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## Preplanned Studies



## Vital Surveillances



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Preplanned Studies

# Synergistic Effects of Rotavirus and Co-Infecting Viral Enteric Pathogens on Diarrheal Disease — Guangzhou City, Guangdong Province, China, 2019

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**Summary**

**What is already known about this topic?**

Diarrhea represents a substantial public health issue, contributing globally to a high number of pediatric medical consultations, hospital admissions, and mortality rates.

**What is added by this report?**

An increase in diarrheal frequency serves as a critical benchmark for evaluating severity. The predominant pathogens associated with pediatric diarrhea are rotavirus and norovirus, with co-infections exerting a notable compounding effect that leads to more severe diarrhea.

**What are the implications for public health practice?**

Implementing sensitive diagnostic techniques and comprehensive monitoring is paramount in identifying co-infections. Such strategies can provide physicians with critical insights into disease progression, thus considerably reducing the burden of diarrhea.

Despite a reduction in mortality rates over the past several decades, diarrhea remains a significant factor in both morbidity and mortality among children under the age of five worldwide (*1*–*3*). Diarrhea is typified by primary clinical symptoms of diarrhea and vomiting, which can result in dehydration, sepsis, and in severe instances, death. The presence of numerous enteric viruses, bacterial pathogens, and parasites is the root cause of this condition (*2*–*3*). Among these, enteric viruses are the most prevalent source of diarrhea in children (*2*,*4*–*5*). The significant enteric viruses include human group A rotaviruses (RVA), noroviruses (NoVs), astroviruses (As), and adenoviruses (Ad), with transmission primarily occurring via the fecal-oral route. RVA is the leading pathogen associated with childhood diarrhea (*6*), and NoVs present an increased risk of diarrhea outbreaks in communal settings (*5*). What is particularly noteworthy is the common occurrence of co-infections, wherein multiple etiologic agents emerge in individuals with diarrhea. Prior studies have found co-infections in 10% to 40% of diarrhea cases and in 0% to 15% of non-diarrheal children, with infections from as many as 2 to 5 pathogens (*2*,*4*,*7*).

Current research on the impact of co-infections of enteric viral pathogens on human health and the nature of their interactions, whether synergistic or antagonistic, is lacking. This study employed hospital-based, case-control data to evaluate the prevalence and pathogenicity of common enteric viral pathogens in a population comprised of children under the age of five in northern China from January 1 through December 31, 2019. To assess pathogenicity, a clear distinction was made between single infections and co-infections. Potential interactions between co-infecting pathogens were examined by evaluating their biological synergy through the use of both additive and multiplicative models. This research received ethical approval from the Ethical Review Committee of Guangzhou Women and Children's Medical Center (No. 2017111501) and was registered in the Chinese Clinical Trial Registry (ChiCTR-ROC-17013620). Sentinel surveillance hospitals for this research included Guangzhou Women and Children's Medical Center, Guangzhou Children's Hospital, and Guangzhou Maternity and Child Health Care Hospital. For the purposes of this study, acute diarrhea is characterized as children experiencing three or more bowel movements in the past 24 hours with abnormal stool consistency (*4*). Children with acute diarrhea were recorded as cases from the outpatient and inpatient departments of the gastroenterology department. Children without diarrhea were identified as controls from other inpatient departments and internal medicine outpatient centers. Consent was obtained from either the parents or legal guardians of the children prior to their inclusion in the study. Uniform inclusion criteria for both cases and controls included: being under the

age of five, no gender bias, and parental informed consent. Exclusion criteria applicable to both groups included the presence of other gastrointestinal diseases, severe illnesses, mental disorders, and the use of antiviral drugs and antibiotics in the past two months. Additional criteria for cases included experiencing diarrhea for less than 14 days prior to a doctor's visit. Controls were similar in age and gender to the cases experiencing diarrhea.

In this study, trained nurses performed field questionnaire surveys to gather epidemiological data. Information collected included participant's gender, age, date of visit, any known food allergies, medical history and primary clinical manifestations. The frequency of diarrhea, for instance, was noted as a significant factor in evaluating the severity of the condition. Concurrently, stool samples were collected in sterile conditions. These were then stored in a bio-safe transport box at temperatures of 4–8 °C, and transported to the laboratory at the Guangzhou Women and Children's Medical Center within a 12-hour timeframe. Upon receipt, the samples were frozen at −70 °C in preparation for centralized testing. The study made use of an automated system for extracting total nucleic acid from the stool samples. A real-time reverse transcription-polymerase chain reaction (real-time RT-PCR) was then administered to detect the nucleic acids of RVA, NoVs, As, and Ad (*8–10*).

Qualitative data were analyzed using frequencies, percentages, odds ratios (*OR*s), and 95% confidence intervals (*CI*s), and compared using the chi-square test or Fisher's exact test. Quantitative variables were described using medians and interquartile ranges (*IQR*s) and compared using the Kruskal-Wallis *H* test or Mann-Whitney *U* test. The interactions among the pathogens were evaluated using logistic regression models, adjusting for relevant host factors (*3–4*). Statistical significance was determined at a two-tailed *P*-value less than 0.05. All statistical analyses were performed using R software (version 4.2.1; R Foundation for Statistical Computing, Vienna, Austria).

The study was performed with a total of 930 children participants under the age of five. Of these participants, 67.7% (*n*=630) were identified as children with diarrhea, and 32.3% (*n*=300) were classified as non-diarrheic participants. The participant pool was predominantly comprised of males (*n*=611, 65.7%) and a significant number were under the age of 2 (*n*=638, 68.6%) and were originally recruited from outpatient clinics (*n*=760, 81.7%). The median age of the participants stood at 14 months with an *IQR* of 7 to 28 months. There were balanced distributions between the two groups concerning age, gender, collection season, case source, and underlying diseases (Table 1). Amongst the diarrheic cases, the median number of defecation episodes in the 24-hour period preceding the medical consultation was 5 with an *IQR* of 4 to 7 occurrences.

In this study, the prevalence of infection with at least one viral pathogen was significantly higher among children with diarrhea compared to those without diarrhea (37.5% *vs.* 17.0%. $\chi^2$=39.875, *P*<0.001). Specifically, the detection rates of RVA and NoVs GII were substantially elevated in the group of children experiencing diarrhea compared to their counterparts [($\chi^2$=340.994, *P*<0.001) & ($\chi^2$=13.214, *P*<0.001), respectively]. However, there was no statistically meaningful discrepancy in the detection rates of NoVs GI, As, and Ad between the two groups. Within the population of children with diarrhea, RVA presented the highest rate of infection, followed by NoVs, As, and Ad. Among all the detected viral pathogens, RVA exhibited the highest detection rate, subsequently followed by NoVs GII, As, and Ad.

The co-infection rate was decidedly higher in children with diarrhea than those without (7.1% *vs.* 2.0%, $\chi^2$=10.371, *P*=0.001). Eight distinct forms of co-infection were identified across the five viral pathogens. Remarkably, only three cases of triple co-infection were found, and all were exclusive to children with diarrhea (0.5%, 3/630). Pairwise co-infections were similarly more prevalent in children with diarrhea than those without (4.8% *vs.* 1.3%, $\chi^2$=6.782, *P*=0.009). The co-infection of RVA-NoVs GII was the most commonly observed, with a higher prevalence amongst children with diarrhea. Importantly, RVA was a key player in various co-infection combinations. Notably, after excluding co-infection cases, both RNA and NoVs GII were significantly associated with singular infection diarrhea cases[($\chi^2$=24.367, *P*<0.001) & ($\chi^2$=3.893, *P*=0.048) (Table 1).

The frequency of diarrheal episodes among children varies substantially depending on whether they experience a co-infection or a single infection (*H*=44.187, *P*<0.001). Notably, RVA-NoVs GII-As, RVA-NoVs GII-Ad, and RVA-NoVs GII co-infections exhibit the highest frequency of diarrheal episodes, with an average of eight episodes. This is closely followed by the co-infection of RVA-Ad, which has an average of seven episodes. Single infections of RVA,

TABLE 1. Epidemiological characteristics and co-infections of viral enteric pathogens in children with diarrhea and healthy individuals in Guangzhou City, Guangdong Province, China, 2019.

| Variable | Subgroup | Non-diarrhea, *N*=300 *n* (%) | Diarrhea, *N*=630 *n* (%) | $\chi^2$ | *P* | *OR* (95% *CI*s) |
|---|---|---|---|---|---|---|
| Age | <24 months | 231 (77.0) | 472 (74.9) | 0.476 | 0.491 | 1 (reference) |
| | 24–60 months | 69 (23.0) | 158 (25.1) | | | 1.121 (0.811, 1.549) |
| Gender | Female | 104 (34.7) | 215 (34.1) | 0.026 | 0.871 | 1 (reference) |
| | Male | 196 (65.3) | 415 (65.9) | | | 1.024 (0.767, 1.368) |
| Season | Spring | 80 (26.7) | 255 (40.5) | 2.557 | 0.457 | 1 (reference) |
| | Summer | 98 (32.7) | 144 (22.9) | | | 0.461 (0.322, 0.660) |
| | Autumn | 51 (17.0) | 117 (18.6) | | | 0.720 (0.476, 1.089) |
| | Winter | 71 (23.7) | 114 (18.1) | | | 0.504 (0.342, 0.743) |
| Subjects source | Outpatient | 244 (81.3) | 516 (81.9) | 0.044 | 0.833 | 1 (reference) |
| | Inpatient | 56 (18.7) | 114 (18.1) | | | 0.963 (0.675, 1.372) |
| Lactose intolerance | No | 292 (97.3) | 618 (98.1) | 0.561 | 0.545 | 1 (reference) |
| | Yes | 8 (2.7) | 12 (1.9) | | | 0.709 (0.287, 1.753) |
| Systemic lupus erythematosus | No | 299 (99.7) | 620 (99.8) | – | 0.541 | 1 (reference) |
| | Yes | 1 (0.3) | 1 (0.2) | | | 0.475 (0.030, 7.626) |
| Allergic purpura | No | 298 (99.3) | 628 (99.7) | – | 0.598 | 1 (reference) |
| | Yes | 2 (0.7) | 2 (0.3) | | | 0.475 (0.067, 3.385) |
| Milk protein allergy | No | 299 (99.7) | 623 (98.9) | 1.442 | 0.231 | 1 (reference) |
| | Yes | 1 (0.3) | 7 (1.1) | | | 3.360 (0.411, 27.431) |
| Any viral pathogen | No | 249 (83.0) | 394 (62.5) | 39.873 | <0.001 | 1 (reference) |
| | Yes | 51 (17.0) | 236 (37.5) | | | 2.924 (2.078, 4.116) |
| Number of viral pathogens | No | 249 (83.0) | 394 (62.5) | 41.573 | <0.001 | 1 (reference) |
| | Only one pathogen | 46 (15.3) | 192 (30.5) | | | 2.638 (1.843, 3.776) |
| | Only two pathogens | 5 (1.7) | 41 (6.5) | | | 5.182 (2.021, 13.292) |
| | Three pathogens | 0 (0.0) | 3 (0.5) | | | – |
| RVA | No | 274 (91.3) | 460 (73.0) | 40.994 | <0.001 | 1 (reference) |
| | Yes | 26 (8.7) | 170 (27.0) | | | 3.895 (2.511, 6.041) |
| NoVs GII | No | 288 (96.0) | 559 (88.7) | 13.214 | <0.001 | 1 (reference) |
| | Yes | 12 (4.0) | 71 (11.3) | | | 3.048 (1.627, 5.712) |
| As | No | 287 (95.7) | 605 (96.0) | 0.069 | 0.793 | 1 (reference) |
| | Yes | 13 (4.3) | 25 (4.0) | | | 0.912 (0.460, 1.809) |
| Ad | No | 295 (98.3) | 613 (97.3) | 0.937 | 0.333 | 1 (reference) |
| | Yes | 5 (1.7) | 17 (2.7) | | | 1.636 (0.598, 4.478) |
| NoVs GI | No | 299 (99.7) | 629 (99.8) | 0.289 | 0.591 | 1 (reference) |
| | Yes | 1 (0.3) | 1 (0.2) | | | 0.475 (0.030, 7.626) |
| Co-infection of any type | No | 294 (98.0) | 585 (92.9) | 10.371 | 0.001 | 1 (reference) |
| | Yes | 6 (2.0) | 45 (7.1) | | | 3.769 (1.590, 8.937) |
| Co-infection of three pathogens | No | 300 (100.0) | 627 (99.5) | – | 0.555 | 1 (reference) |
| | Yes | 0 (0.0) | 3 (0.5) | | | – |
| RVA-NoVs GII-As | No | 300 (100.0) | 629 (99.8) | – | 0.998 | 1 (reference) |
| | Yes | 0 (0.0) | 1 (0.2) | | | – |
| RVA-NoVs GII-Ad | No | 300 (100.0) | 628 (99.7) | – | 0.997 | 1 (reference) |
| | Yes | 0 (0.0) | 2 (0.3) | | | – |

