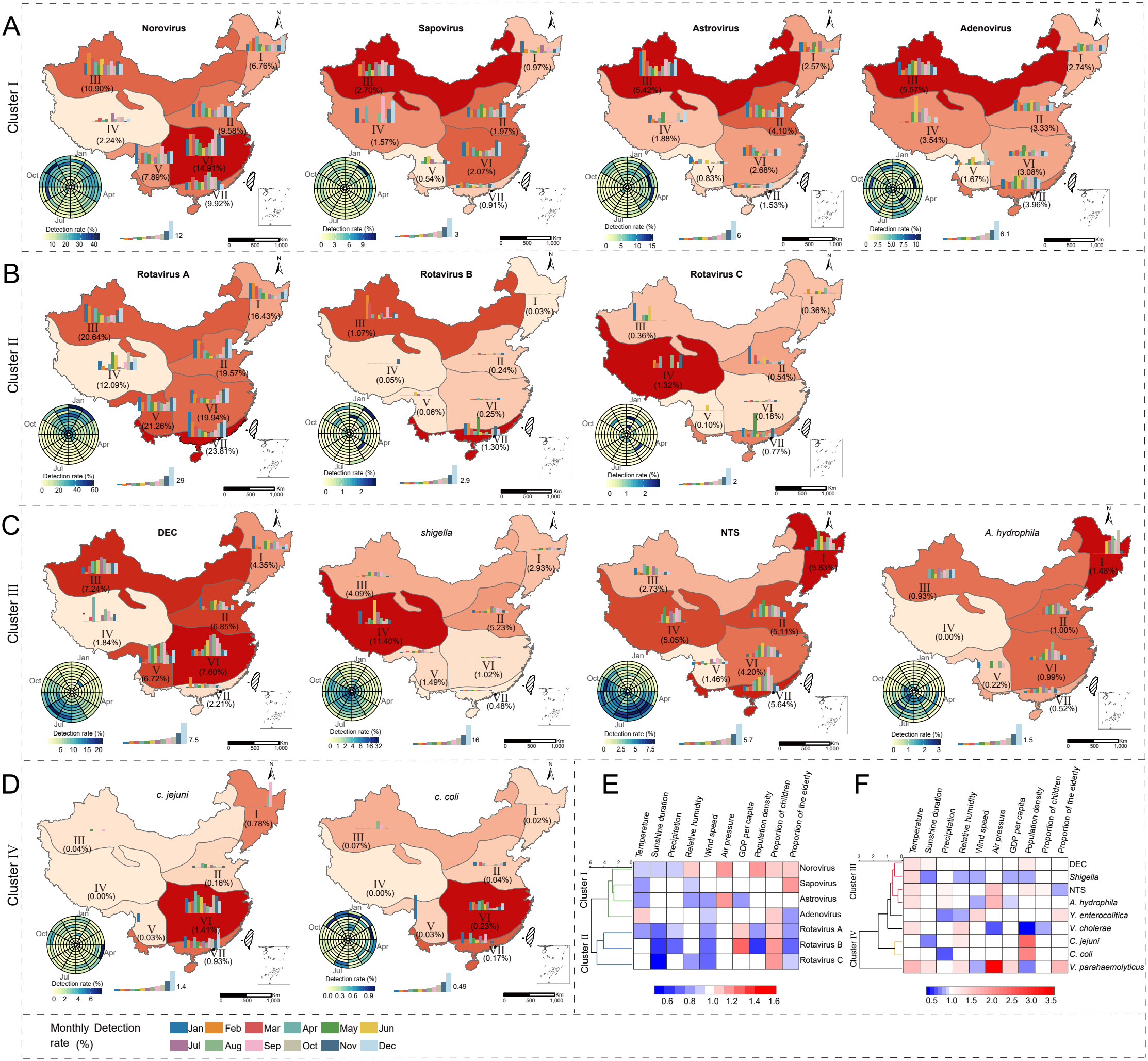
Histograms within each ecological region indicate the monthly detection rate averaged from 10-year data. The height of the bars indicates the detection rate of each month. *No sample in the month.

The dendrogram in panels E–F display the clusters I–IV. Green lines mean cluster I. Blue lines mean cluster II. Red lines mean cluster III. Yellow lines mean cluster IV. The incidence rate ratio, ranging from negative influence (blue) to positive influence (red). The features used for clustering are variables with statistically significant differences in the negative binomial model.