Continued

| Variable | Subgroup | Non-diarrhea, *N*=300 *n* (%) | Diarrhea, *N*=630 *n* (%) | $\chi^2$ | *P* | *OR* (95% *CI*s) |
|---|---|---|---|---|---|---|
| Co-infection of two pathogens | No | 296 (98.7) | 600 (95.2) | 6.782 | 0.009 | 1 (reference) |
| | Yes | 4 (1.3) | 30 (4.8) | | | 3.700 (1.293, 10.601) |
| RVA-NoVs GII | No | 298 (99.3) | 597 (94.8) | 11.726 | 0.001 | 1 (reference) |
| | Yes | 2 (0.7) | 33 (5.2) | | | 8.236 (1.963, 34.556) |
| RVA-As | No | 299 (99.7) | 623 (98.9) | 1.442 | 0.231 | 1 (reference) |
| | Yes | 1 (0.3) | 7 (1.1) | | | 3.361 (0.412, 27.431) |
| RVA-Ad | No | 299 (99.7) | 623 (98.9) | 1.442 | 0.231 | 1 (reference) |
| | Yes | 1 (0.3) | 7 (1.1) | | | 3.361 (0.412, 27.431) |
| NoVs GII-As | No | 299 (99.7) | 629 (99.8) | 0.289 | 0.591 | 1 (reference) |
| | Yes | 1 (0.3) | 1 (0.2) | | | 0.475 (0.030, 7.626) |
| NoVs GII-Ad | No | 300 (100.0) | 628 (99.7) | – | 0.997 | 1 (reference) |
| | Yes | 0 (0.0) | 2 (0.3) | | | – |
| As-Ad | No | 299 (99.7) | 629 (99.8) | – | 0.591 | 1 (reference) |
| | Yes | 1 (0.3) | 1 (0.2) | | | 0.475 (0.030, 7.626) |
| RVA single | No | 278 (92.7) | 504 (80.0) | 24.367 | <0.001 | 1 (reference) |
| | Yes | 22 (7.3) | 126 (20.0) | | | 3.159 (1.963, 5.085) |
| NoVs GII single | No | 291 (97.0) | 592 (94.0) | 3.893 | 0.048 | 1 (reference) |
| | Yes | 9 (3.0) | 38 (6.0) | | | 2.089 (1.004, 4.364) |
| As single | No | 289 (96.3) | 612 (97.1) | 0.441 | 0.507 | 1 (reference) |
| | Yes | 11 (3.7) | 18 (2.9) | | | 0.773 (0.360, 1.657) |
| Ad single | No | 296 (98.7) | 620 (98.4) | 0.088 | 0.766 | 1 (reference) |
| | Yes | 4 (1.3) | 10 (1.6) | | | 1.194 (0.371, 3.837) |
| NoVs GI single | No | 299 (99.7) | 629 (99.8) | 0.289 | 0.591 | 1 (reference) |
| | Yes | 1 (0.3) | 1 (0.2) | | | 0.475 (0.030, 7.626) |

Note: The "–" symbol indicates the data can not be calculated.
Abbreviation: *CI*=confidence interval; *OR*=odds ratio; RVA=human group A rotaviruses; NoVs=noroviruses; Ad=adenoviruses; As=astroviruses.

NoVs GII, and the co-infection of RVA-Ad, each average around six episodes. Additional types of single infections and co-infections result in a milder form of the diarrhea illness, with the number of episodes ranging from three to six. This study suggests that the co-infection of RVA-NoVs GII is associated with a higher frequency of diarrheal episodes and a more severe diarrheal illness.

The observed association between RVA-NoVs GII co-infection and diarrhea demonstrated a strength of 8.236 (95% *CI*: 1.963, 34.556). In cases of RVA solo infection, diarrhea demonstrated a strength of 3.159 (95% *CI*: 1.963, 5.085), whereas in NoVs GII single infection cases, the strength was 2.089 (95% *CI*: 1.004, 4.364). Subsequently, the interaction contrast ratio (ICR) was calculated to be 3.996, and the multiplicative interaction value equated to 1.248. These findings suggest a notable additive interaction between RVA-NoVs GII in the progression of diarrhea.

Our co-occurrence examination of two pathogens indicated that 93.3% (14/15) of classifiable species pairs exhibited random associations (Figure 1). No negative co-occurrences were identified. However, positive co-occurrences were noted in only 7.7% (1/15) of acute diarrhea cases in children, specifically with an RVA-NoVs GII co-infection.

## DISCUSSION

Our study found that RVA is the primary cause of diarrhea in children, irrespective of their immunization status. We also identified an array of other viral etiologies and noted co-infection with various combinations of pathogens, underscoring the widespread nature of co-infection. Nevertheless, the

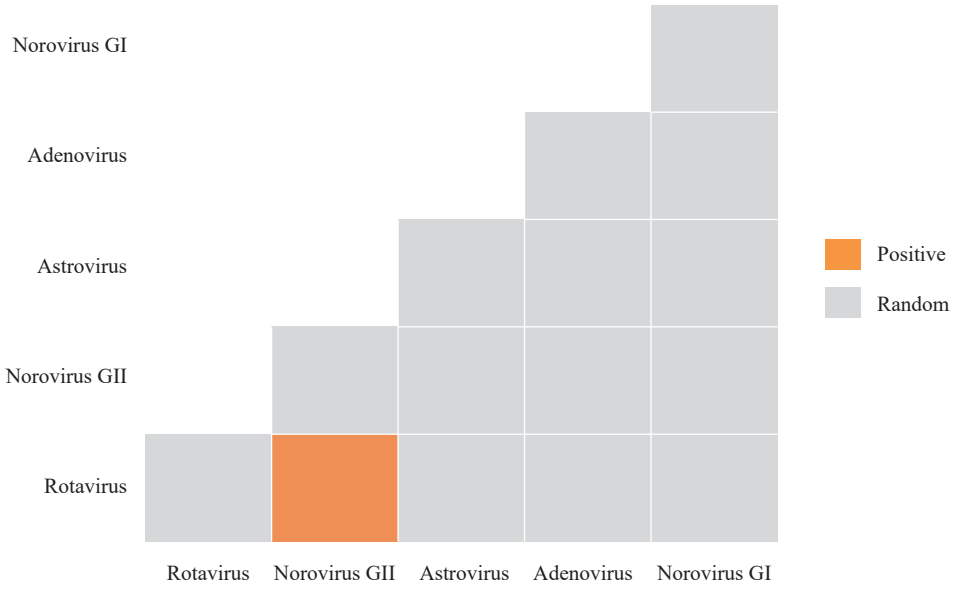


FIGURE 1. Heatmap showing associations between significant enteric viral pathogen species determined using the probabilistic co-occurrence model for viral pathogens detected in 630 children (<5 years) suffering from acute diarrhea in Guangzhou City, Guangdong Province, China, 2019.
Note: The columns and rows represent pairwise relationship between two enteric viral pathogens. Boxes in grey indicate random co-occurrences, orange boxes indicate associations that were more common than expected by chance.

presence of co-infecting pathogens may complicate the assertion of causal relationships and the measurement of associations between a specific pathogen and diarrheal disease. Overlooking these co-infections might result in misleading conclusions. Given the high frequency of enteric pathogen co-infections observed, a comprehensive understanding of diarrheal disease's pathogenesis necessitates an exhaustive exploration of these pathogens' biological interactions (*6*–*7*).

Additionally, the existence of co-infections could potentially result in an undervaluation of the protective benefits of RVA vaccines. For a comprehensive understanding of these effects, it is imperative to apply concepts rooted in core epidemiology to examine their synergistic interactions (*6*). It's widely accepted that the efficacy of RVA vaccines in impoverished settings is subpar when compared to developed nations. High-quality evidence supports the fact that a decrease of 11.3% in the efficiency of RVA vaccines can be attributed to the prevalence of co-infections (*6*). Thus, it is vital that future efficacy studies for RVA vaccines consider these co-infections with other enteropathogens in their design.