A
Rotavirus A
Norovirus
Adenovirus
Astrovirus
Sapovirus
Rotavirus B
Rotavirus C
Overall Cases
Sex
Male
Female
Age
<5 y
5–17 y
18–45 y
46–59 y
≥60 y
20.40
12.47
3.33
2.77
1.77
0.43
0.36
21.94*
12.63
3.50*
2.81
1.85*
0.48*
0.43*
18.11
12.24
3.09
2.71
1.66
0.36
0.26
30.39*
11.63
4.96*
3.21
1.89*
0.71*
0.51*
14.91
10.48
3.90
3.24*
1.76
0.30
0.17
4.30
14.07*
1.19
2.34
1.81
0.11
0.21
5.29
14.06
1.18
1.92
1.70
0.18
0.17
4.90
12.87
1.10
1.89
1.19
0.18
0.29
0 10 20 30 40
0 10 20
0 10
0 10
0 10
0 10
0 10
C
E. histolytica
G. lamblia
Cryptosporidium
1.05
0.78
0.27
1.09
0.78
0.36*
1.00
0.78
0.15
0.39
0.22
0.18
1.33
0.68
0.27
1.59
1.23*
0.41
1.97*
1.16
0.35
0.80
0.83
0.14
0 1 2 3 4
0 1 2
0 1 2
Detection Rate (%)
B
DEC
NST
Shigella
V. Parahaemolyticus
A. hydrophila
C. jejuni
P. shigelloides
V. cholerae
Y.enterocolitica
C. coli
V. fluvialis
V. mimicus
Y. pseudotuberculosis
Overall Cases
Sex
Male
Female
Age
<5 y
5–17 y
18–45 y
46–59 y
≥60 y
6.71
4.41
2.44
2.08
0.99
0.87
0.50
0.31
0.30
0.15
0.07
0.01
0.005
6.50
4.37
2.50
1.90
0.95
0.90
0.46
0.28
0.31
0.15
0.08
0.01
0.01
6.99*
4.46
2.35
2.33*
1.04
0.84
0.55
0.35
0.29
0.14
0.07
0.01
0.004
5.55
5.47*
2.39
0.19
0.72
0.64
0.10
0.09
0.32
0.11
0.02
0.01
0.01
6.85
4.44
5.80*
1.06
0.74
1.41*
0.37
0.36
0.46*
0.34*
0.14*
0.00
0.00
8.33*
3.64
2.26
4.52*
1.17
1.07
0.90*
0.58*
0.28
0.15
0.14*
0.02
0.00
6.90
3.87
1.93
3.14
1.31*
0.81
0.74
0.37
0.22
0.15
0.08
0.01
0.01
6.46
3.37
1.91
1.86
1.19
0.95
0.63
0.30
0.30
0.17
0.07
0.01
0.00
0.0 2.5 5.0 7.5 10.0
0.0 2.5 5.0 7.5 10.0
0.0 2.5 5.0 7.5 10.0
0.0 2.5 5.0
0.0 2.5
0.0 2.5
0.0 2.5
0.0 2.5
0.0 2.5
0.0 2.5
0.0 2.5
0.0 2.5
0.0 2.5
Detection Rate (%)


A
Rotavirus A
Joinpoint 1: 2
Joinpoint 2: 20
Detection rate (per 100)
Age(year)
Observed
0.0-2.0 APC = 6.53
2.0-20.0 APC = -10.67*
20.0-71.0 APC =0.40
Adenovirus
Joinpoint 1: 3
Joinpoint 2: 23
Observed
0.0-3.0 APC = 12.67*
3.0-23.0 APC = -7.62*
23.0-71.0 APC = -0.24
Rotavirus B
Joinpoint 1: 2
Joinpoint 2: 25
Observed
0.0-2.0 APC =18.16
2.0-25.0 APC = -6.49*
25.0-71.0 APC = 1.03*
Norovirus
Joinpoint 1: 2
Joinpoint 2: 5
Joinpoint 3: 16
Observed
0.0-2.0 APC = 17.22*
2.0-5.0 APC = -18.75
5.0-16.0 APC =6.19*
16.0-71.0 APC = -0.18
Sapovirus
Joinpoint 1: 2
Observed
0.0-2.0 APC =35.37*
2.0-71.0 APC = -0.89*
Astrovirus
Observed
0.0-71.0 APC = -0.82*
Rotavirus C
Joinpoint 1: 57
Observed
0.0-57.0 APC =-1.38*
57.0-71.0 APC = 3.67
B
DEC
Joinpoint 1: 28
Observed
0.0-28.0 APC = 1.74*
28.0-71.0 APC =-0.90*
V. parahaemolyticus
Joinpoint 1: 22
Observed
0.0-22.0 APC = 17.35*
22.0-71.0 APC = -2.19*
P. shigelloides
Joinpoint 1: 24
Joinpoint 2: 27
Observed
0.0-24.0 APC = 12.01*
24.0-27.0 APC = -18.90
27.0-71.0 APC =-0.42
V. cholerae
Joinpoint 1: 2
Joinpoint 2: 19
Joinpoint 3: 27
Observed
0.0-2.0 APC = 141.91
2.0-19.0 APC = 10.12*
19.0-27.0 APC =-6.49
27.0-71.0 APC = -1.16*
A. hydrophila
Joinpoint 1: 18
Observed
0.0-18.0 APC = 3.13*
18.0-71.0 APC =0.19
NTS
Joinpoint 1: 2
Joinpoint 2: 10
Observed
0.0-2.0 APC = 64.58*
2.0-10.0 APC = -10.33*
10.0-71.0 APC =-0.06
Shigella
Joinpoint 1: 2
Joinpoint 2: 5
Joinpoint 3: 30
Observed
0.0-2.0 APC = 179.28*
2.0-5.0 APC = 11.20
5.0-30.0 APC =-5.23*
30.0-71.0 APC = -0.01
C. jejuni
Joinpoint 1: 3
Observed
0.0-3.0 APC = 56.08*
3.0-71.0 APC = -0.64*
Y. enterocolitica
Joinpoint 1: 2
Joinpoint 2: 23
Observed
0.0-2.0 APC = 78.48*
2.0-23.0 APC = -2.42*
23.0-71.0 APC =-0.33
C. coli
Observed
0.0-71.0 APC = 0.69*