Co-infections involving several viral pathogens are often found, even in outwardly healthy children. These co-infections can lead to unexpected health outcomes. An examination of RVA positive instances showed marked changes in their clinical characteristics when co-infections were factored in. Our study particularly led to the observation of an increased severity in diarrhea cases whenever NoVs GII co-infection was present with RVA. This correlation has been reaffirmed by other studies (*4*,*7*). It seems to assist the theory of a synergistic impact between RVA and NoVs GII on diarrheal disease development, suggesting that the pathogenic potential is further magnified in a co-infection scenario. This aligns with previous studies that have reported amplified severity of co-infection cases of diarrhea, for example, RVA-diarrheagenic *Escherichia coli* or RVA-*Giardia lamblia* (*7*). Within RVA-positive diarrhea cases, bacterial co-infections were related to extended periods of diarrhea, while protozoal co-infections were associated with higher hospitalization rates (*7*). Although it is likely that biological mechanisms underlie these synergistic events, they are not often explored or clarified. It's possible that the inflammatory response elicited by RVA may disrupt the epithelium and modify the mucosal structure, thereby enhancing the attachment and invasion of other pathogens. It is therefore crucial for future research to focus on understanding the pathogenic mechanisms of diarrhea during co-infection with RVA in order to fully comprehend the mechanisms at play.

This investigation encompasses several limitations. Initially, it failed to account for numerous unidentified

pathogens, including parasitic and bacterial variants. Second, the research did not incorporate participants suffering from chronic diarrhea nor those exceeding five years in age. Finally, due to the study's execution in a solitary city, this restricts its generalizability.

In conclusion, the study represents a rare comprehensive exploration of pathogenicity in both singular and co-infections in children, with a specific focus on the synergistic interaction among viral pathogens. By harnessing cutting-edge technology for viral diarrhea surveillance, it is possible to establish a dynamic monitoring system with robust predictive capabilities and significant timeliness. The development and implementation of more responsive diagnostic techniques, alongside high-quality, exhaustive screening and examination of diarrhea pathogens, represent a pivotal strategy to identify co-infections. This approach enables physicians to rapidly and thoroughly comprehend co-infections and disease progression, thus allowing for timely intervention, stalling disease progression, and preventing fatalities. Ultimately, this course of action contributes to a reduction in the burden of diarrheal diseases.

**Conflicts of interest**: No conflicts of interest.

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Preplanned Studies

# Comparative Analysis of Vaccine Inequity and COVID-19 Transmission Amid the Omicron Variant Among Countries — Six Countries, Asia-Pacific Region, 2022

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## Summary

### What is already known about this topic?

The coronavirus disease 2019 (COVID-19) persists as a significant global public health crisis. The predominant strain, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), notably the Omicron variant, continues to undergo mutations. While vaccination is heralded as the paramount solution to cease the pandemic, challenges persist in providing equitable access to COVID-19 vaccines.

### What is added by this report?

The distribution of vaccine coverage exhibited disparities between high-income and middle-income countries, with middle-income countries evidencing lower levels of vaccination. The data further suggested that countries with lesser vaccination levels tended to display a higher case fatality rate. Findings indicated that an increase in population-wide vaccination was effective in mitigating COVID-19 related mortalities.

### What are the implications for public health practice?

The findings of this research underscore the pressing necessity for equitable access to vaccines to effectively mitigate the COVID-19 pandemic within the Asia-Pacific region.


Coronavirus disease 2019 (COVID-19) has emerged as a global public health crisis, with equitable access to vaccines representing a significant challenge. Our study aimed to investigate vaccine inequity and the relationship between vaccination and COVID-19 transmission during the Omicron variant period, focusing specifically on six countries within the Asia-Pacific region. We applied Joinpoint regression modeling to analyze the transmission trends of COVID-19, and the beta regression model was employed to explore the impacts of vaccination on daily mortality, morbidity, case fatality rate (CFR), and mortality fatality index (MFI). As of October 18, 2022, the fully vaccinated population percentages in Singapore, Australia, Malaysia, Thailand, Indonesia, and Vietnam were 93.90%, 84.04%, 81.95%, 74.70%, 62.38%, and 86.42%, respectively. When compared with countries boasting a full vaccination coverage rate exceeding 90%, those countries with rates below 70% exhibited increased mortality by an average of 11.88%, morbidity by 19.85%, MFI by 3.06%, and CFR by 1.34%. Clearly, vaccine coverage is uneven throughout the Asia-Pacific region. Elevated levels of population vaccination have been shown to be effective in preventing COVID-19-related deaths. Thus, our findings underscore the pressing need for more uniform vaccine access to efficiently manage and mitigate the ongoing COVID-19 pandemic.

The dataset used in our study is sourced from Our World in Data (*1*). The analysis focuses on six Asia-Pacific countries with relatively comprehensive data at various income levels: Australia and Singapore (high-income), Thailand and Malaysia (upper-middle-income), and Indonesia and Vietnam (lower-middle-income). The study spans from the establishment of the Omicron variant's 100% share in each country to October 18, 2022. Abstraction of definitions pertaining to COVID-19 vaccination, COVID-19 outcomes, and governmental response can be obtained from the Supplementary Methods (available in https://weekly.chinacdc.cn/). A beta regression model was adopted to investigate the association between full vaccination and variables such as daily mortality, morbidity, CFR, and MFI using the logit link model. Both the beta coefficients (β) and the 95% confidence interval (95% *CI*) were calculated. Model accuracy was ensured by assessing the distribution of residuals. The joinpoint regression model was utilized to discern trends over a period of time.

Statistical significance was defined by a two-sided test with $P$ values less than 0.05. All statistical computations were performed using R software (version 4.1.3; R Foundation for Statistical

Computing, Vienna, Austria) and the NCI Joinpoint Regression Program (version 4.9.1.0; National Cancer Institute: Rockville, MD, USA).

Supplementary Table S1 (available in https://weekly.chinacdc.cn/) delineates the distribution of cases, deaths, and full vaccinations. Throughout the designated COVID-19 period (Table 1), Singapore was the inaugural country to initiate vaccinations, while Vietnam and Thailand were the last.

As of October 18, 2022, the percentage of the population that had received the complete vaccination protocol in Singapore, Australia, Malaysia, Thailand, Indonesia, and Vietnam was 93.92%, 84.04%, 81.96%, 74.70%, 62.41%, and 86.57%, respectively. The highest fully vaccinated rate was reported in Singapore, and the lowest in Indonesia (Figure 1A). According to Supplementary Table S2 (available in https://weekly.chinacdc.cn/), Indonesia demonstrated the greatest increase in full vaccination rates amongst the six countries. Government response indicators shone brightest in Malaysia, whereas Australia showed the lowest (Figure 1B).

As outlined in Figure 1, Australia and Singapore observed lower CFR but higher morbidity and mortality, whereas the inverse trend was noted in Indonesia and Thailand. Additionally, Thailand, Indonesia, and Australia reported higher MFI while Singapore, Malaysia, and Vietnam reported lower MFI.

Increasing trends in cumulative morbidity, mortality, CFR, and MFI were noted across these six countries (Supplementary Tables S3–S6, available in https://weekly.chinacdc.cn/).

We employed residual simulation and the Akaike information criterion to evaluate model fitness. Compared with level 1 at full vaccination (Table 2), mortality increased by an average of 10.55%, 5.33%, and 11.88%, morbidity increased by an average of 4.97%, 4.54%, and 19.85%, CFR increased by an average of 0.36%, 0.48%, and 1.34%, MFI increased

TABLE 1. Distribution of vaccination rates over time, by country.

| Variables | High income | | Upper middle income | | Lower middle income | |
|---|---|---|---|---|---|---|
| | Singapore | Australia | Malaysia | Thailand | Indonesia | Vietnam |
| One vaccination | | | | | | |
| 0% | Dec-20 (+0 m) | Feb-21 (+0 m) | Feb-21 (+0 m) | Mar-21 (+0 m) | Jan-21 (+0 m) | Mar-21 (+0 m) |
| 20% | Apr-21 (+4 m) | June-21 (+4 m) | July-21 (+4 m) | Aug-21 (+5 m) | Aug-21 (+7 m) | Sep-21 (+6 m) |
| 40% | May-21 (+5 m) | Aug-21 (+6 m) | July-21 (+4 m) | Sep-21 (+6 m) | Oct-21 (+9 m) | Oct-21 (+7 m) |
| 60% | June-21 (+6 m) | Sep-21 (+7 m) | Aug-21 (+5 m) | Nov-21 (+8 m) | Jan-22 (+12 m) | Nov-21 (+8 m) |
| 80% | Aug-21 (+8 m) | Jan-22 (+11 m) | Jan-22 (+11 m) | – | – | Jan-22 (+10 m) |
| 18 Oct 2022 | 94.65% | 86.58% | 83.72% | 79.62% (+19 m) | 74.62% (+21 m) | 92.37% |
| Full vaccination | | | | | | |
| 0% | Jan-21 (+1 m) | Feb-21 (+0 m) | Feb-21 (+0 m) | Mar-21 (+0 m) | Jan-21 (+0 m) | Apr-21 (+1 m) |
| 20% | May-21 (+5 m) | Aug-21 (+6 m) | July-21 (+5 m) | Sep-21 (+6 m) | Oct-21 (+9 m) | Oct-21 (+7 m) |
| 40% | July-21 (+7 m) | Sep-21 (+7 m) | Aug-21 (+6 m) | Oct-21 (+7 m) | Dec-21 (+11 m) | Dec-21 (+9 m) |
| 60% | Aug-21 (+8 m) | Oct-21 (+8 m) | Sep-21 (+7 m) | Dec-21 (+9 m) | Apr-22 (+15 m) | Dec-21 (+9 m) |
| 80% | Nov-21 (+11 m) | Mar-22 (+13 m) | May-22 (+15 m) | – | – | Apr-22 (+13 m) |
| 18 Oct 2022 | 93.92% | 84.04% | 81.96% | 74.70% (+19 m) | 62.41% (+21 m) | 86.57% |
| Boosters | | | | | | |
| 0% | Sep-21 (+9 m) | Oct-21 (+8 m) | Sep-21 (+7 m) | Aug-21 (+5 m) | Feb-22 (+13 m) | Feb-22 (+11 m) |
| 20% | Nov-21 (+11 m) | Jan-22 (+11 m) | Jan-22 (+11 m) | Jan-22 (+10 m) | July-22 (+18 m) | – |
| 40% | Dec-21 (+12 m) | Feb-22 (+12 m) | Feb-22 (+12 m) | Jun-22 (+20 m) | – | Mar-22 (+14 m) |
| 60% | Feb-22 (+14 m) | – | – | – | – | June-22 (+15 m) |
| 80% | Aug-22 (+20 m) | – | – | – | – | – |
| 18 Oct 2022 | 81.13% | 55.03% (+20 m) | 49.92% (+20 m) | 44.89% (+19 m) | 23.30% (+21 m) | 71.62% (+19 m) |

Note: The distribution of time is represented in terms of months since the initiation of the vaccine rollout. "–" means unavailable; "m" means month.

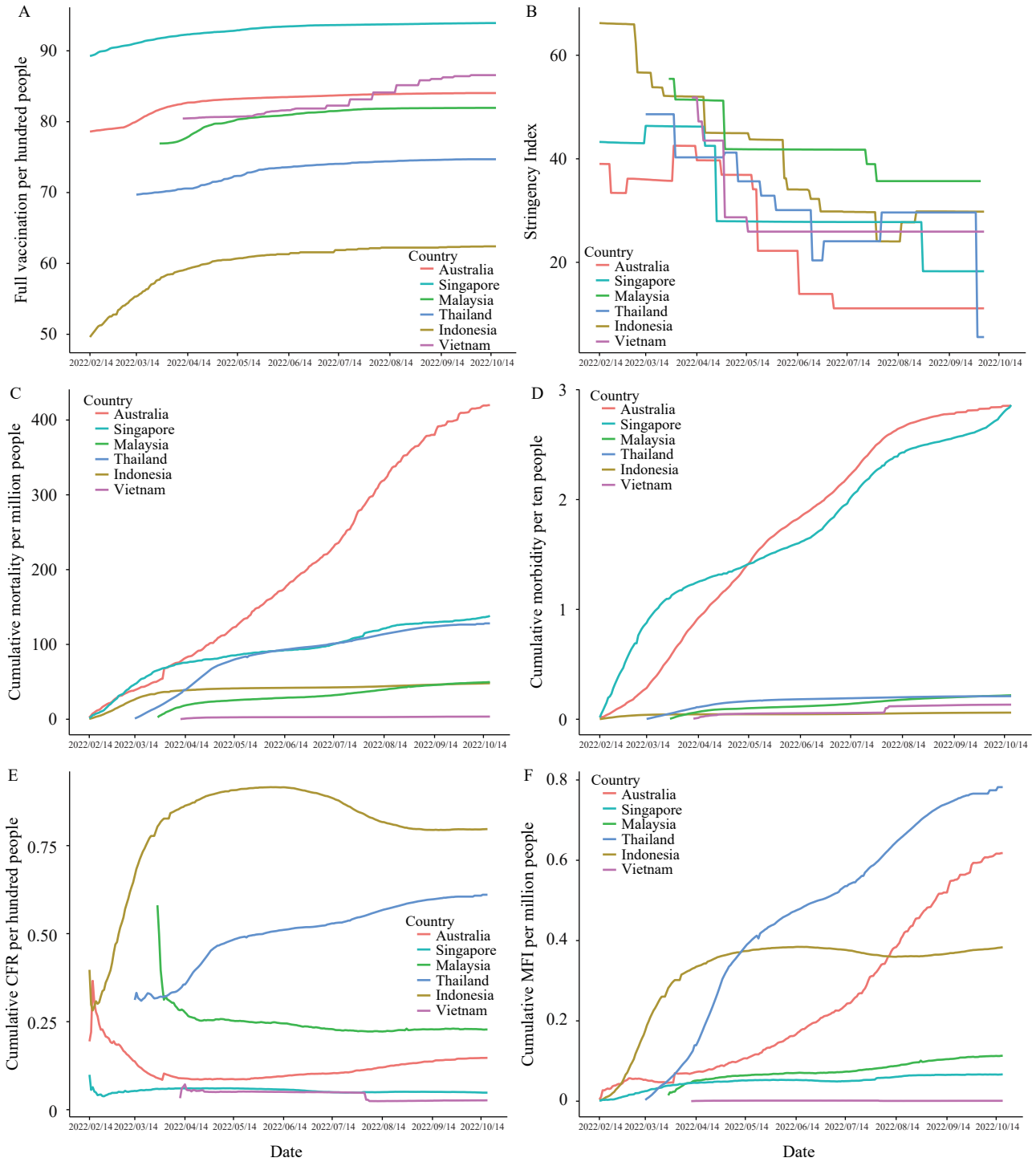


FIGURE 1. Trends by country during the Omicron period. (A) Full vaccination; (B) Stringency Index; (C) mortality; (D) morbidity; (E) case fatality rate (CFR); (F) mortality fatality index (MFI).

by an average of 4.98%, 2.12%, and 3.06% in levels 2-4, respectively.

## DISCUSSION

In this study, six representative countries from the Asia-Pacific region categorized by economic tiers were analyzed to investigate the correlation between immunization and COVID-19 results. The findings suggest that countries with high-income scales exhibit higher rates of complete vaccination, early commencement of vaccination programs, and lower

TABLE 2. Association between full vaccination status and measures of disease severity including MFI, CFR, mortality, and morbidity during the Omicron variant period.

| Full vaccination | Beta coefficients | | Average marginal effects | |
|---|---|---|---|---|
| | β (95% *CI*) | *P*-value | AME (95% *CI*), % | *P*-value |
| Mortality fatality index | | | | |
| Level 1 | Reference | – | Reference | – |
| Level 2 | 0.94 (0.60, 1.28) | <0.001 | 4.98 (3.31, 6.65) | <0.001 |
| Level 3 | 0.55 (0.13, 0.97) | 0.001 | 2.12 (0.82, 3.41) | 0.001 |
| Level 4 | 0.68 (0.11, 1.25) | 0.019 | 3.06 (0.57, 2.55) | 0.016 |
| Case fatality rate | | | | |
| Level 1 | Reference | – | Reference | – |
| Level 2 | 1.00 (0.68, 1.33) | <0.001 | 0.36 (0.22, 0.49) | <0.001 |
| Level 3 | 1.26 (0.88, 1.64) | <0.001 | 0.48 (0.29, 0.66) | <0.001 |
| Level 4 | 1.46 (0.99, 1.93) | <0.001 | 1.34 (0.66, 2.02) | <0.001 |
| Mortality | | | | |
| Level 1 | Reference | – | Reference | – |
| Level 2 | 2.05 (1.78, 2.33) | <0.001 | 10.55 (7.61, 13.49) | <0.001 |
| Level 3 | 1.71 (1.34, 2.07) | <0.001 | 5.33 (2.45, 8.22) | <0.001 |
| Level 4 | 2.18 (1.63, 2.73) | <0.001 | 11.88 (4.65, 19.10) | 0.001 |
| Morbidity | | | | |
| Level 1 | Reference | – | Reference | – |
| Level 2 | 1.47 (1.26, 1.69) | <0.001 | 4.97 (3.86, 6.09) | <0.001 |
| Level 3 | 1.55 (1.25, 1.85) | <0.001 | 4.54 (3.12, 5.96) | <0.001 |
| Level 4 | 2.47 (1.94, 2.99) | <0.001 | 19.85 (13.00, 26.71) | <0.001 |

Note: 1) The model has been adjusted for factors including a 28-day lag for full vaccination, a 14-day lag for Stringency Index, booster shots, population density, gross domestic product, the number of hospital beds per thousand, the proportion of the population aged 65 years and older, and the reproduction rate. 2) The full vaccination rate is regarded as a categorical variable that is divided into four levels. Level 1 signifies a full vaccination rate higher than 90%, level 2 denotes a rate between 80% and 90%, level 3 indicates a rate from 70% to 80%, and level 4 represents a full vaccination rate below 70%.

"–" means unavailable.

Abbreviation: CFR=case fatality rate; MFI=mortality fatality index; AME=average marginal effects; β=beta coefficients; *CI*=confidence interval.

CFR. Additionally, a notable increase in both CFR and MFI was seen in countries with lower vaccination rates in comparison to the country with the highest rate of full vaccination.

The Omicron variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) demonstrates greater transmissibility, increased upper respiratory tract prevalence, and lower disease severity compared to previous variants (*2*). Despite the decrease in disease severity, Omicron's rapid transmission rates persist as a significant obstacle to pandemic control. The administration of booster doses has been shown to enhance defense against severe COVID-19 during the Omicron surge, with elevated antibody levels sustained for the initial four months post-vaccination (*3*). Yet, the effectiveness of vaccines appears to diminish over time (*4*). In summary, while vaccines have significantly curtailed the severity and death rate from COVID-19, they do not offer absolute protection from infection, with cases of "long COVID" prevalent even amidst those who experienced mild or asymptomatic cases of the virus (*5*). Particularly vulnerable to severe outcomes, including hospitalization and death from COVID-19, are older adults, especially those contending with multiple chronic illnesses, notably cardiovascular or respiratory conditions, or dementia (*6*).

This study reveals that lower-income countries exhibit lower rates of complete vaccination and later initiation of the vaccination process. This highlights the disparity in vaccine coverage within the Asia-Pacific region and underscores the urgent need for rectification. Our models indicate that by raising the full vaccination rate from less than 70% to more than

90% as accomplished in Indonesia, the MFI decreased by 19.90% and the CFR declined by 8.02%. Consistent with our findings, Watson et al. (*7*) pointed out that COVID-19 vaccinations have significantly influenced the pandemic's trajectory. However, limited vaccine accessibility in economically disadvantaged countries has restricted its benefits, reinforcing the urgency for global vaccine equality and comprehensive coverage. The primary global objective should remain focused on amplifying vaccination coverage across the world's eligible populace, giving special regard to individuals at an elevated risk of severe illness, such as older demographics, cardiac patients, and individuals with dementia (*8*). This is a significant global concern as stated by COVAX, the World Health Organization' s initiative promoting global equality of COVID-19 vaccine access, which maintains that until all individuals are protected, no one is truly safe (*9*). Several stratagems to ensure equalized COVID-19 vaccine coverage have been proposed, including expansion of the COVAX facility, waivers for intellectual property rights, amplified manufacturing capabilities within economically disadvantaged nations, reinforced and improved health infrastructure, and implementation of extensive COVID-19 vaccination initiatives (*10*). In the future, prioritizing and enhancing routine vaccination schedules within high-risk areas of low- and mid-income nations will abet improved control of future pandemics by addressing vaccine scarcity and unequal accessibility.

In the present study, the severity of COVID-19 across six representative countries was evaluated using an array of outcome measures, including mortality, morbidity, CFR, and MFI. An infectious disease's burden is not solely determined by its case and death counts but also significantly impacted by the total population. Mortality is assessed based on both the number of deaths and the total target population, while CFR factors in the number of cases and deaths. The MFI, a more comprehensive indicator developed for this study, integrates case and death counts with the total targeted population to evaluate COVID-19's severity. As a general metric, the MFI presents a valuable tool for evaluating and comparing the burden of COVID-19 across various regions. The data analyzed in this study pertain to a period when the Omicron variant represented 100% of COVID-19 cases, thus presenting a picture of the ongoing prevalence of this variant relative to studies featuring earlier variants.

However, some limitations warrant consideration. First, given that reporting of the SARS-CoV-2 variant appears every two weeks, the timing of Omicron's dominance may be inaccurately represented. Second, the disparity in vaccine types and disease surveillance reporting systems across different countries could potentially bias the results. Third, the beta regression model displayed some underdispersion — an inherent trait of such models — which, while not significantly detracting from our conclusions, invites a more conservative interpretation of hypothesis tests. Furthermore, the existing study lacks data from asymptomatic, mild, moderate, severe, critical, and fatal cases, a spectrum that future research should consider in order to enhance the MFI's efficiency and accuracy. Despite controlling for potential confounding variables, some factors not accounted for in this research, such as vaccine type, could potentially impact COVID-19 transmission. Thus, caution must be exercised when interpreting the study results.

**Conflicts of interest**: No conflicts of interest.

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# SUPPLEMENTARY MATERIAL

## Methods

### Sources of Data and the Study Population

The Our World in Data project, overseen by the Global Change Data Lab registered in England and Wales, maintains the dataset related to coronavirus disease 2019 (COVID-19) (*1*). The Oxford COVID-19 Government Response Tracker (OxCGRT), which relies on publicly available information, provided the indicators of government response data that we gathered (*2*). Given that our analysis focused on routinely collected, publicly available de-identified data, the approval of an ethics committee was deemed unnecessary.

In this study, we utilized the World Bank's classification to determine the income levels of various countries (*3*). The research includes a selection of six countries in the Asia-Pacific region, chosen based on the relative completeness of their data. These countries represented high-income (Australia and Singapore), upper-middle-income (Thailand and Malaysia), and lower-middle-income tiers (Indonesia and Vietnam). However, the study only includes countries within these specific income level classifications due to insufficient reporting of COVID-19 data from low-income nations in the Asia-Pacific region. Our analysis encompassed data gathered from the date each country reported a 100% Omicron variant prevalence up to October 18, 2022. Data collection commenced on different dates for each country: Australia, Singapore, and Indonesia began on February 14, 2022, Malaysia on March 28, 2022, Thailand on March 14, 2022, and Vietnam on April 11, 2022.

### COVID-19 Vaccination and Government Responses

In this study, "full vaccination" is identified as the proportion of individuals who have received all doses required by the preliminary vaccination protocol, per hundred individuals in the overall population. "One vaccination" refers to the proportion of individuals who have obtained at least one dose of the vaccine, per hundred individuals in the total population. Booster vaccination is described as the percentage of individuals who have received supplemental booster doses, exceeding the doses dictated by the initial vaccination protocol, per hundred individuals in the total population.

The OxCGRT government response indicators consist of nine policies, each rated on an ordinal scale. These include school and workplace closures, public event cancellations, public gathering restrictions, public transportation closures, stay-at-home requirements, public information campaigns, internal movement restrictions, and international travel controls. The Stringency Index, a measure used to gauge governmental restrictions, is an aggregate of these nine indicators. Its value ranges from 0 to 100, with 100 indicating the severest government response and 0 signifying a lack of government response (*2*).

### COVID-19 Outcomes

The outcomes of COVID-19 evaluated in this study encompass daily and cumulative morbidity, mortality, CFR, and MFI. These were calculated as follows:

$$\text{Daily morbidity} = \frac{\text{Number of new confirmed cases}}{\text{Total population}} \times 1,000,000$$

$$\text{Daily mortality} = \frac{\text{Number of new confirmed deaths}}{\text{Total population}} \times 1,000,000$$

$$\text{Daily CFR} = \frac{\text{Number of new confirmed deaths}}{\text{Number of new confirmed cases 10 days earlier}} \times 100$$

$$\text{Daily MFI} = \frac{\text{Number of new confirmed deaths}^2}{\text{Number of new confirmed cases 10 days earlier} \times \text{Total population}} \times 1,000,000$$

$$\text{Cumulative morbidity} = \frac{\text{Number of total confirmed cases}}{\text{Total population}} \times 1,000,000$$

$$\text{Cumulative mortality} = \frac{\text{Number of total confirmed deaths}}{\text{Total population}} \times 1,000,000$$

$$\text{Cumulative CFR} = \frac{\text{Number of total confirmed deaths}}{\text{Number of total confirmed cases}} \times 100$$

$$\text{Cumulative MFI} = \frac{\text{Number of total confirmed deaths}^2}{\text{Number of total confirmed cases 10 days earlier} \times \text{Total population}} \times 1,000,000$$

In the present study, the daily CFR was computed utilizing the number of newly confirmed cases from 10 days prior, as documented by *Our World in Data* (*1*). Moreover, the term 'death' used in the aforementioned formulas represents the reported fatalities attributed to COVID-19. Given that both the morbidity rate and the CFR impact the overall burden of COVID-19, a MFI was formulated. This index incorporates confirmed COVID-19 cases, associated fatalities, and the concurrent population size to provide a more comprehensive assessment of the disease's severity (*4*).

## Statistical Analyses

Descriptive statistics were utilized to analyze the count of cases, mortality, and vaccination rates. A beta regression model (*5*) was conducted to investigate the relationship between full vaccination status and daily CFR and MFI using a logit link. The beta coefficients (b) and 95% confidence intervals (95% *CI*) were determined. The model accounted for variables such as 28-day lag time for full vaccination, 14-day lag time for the Stringency Index, booster presence, population density, gross domestic product, hospital beds per capita, proportion of the population aged 65 and older, and reproduction rate. Full vaccination status was treated as either a categorical variable split into four levels (Level 1–4). Level 1 represented a full vaccination rate above 90%, level 2, between 80% and 90%; level 3, between 70% and 80%; and level 4, less than 70%. Missing data was addressed using the listwise deletion technique (*6*). To correct for temporal variations in full vaccination coverage and the Stringency Index, varying lag times (0, 1, 2, 3, and 4 weeks) were implemented to adjust for lagged effects. When referencing a 1-week lag, the beta regression model utilized vaccination rates (Stringency Index) a week prior. The most suitable lag periods were selected based on the Akaike information criterion (AIC) of each model, with the lowest AIC indicating the most optimal model. Finally, the residual distribution was evaluated to ascertain the fit of the beta regression model.

The Joinpoint regression model was employed to investigate the temporal trends of full vaccination, cumulative morbidity, mortality, CFR, and MFI in each country. This model measured both the average weekly percentage change (AWPC) over the complete observation duration and the weekly percentage change (WPC) for each identified linear trend segment. All computations were executed using the default method and parameters in the Joinpoint statistical software (*7*).

Two-sided test with $P$ values <0.05 was considered statistically significant. All statistical analyses were completed using R version 4.1.3 software (R Foundation for Statistical Computing, Vienna, Austria) and the NCI Joinpoint Regression Program version 4.9.1.0 (National Cancer Institute: Rockville, MD, USA, 2022).

SUPPLEMENTARY TABLE S1. Cases, deaths, and full vaccination rates by country as of the date when the Omicron variant reached 100% prevalence on October 18, 2022.

| Variables | High-income levels | | Upper-middle-income levels | | Lower-middle-income levels | |
|---|---|---|---|---|---|---|
| | Singapore | Australia | Malaysia | Thailand | Indonesia | Vietnam |
| Start time | February 14, 2022 | February 14, 2022 | March 28, 2022 | March 14, 2022 | February 14, 2022 | April 11, 2022 |
| Total population* | 5,453,600 | 25,921,089 | 33,573,874 | 71,601,103 | 273,753,191 | 97,468,028 |
| Stringency Index | 28 (18, 46) | 22(11, 43) | 42(36, 56) | 30 (6, 49) | 34 (24, 66) | 26 (26, 52) |
| Cases, per 100 people | | | | | | |
| N1 | 8.78 | 11.36 | 12.37 | 4.48 | 1.77 | 10.52 |
| N2 | 37.21 | 39.79 | 14.51 | 6.55 | 2.36 | 11.79 |
| DPC | 0.118 | 0.118 | 0.011 | 0.010 | 0.002 | 0.007 |
| Deaths, per 10,000 people | | | | | | |
| N1 | 1.66 | 1.80 | 10.38 | 3.32 | 5.31 | 4.39 |
| N2 | 3.03 | 5.98 | 10.85 | 4.59 | 5.78 | 4.43 |
| DPC | 0.006 | 0.017 | 0.002 | 0.006 | 0.002 | 0 |
| Full vaccination, per 100 people | | | | | | |
| N1 | 89.28 | 78.60 | 76.92 | 69.71 | 49.61 | 80.43 |
| N2 | 93.90 | 84.04 | 81.95 | 74.70 | 62.38 | 86.42 |
| DPC | 0.019 | 0.023 | 0.025 | 0.024 | 0.053 | 0.033 |

Note: N1, Number at 100% share of Omicron variant in all analyzed sequences in the preceding two weeks; N2, Number at 18/10/2022. The acronym DPC stands for Daily Percent Change. Stringency Index, Median (Min, Max).

* Source of total population: https://github.com/owid/covid-19-data/blob/485449bc78681595a553320eaa0c95c139207280/scripts/input/un/population_latest.csv.

SUPPLEMENTARY TABLE S2. Trends in full vaccination across various countries during the Omicron phase in 2022.

| Full vaccination | High income | | Upper middle income | | Lower middle income | |
|---|---|---|---|---|---|---|
| | Singapore | Australia | Malaysia | Thailand | Indonesia | Vietnam |
| Start to October 18 | 93.90 | 84.04 | 81.95 | 74.70 | 62.38 | 86.42 |
| AWPC (95% *CI*) | 0.02 (0.02, 0.02) | 0.03 (0.03, 0.03) | 0.03 (0.03, 0.04) | 0.03 (0.03, 0.03) | 0.09 (0.09, 0.10) | 0.04 (0.03, 0.05) |
| Period-1 | | | | | | |
| Time | February 14–28 | February 14–March 6 | March 27–April 10 | March 13–April 17 | February 14–28 | April 10–July 10 |
| WPC (95% *CI*) | 0.09 (0.08, 0.10) | 0.04 (0.03, 0.04) | 0.06 (0.03, 0.09) | 0.04 (0.04, 0.04) | 0.45 (0.41, 0.48) | 0.02 (0.02, 0.03) |
| Period-2 | | | | | | |
| Time | February 28–April 3 | March 6–27 | April 10–May 1 | April 17–May 29 | February 28–March 27 | July 10–September 11 |
| WPC (95% *CI*) | 0.05 (0.05, 0.05) | 0.15 (0.15, 0.16) | 0.15 (0.12, 0.18) | 0.09 (0.08, 0.09) | 0.32 (0.30, 0.34) | 0.08 (0.07, 0.09) |
| Period-3 | | | | | | |
| Time | April 3–May 29 | March 27–April 17 | May 1–July 24 | May 29–July 3 | March 27–April 24 | September 11–October 18 |
| WPC (95% *CI*) | 0.02 (0.02, 0.02) | 0.06 (0.05, 0.06) | 0.03 (0.02, 0.03) | 0.03 (0.02, 0.03) | 0.14 (0.12, 0.16) | 0.01 (−0.01, 0.04) |
| Period-4 | | | | | | |
| Time | May 29–June 26 | April 17–May 8 | July 24–October 18 | July 3–August 28 | April 24–May 22 | |
| WPC (95% *CI*) | 0.01 (0.01, 0.02) | 0.02 (0.02, 0.03) | 0 (0, 0) | 0.01 (0.01, 0.02) | 0.05 (0.04, 0.07) | |
| Period-5 | | | | | | |
| Time | June 26–October 18 | May 8–August 7 | | August 28–October 18 | May 22–August 7 | |
| WPC (95% *CI*) | 0 (0, 0) | 0.01 (0.01, 0.01) | | 0 (0, 0.01) | 0.02 (0.02, 0.03) | |
| Period-6 | | | | | | |
| Time | | August 7–October 18 | | | August 7–October 18 | |
| WPC (95% *CI*) | | 0 (0, 0) | | | 0.01 (0, 0.01) | |

Note: The AWPC and the WPC exhibit significant deviations from zero at an alpha level of 0.05.
Abbreviation: AWPC=average weekly percentage change; WPC=weekly percentage change.

SUPPLEMENTARY TABLE S3. Trends in the cumulative morbidity of COVID-19 in various countries during the Omicron period in 2022.

| Morbidity | High income | | Upper middle income | | Lower middle income | |
|---|---|---|---|---|---|---|
| | Singapore | Australia | Malaysia | Thailand | Indonesia | Vietnam |
| Start to October 18 | 2.86 | 2.85 | 0.22 | 0.21 | 0.06 | 0.13 |
| AWPC (95% *CI*) | 2.06 (1.86, 2.26) | 2.21 (2.08, 2.34) | 1.87 (1.75, 2.00) | 1.86 (1.78, 1.95) | 1.44 (1.35, 1.54) | 1.60 (1.51, 1.68) |
| Period-1 | | | | | | |
| Time | February 14–28 | February 14–28 | March 27–April 10 | March 13–27 | February 14–28 | April 10–24 |
| WPC (95% *CI*) | 30.31 (25.86, 34.92) | 18.53 (16.47, 20.63) | 21.13 (18.93, 23.37) | 22.35 (21.11, 23.60) | 24.51 (22.47, 26.59) | 15.24 (14.49, 16.00) |
| Period-2 | | | | | | |
| Time | February 28–October 18 | February 28–April 10 | April 10–October 18 | Mar 27–1 | February 28–October 18 | April 24–July 24 |
| WPC (95% *CI*) | 0.56 (0.52, 0.61) | 4.60 (4.19, 5.01) | 0.58 (0.54, 0.61) | 2.64 (2.32, 2.98) | 0.19 (0.17, 0.21) | 0.20 (0.16, 0.23) |
| Period-3 | | | | | | |
| Time | | April 10–July 17 | | May 1–October 18 | | July 24–August 14 |
| WPC (95% *CI*) | | 0.93 (0.84, 1.03) | | 0.16 (0.14, 0.18) | | 3.65 (2.97, 4.33) |
| Period-4 | | | | | | |
| Time | | July 17–October 18 | | | | August 14–October 18 |
| WPC (95% *CI*) | | 0.19 (0.10, 0.28) | | | | 0.12 (0.06, 0.18) |

Note: The WPC and AWPC are statistically significant at an alpha level of 0.05, indicating significant differences from zero.
Abbreviation: COVID-19=coronavirus disease 2019; AWPC=average weekly percentage change; WPC=weekly percentage change.

SUPPLEMENTARY TABLE S4. Trends in cumulative mortality due to COVID-19 by country during the Omicron variant period in 2022.

| Mortality | High income | | Upper middle income | | Lower middle income | |
|---|---|---|---|---|---|---|
| | Singapore | Australia | Malaysia | Thailand | Indonesia | Vietnam |
| Start to October 18 | 135.14 | 416.07 | 49.09 | 126.41 | 47.70 | 3.50 |
| AWPC (95% *CI*) | 1.77 (1.67, 1.88) | 2.12 (1.94, 2.30) | 1.43 (1.34, 1.52) | 2.18 (2.09, 2.28) | 1.76 (1.70, 1.82) | 1.42 (1.33, 1.50) |
| Period-1 | | | | | | |
| Time | February 14–28 | February 14–28 | March 27–April 10 | March 13–27 | February 14–28 | April 10–24 |
| WPC (95% *CI*) | 20.74 (19.18, 22.32) | 18.34 (15.00, 21.77) | 14.94 (13.43, 16.46) | 21.98 (20.57, 23.40) | 25.12 (24.13, 26.13) | 18.26 (16.90, 19.65) |
| Period-2 | | | | | | |
| Time | February 28–March 27 | February 28–May 15 | April 10–October 18 | Mar 27–1 | February 28–March 27 | April 24–October 18 |
| WPC (95% *CI*) | 3.48 (2.81, 4.16) | 2.03 (1.80, 2.26) | 0.49 (0.47, 0.52) | 3.91 (3.53, 4.29) | 3.33 (2.92, 3.74) | 0.18 (0.15, 0.20) |
| Period-3 | | | | | | |
| Time | March 27–October 18 | May 15–October 18 | | May 1–October 18 | March 27–October 18 | |
| WPC (95% *CI*) | 0.35 (0.33, 0.37) | 0.81 (0.74, 0.88) | | 0.34 (0.31, 0.36) | 0.11 (0.10, 0.12) | |

Note: The WPC and AWPC are statistically significant at an alpha level of 0.05, indicating significant differences from zero.
Abbreviation: COVID-19=coronavirus disease 2019; AWPC=average weekly percentage change; WPC=weekly percentage change.

SUPPLEMENTARY TABLE S5. Trends in the cumulative CFR by country during the Omicron period of 2022.

| CFR | High income | | Upper middle income | | Lower middle income | |
|---|---|---|---|---|---|---|
| | Singapore | Australia | Malaysia | Thailand | Indonesia | Vietnam |
| Start to October 18 | 491.28 | 1,464.25 | 2,289.61 | 6,079.1 | 7,960.66 | 264.25 |
| AWPC (95% *CI*) | −0.23 (−0.36, −0.11) | −0.12 (−0.20, −0.04) | −0.44 (−0.51, −0.36) | 0.30 (0.27, 0.34) | 0.34 (0.24, 0.44) | −0.15 (−0.19, −0.11) |
| Period-1 | | | | | | |
| Time | February 14–28 | February 14–28 | March 27–April 10 | March 13–April 3 | February 14–March 27 | April 10–24 |
| WPC (95% *CI*) | −4.68 (−6.20, −3.14) | −0.16 (−1.13, 0.82) | −5.12 (−6.18, −4.04) | 0.09 (−0.06, 0.24) | 2.20 (1.80, 2.60) | 2.89 (2.57, 3.20) |
| Period-2 | | | | | | |
| Time | February 28–March 27 | February 28–March 27 | April 10–October 18 | April 3–May 1 | March 27–May 29 | April 24–July 24 |
| WPC (95% *CI*) | 1.31 (0.50, 2.12) | −2.75 (−3.23, −2.28) | −0.08 (−0.10, −0.06) | 1.28 (1.12, 1.43) | 0.16 (−0.09, 0.42) | −0.08 (−0.10, −0.07) |
| Period-3 | | | | | | |
| Time | March 27–October 18 | March 27–May 15 | | May 1–22 | May 29–October 18 | July 24–August 14 |
| WPC (95% *CI*) | −0.13 (−0.16, −0.11) | −0.16 (−0.33, 0) | | 0.37 (0.07, 0.68) | −0.13 (−0.20, −0.07) | −3.39 (−3.68, −3.10) |
| Period-4 | | | | | | |
| Time | | May 15–October 18 | | May 22–July 17 | | August 14–October 18 |
| WPC (95% *CI*) | | 0.38 (0.36, 0.41) | | 0.12 (0.08, 0.16) | | 0.20 (0.17, 0.23) |
| Period-5 | | | | | | |
| Time | | | | July 17–September 4 | | |
| WPC (95% *CI*) | | | | 0.23 (0.18, 0.28) | | |
| Period-6 | | | | | | |
| Time | | | | September 4–October 18 | | |
| WPC (95% *CI*) | | | | 0.07 (0.01, 0.12) | | |

Note: The WPC and AWPC are statistically significant at an alpha level of 0.05, indicating significant differences from zero.
Abbreviation: CFR=case fatality rate; AWPC=average weekly percentage change; WPC=weekly percentage change.

SUPPLEMENTARY TABLE S6. Trends in the cumulative MFI by country during the Omicron period in 2022.

| MFI | High income | | Upper middle income | | Lower middle income | |
|---|---|---|---|---|---|---|
| | Singapore | Australia | Malaysia | Thailand | Indonesia | Vietnam |
| Start to October 18 | 0.07 | 0.61 | 0.11 | 0.77 | 0.38 | <0.01 |
| AWPC (95% *CI*) | 1.52 (1.40, 1.65) | 1.98 (1.75, 2.21) | 0.99 (0.88, 1.10) | 2.50 (2.39, 2.60) | 2.07 (1.98, 2.17) | 1.20 (0.61, 1.79) |
| Period-1 | | | | | | |
| Time | February 14–28 | February 14–28 | March 27–April 10 | March 13–27 | February 14–28 | April 10–24 |
| WPC (95% *CI*) | 14.67 (13.51, 15.85) | 15.00 (10.48, 19.71) | 9.06 (7.29, 10.85) | 22.44 (20.77, 24.13) | 25.70 (24.59, 26.82) | 23.28 (13.78, 33.56) |
| Period-2 | | | | | | |
| Time | February 28–March 20 | February 28–October 18 | April 10–October 18 | March 27–May 8 | February 28–March 20 | April 24–October 18 |
| WPC (95% *CI*) | 5.60 (4.52, 6.68) | 1.24 (1.19, 1.29) | 0.41 (0.39, 0.44) | 4.34 (4.02, 4.66) | 7.37 (6.43, 8.33) | −0.39 (−0.54, −0.23) |
| Period-3 | | | | | | |
| Time | March 20–April 24 | | | May 8–October 18 | March 20–May 1 | |
| WPC (95% *CI*) | 1.06 (0.73, 1.39) | | | 0.46 (0.43, 0.49) | 0.84 (0.64, 1.04) | |
| Period-4 | | | | | | |
| Time | April 24–July 24 | | | | May 1–October 18 | |
| WPC (95% *CI*) | 0.02 (−0.05, 0.08) | | | | −0.01 (−0.03, 0.01) | |
| Period-5 | | | | | | |
| Time | July 24–August 21 | | | | | |
| WPC (95% *CI*) | 0.80 (0.29, 1.32) | | | | | |
| Period-6 | | | | | | |
| Time | August 21–October 18 | | | | | |
| WPC (95% *CI*) | 0.07 (−0.05, 0.18) | | | | | |

Note: Both the AWPC and the WPC significantly deviate from zero at the alpha=0.05 level.
Abbreviation: MFI=mortality fatality index; AWPC=average weekly percentage change; WPC=weekly percentage change.

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Vital Surveillances

# Epidemiological Evaluation of *Bacillus cereus*-Induced Foodborne Outbreaks — China, 2010–2020

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## ABSTRACT

**Introduction**: *Bacillus cereus* (*B. cereus*) is a common gram-positive bacterium that contaminates starch-rich food and can cause outbreaks of foodborne diseases. This study describes the characteristics of outbreaks caused by *B. cereus* in China during 2010–2020 and explore the possible reasons for changes in the number of outbreaks over time. Results of this analysis can efficiently help guide and allocate public resources to prevent *B. cereus*-caused foodborne diseases.

**Methods**: Descriptive statistical methods were used to analyze the data on *B. cereus* outbreaks in China during this period. The data were identified and reported at all levels in China through National Foodborne Disease Outbreak Surveillance System.

**Results**: From 2010 to 2020, a total of 419 foodborne outbreaks prompted by *B. cereus* were reported in China, leading to 7,892 cases, 2,786 hospital admissions, and 5 fatalities. The bulk of the outbreaks were recorded in the summer, primarily between May and September. The most recurrent food vehicle was linked with rice or flour-based products, notably those made with rice or fried rice. School canteens bore the brunt of the *B. cereus* outbreaks. In multifactor outbreaks, food contamination was identified as the most common culprit; while in instances where only one factor contributed, improper storage was most frequently implicated.

**Conclusion**: The prevalence of *B. cereus* outbreaks remained relatively consistent throughout the studied period. Understanding the types of foods, causative factors, and contributing elements leading to *B. cereus* outbreaks can help inform prevention strategies for foodborne illnesses. The majority of outbreaks were associated with rice- or flour-based foods in school canteens, suggesting contamination and improper storage during food preparation. Consequently, it is essential to prioritize continuous education for canteen staff on food safety, efficacious management, and proper practices. The implementation of comprehensive guidelines, encompassing multiple critical aspects, can potentially reduce the occurrence of *B. cereus* outbreaks.

*Bacillus cereus* (*B. cereus)* frequently contaminates food and functions as an opportunistic pathogen, leading to outbreaks of foodborne diseases (*1–2*). Over the past decade in China, it ranks as the fourth leading bacterial pathogen associated with foodborne outbreaks (*3*). *B. cereus* produces a spectrum of toxins that can be primarily classified into vomiting-type and diarrhea-type enterotoxins based on symptoms they cause (*4–5*). Its foodborne infections manifest as severe symptoms, such as nausea, vomiting, and diarrhea; in some instances, it can be fatal and typically presents sudden onset (*6–8*). Consequently, the results of our analysis can be efficiently utilized to direct and allocate public health resources to mitigate *B. cereus* associated foodborne diseases.

## METHODS

Between 2010 and 2020, the National Foodborne Disease Outbreak Surveillance System was used by all sectors of CDC to document incidents of foodborne outbreaks. This study specifically collected data on outbreaks caused by *B. cereus*. Required data for each outbreak comprised of date of occurrence, geographical region, case count, number of hospitalizations and deaths, setting for food preparation, etiologic agents, and implicated food, among other factors. The population statistics were derived from the seventh national census conducted in 2020.

The National Foodborne Disease Outbreaks Surveillance System processed and disseminated all monitoring data. Data cleansing and database creation

were carried out using Microsoft Office (version 2010, Microsoft, Washington, USA), while SPSS (version 16.0, SPSS Inc, Chicago, USA) was employed for the related statistical analysis.

Correlational definitions:

An outbreak of foodborne illness is cited when two or more cases of the disease are documented.

The term "multifactor" is employed to represent the simultaneous presence of two or more elements of food contamination. These elements may include improper storage, contamination or spoilage of ingredients, cross-contamination between raw and cooked foods, and food expiration among others.

## RESULTS

Between 2010 and 2020, we documented a total of 419 foodborne outbreaks attributed to *B. cereus*, resulting in 7,892 cases, 2,786 hospital admissions, and 5 fatalities.

Figure 1 illustrates the distribution of outbreak cases over a decade. In 2018, out of all reported outbreaks, 56 instances, constituting 13.37%, were noted, marking the highest count from 2010 to 2020. Notably, the year 2012 reported the most cases, with a sum of 979, constituting 12.40% of all instances. However, the year 2011 recorded the peak for hospitalization rate. The period from 2014 to 2016 experienced five fatalities: one in 2014, two in 2015, and the remaining two in 2016.

The frequency of reported outbreaks varied on a monthly basis (Figure 2), predominantly occurring between May and September. In June, 73 outbreaks were noted, comprising 17.42% of the total outbreaks. The peak in the number of cases was observed in September, with 1,975 cases recorded, affecting the greatest number of individuals (25.01%). The month of May reported the highest rate of hospitalizations (51.04%). Mortalities were relatively low, with two reported in February and one each in April, July, and August.

The data highlighted notable differences in the proportion of outbreak cases attributed to various food sources (Table 1). Foods derived from rice or flour were identified as the primary cause of most outbreaks (46.30%) and associated cases (40.81%). Bakery products were responsible for the highest hospitalization rate (67.78%). Furthermore, five mortalities were chiefly associated with rice or flour-based products and complex foods.

Upon conducting further analysis of each category of rice or flour products implicated in foodborne outbreaks associated with *B. cereus*, it was found that rice and rice products accounted for a higher number of outbreaks (158 outbreaks), compared to flour and flour products (36 outbreaks).

The number of outbreak instances was subject to variation based on the location of food preparation, as outlined in Figure 3. The primary source of these outbreaks, as well as the related cases, was found to be school cafeterias. In fact, 26.25% of outbreaks could be traced back to food prepared in these school canteens, accounting for 48.34% of cases associated with such

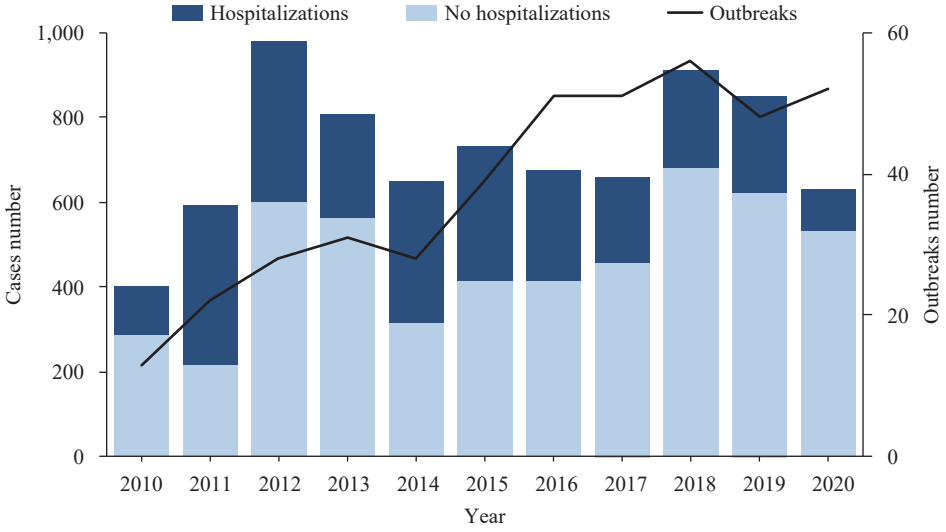


FIGURE 1. Annual distribution of foodborne outbreaks, instances, and hospitalizations attributed to *B. cereus* in China from 2010 to 2020.

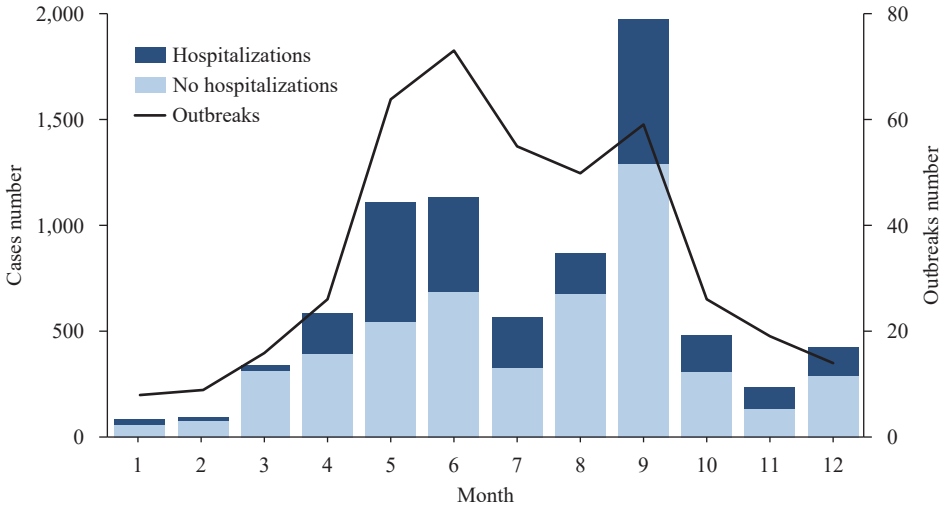


FIGURE 2. Monthly distribution of foodborne outbreaks, cases, and hospitalizations resulting from *B. cereus* in China from 2010 to 2020.

TABLE 1. Number and proportion of *B. cereus* foodborne outbreaks, incidents, hospitalization cases, and deaths organized by food category in China from 2010 to 2020.

| Food category | Outbreaks | | Cases | | Hospitalizations | | Deaths | |
|---|---|---|---|---|---|---|---|---|
| | Number | Proportion (%)[§] | Number | Proportion (%)[¶] | Number | Rate (%)[**] | Number | Fatality rate (%)[††] |
| Rice or flour | 194 | 46.30 | 3,221 | 40.81 | 1,230 | 38.19 | 3 | 0.09 |
| Complex food* | 54 | 12.89 | 1,430 | 18.12 | 347 | 24.27 | 2 | 0.14 |
| Multiple food[†] | 51 | 12.17 | 1,174 | 14.88 | 353 | 30.07 | 0 | 0.00 |
| Meat | 29 | 6.92 | 398 | 5.04 | 251 | 63.07 | 0 | 0.00 |
| Bean | 21 | 5.01 | 630 | 7.98 | 275 | 43.65 | 0 | 0.00 |
| Vegetable | 17 | 4.06 | 237 | 3.00 | 68 | 28.69 | 0 | 0.00 |
| Pastry | 14 | 3.34 | 239 | 3.03 | 162 | 67.78 | 0 | 0.00 |
| Aquatic animal | 8 | 1.91 | 125 | 1.58 | 44 | 35.20 | 0 | 0.00 |
| Beverage and frozen drink | 5 | 1.19 | 57 | 0.72 | 11 | 19.30 | 0 | 0.00 |
| Dairy | 3 | 0.72 | 93 | 1.18 | 9 | 9.68 | 0 | 0.00 |
| Fruit | 2 | 0.48 | 26 | 0.33 | 0 | 0.00 | 0 | 0.00 |
| Egg | 2 | 0.48 | 8 | 0.10 | 0 | 0.00 | 0 | 0.00 |
| Condiment | 2 | 0.48 | 6 | 0.08 | 3 | 50.00 | 0 | 0.00 |
| Other food | 3 | 0.72 | 31 | 0.39 | 19 | 61.29 | 0 | 0.00 |
| Unknown food | 14 | 3.34 | 217 | 2.75 | 14 | 6.45 | 0 | 0.00 |
| Total | 419 | 100.00 | 7,892 | 100.00 | 2,786 | 35.30 | 5 | 0.06 |

* Complex food: These are items that contain multiple components, but the specific ingredient causing the outbreak cannot be accurately identified.
[†] Multiple food: The causative agent originates from diverse food categories.
[§] Proportion (%)=Outbreaks number/Total number×100%.
[¶] Proportion (%)=Cases number/Total number×100%.
[**] Rate (%)=Hospitalizations number/Cases number×100%.
[††] Fatality rate(%)=Deaths number/Cases number×100%.

outbreaks. However, the household held the record for the highest hospitalization rate at 53.92%, along with the highest mortality rate at 1.37%.

Multifactor contamination was identified as the cause for 39.14% of outbreaks and 41.02% of associated cases. This was closely followed by improper storage, accounting for 111 outbreaks (26.49%) and 1,981 cases (25.10%). The highest rate of

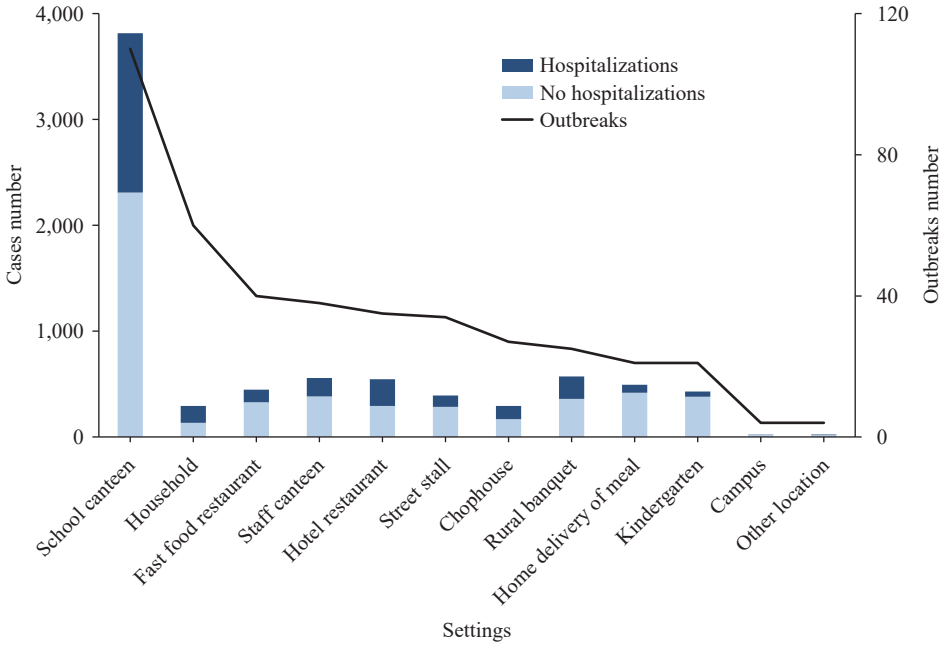


FIGURE 3. Distribution of foodborne outbreaks, cases, and hospitalizations caused by *B. cereus* in various settings in China from 2010–2020.

hospitalization was attributed to food mishandling and ingestion errors, which stood at 71.93%. Moreover, two out of the reported five fatalities were due to undetermined causes.

In the multifactor composition, the occurrence of two factors was most prevalent, accounting for 70.12% of the cases. Conversely, instances involving more than two factors represented 29.88% of the cases. Of the pairings in the two-factor configuration, the most frequent combination, comprising 48.78%, was inadequate storage and inappropriate processing. Meanwhile, the combination of ingredient contamination or spoilage with improper storage made up 9.76%. For configurations involving more than two factors, the most common trio was ingredient contamination or spoilage, inappropriate storage, and improper processing, which accounted for 53.33% of such cases.

## DISCUSSION

From 2010 to 2020, microbial agents notably contributed to the incidence of foodborne disease outbreaks in China. These microbial outbreak cases were second only to mushroom poisoning in regards to the number of cases reported. This pattern supports previous studies (*9*), with *B. cereus* ranking fourth among factors associated with microbial foodborne disease outbreaks. However, the fatality rate associated with *B. cereus* was significantly higher compared to other contributing factors. Thus, increased vigilance towards outbreaks of *B. cereus* is highly recommended for relevant departments.

Between 2010 and 2016, China experienced a gradual increase in *B. cereus*-related outbreaks, which subsequently stabilized to approximately 50 outbreaks annually over the subsequent five years. Remarkably, 2018 saw the highest number of these reported outbreaks. The majority of these foodborne diseases related to *B. cereus* typically occurred between May and September, demonstrating a certain level of annual consistency. Notably, the majority of these incidents were reported during the summer, followed by the spring and fall. Attributable to its optimal growth temperature (28–35 °C), *B. cereus* has the potential to proliferate rapidly and generate substantial quantities of toxins, thereby inducing foodborne cases, according to a previous study (*2*). This trend substantiates that the *B. cereus* poisoning peak season is typically the summer. Domestic and international studies (*10*–*11*) further reveal that the most pathogenic food in *B. cereus* outbreaks is primarily rice or flour products, representing nearly half of all categories. Moreover, the proportion of rice and rice products in all types of rice or flour products exceeds 80%. Further breakdown showed that rice and fried rice constituted 36% and 33% within the category of rice and rice products, respectively.

School canteens and households appeared most frequently as sources of food preparation connected to *B. cereus* outbreaks. Nevertheless, the number of instances linked to food prepared in school canteens was markedly greater than those connected to households, constituting nearly half of all affected cases. Given the difficulties students face in discerning food quality and the inherent nature of communal dining in schools, they are at a heightened risk for foodborne disease outbreaks. Therefore, to mitigate the frequency of such outbreaks, supervisory bodies should enhance their oversight and management of food safety in school canteens.

Food contamination is influenced by a myriad of complex factors. Our findings are consistent with prior research (*12*–*13*), revealing that the simultaneous or interactive presence of several factors is most often the cause of food contamination. For instance, improper handling, excessive propagation, and subsequent toxin secretion due to inadequate preservation can result in contamination by *B. cereus*. To mitigate the risk of foodborne outbreaks attributed to *B. cereus*, it is essential to address a multitude of core control and management factors. These include utilizing safe food ingredients, ensuring cleanliness and standardization throughout the food processing procedure, preventing cross-contamination, thoroughly cooking the food, among others. Concurrently, implementing proper preservation to inhibit the growth of *B. cereus* is of great significance.

This study focuses solely on outbreaks investigated by the China CDC, which may not accurately reflect the true incidence. Monitoring foodborne disease outbreaks is a multifaceted endeavor necessitating government support, swift diagnosis from medical institutions, thorough food hygiene assessments by the Market Supervision and Administration Department, diligent epidemiological inquiry by the CDC, and exact laboratory testing.

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Notifiable Infectious Diseases Reports

# Reported Cases and Deaths of National Notifiable Infectious Diseases — China, April 2023*

| Diseases | Cases | Deaths |
|---|---|---|
| Plague | 0 | 0 |
| Cholera | 0 | 0 |
| SARS-CoV | 0 | 0 |
| Acquired immune deficiency syndrome† | 4,937 | 1,741 |
| Hepatitis | 142,746 | 96 |
| Hepatitis A | 1,114 | 0 |
| Hepatitis B | 116,400 | 19 |
| Hepatitis C | 21,597 | 76 |
| Hepatitis D | 19 | 0 |
| Hepatitis E | 3,006 | 1 |
| Other hepatitis | 610 | 0 |
| Poliomyelitis | 0 | 0 |
| Human infection with H5N1 virus | 0 | 0 |
| Measles | 85 | 0 |
| Epidemic hemorrhagic fever | 305 | 1 |
| Rabies | 14 | 11 |
| Japanese encephalitis | 1 | 0 |
| Dengue | 9 | 0 |
| Anthrax | 19 | 0 |
| Dysentery | 2,794 | 0 |
| Tuberculosis | 72,846 | 335 |
| Typhoid fever and paratyphoid fever | 452 | 0 |
| Meningococcal meningitis | 11 | 0 |
| Pertussis | 1,074 | 0 |
| Diphtheria | 0 | 0 |
| Neonatal tetanus | 1 | 0 |
| Scarlet fever | 1,102 | 0 |
| Brucellosis | 7,677 | 0 |
| Gonorrhea | 7,931 | 0 |
| Syphilis | 48,926 | 1 |
| Leptospirosis | 8 | 0 |
| Schistosomiasis | 1 | 0 |
| Malaria | 189 | 0 |
| Human infection with H7N9 virus | 0 | 0 |
| Influenza | 1,677,011 | 31 |
| Mumps | 7,028 | 0 |
| Rubella | 75 | 0 |

Continued

| Diseases | Cases | Deaths |
|---|---|---|
| Acute hemorrhagic conjunctivitis | 2,210 | 0 |
| Leprosy | 41 | 0 |
| Typhus | 119 | 0 |
| Kala azar | 34 | 1 |
| Echinococcosis | 347 | 0 |
| Filariasis | 0 | 0 |
| Infectious diarrhea[§] | 103,060 | 0 |
| Hand, foot and mouth disease | 20,105 | 0 |
| Total | 2,101,158 | 2,217 |

* According to the National Bureau of Disease Control and Prevention, coronavirus disease 2019 (COVID-19) is not included.
† The number of deaths of acquired immune deficiency syndrome (AIDS) is the number of all-cause deaths reported in the month by cumulative reported AIDS patients.
§ Infectious diarrhea excludes cholera, dysentery, typhoid fever and paratyphoid fever.
The numbers of cases and cause-specific deaths refer to data recorded in National Notifiable Disease Reporting System in China, which includes both clinically-diagnosed cases and laboratory-confirmed cases. Only reported cases of the 31 provincial-level administrative divisions in Chinese mainland are included in the table, whereas data of Hong Kong Special Administrative Region, Macau Special Administrative Region, and Taiwan, China are not included. Monthly statistics are calculated without annual verification which is usually conducted in February of the next year for de-duplication and verification of reported cases in annual statistics. Therefore, 12-month cases could not be added together directly to calculate the cumulative cases because the individual information might be verified via National Notifiable Disease Reporting System according to information verification or field investigations by local CDCs.

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