A
B
C
Positive Proportion (%)
The Top Five Co-detection
The Top Three Co-detection
All cases
Age group
<6 m
6–11 m
1–4 y
5–17 y
18–45 y
46–59 y
≥60 y
Rotavirus A
Norovirus
Adenovirus
Astrovirus
Sapovirus
Rotavirus B
Rotavirus C
DEC
NTS
Shigella
V. Parahaemolyticus
A. hydrophila
C. jejuni
P. shigelloides
V. cholerae
Y. enterocolitica
C. coli
V. fluvialis
V. mimicus
Y. pseudotuberculosis
E. histolytica
G. lamblia
Cryptosporidium
1st
2nd
3rd
4th
5th


A
Cluster I
Norovirus
I (6.76%)
II (9.58%)
III (10.90%)
IV (2.24%)
V (7.89%)
VI (14.91%)
VII (9.92%)
Sapovirus
I (0.97%)
II (1.97%)
III (2.70%)
IV (1.57%)
V (0.54%)
VI (2.07%)
VII (0.91%)
Astrovirus
I (2.57%)
II (4.10%)
III (5.42%)
IV (1.88%)
V (0.83%)
VI (2.68%)
VII (1.53%)
Adenovirus
I (2.74%)
II (3.33%)
III (5.57%)
IV (3.54%)
V (1.67%)
VI (3.08%)
VII (3.96%)
Jan
Apr
Jul
Oct
Detection rate (%)
N
Km
0 500 1,000
B
Cluster II
Rotavirus A
I (16.43%)
II (19.57%)
III (20.64%)
IV (12.09%)
V (21.26%)
VI (19.94%)
VII (23.81%)
Rotavirus B
I (0.03%)
II (0.24%)
III (1.07%)
IV (0.05%)
V (0.06%)
VI (0.25%)
VII (1.30%)
Rotavirus C
I (0.36%)
II (0.54%)
III (0.36%)
IV (1.32%)
V (0.10%)
VI (0.18%)
VII (0.77%)
C
Cluster III
DEC
I (4.35%)
II (6.85%)
III (7.24%)
IV (1.84%)
V (6.72%)
VI (7.60%)
VII (2.21%)
shigella
I (2.93%)
II (5.23%)
III (4.09%)
IV (11.40%)
V (1.49%)
VI (1.02%)
VII (0.48%)
NTS
I (5.83%)
II (5.11%)
III (2.73%)
IV (5.05%)
V (1.46%)
VI (4.20%)
VII (5.64%)
A. hydrophila
I (1.48%)
II (1.00%)
III (0.93%)
IV (0.00%)
V (0.22%)
VI (0.99%)
VII (0.52%)
D
Cluster IV
c. jejuni
I (0.78%)
II (0.16%)
III (0.04%)
IV (0.00%)
V (0.03%)
VI (1.41%)
VII (0.93%)
c. coli
I (0.02%)
II (0.04%)
III (0.07%)
IV (0.00%)
V (0.03%)
VI (0.23%)
VII (0.17%)
E
Temperature
Sunshine duration
Precipitation
Relative humidity
Wind speed
Air pressure
GDP per capita
Population density
Proportion of children
Proportion of the elderly
Cluster I
Cluster II
Norovirus
Sapovirus
Astrovirus
Adenovirus
Rotavirus A
Rotavirus B
Rotavirus C
0.6 0.8 1.0 1.2 1.4 1.6
F
Cluster III
Cluster IV
DEC
Shigella
NTS
A. hydrophila
Y. enterocolitica
V. cholerae
C. jejuni
C. coli
V. parahaemolyticus
0.5 1.0 1.5 2.0 2.5 3.0 3.5
Monthly Detection rate (%)
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec