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Coronavirus Pandemic

Trends in typhoid fever during the COVID-19 pandemic in Pakistan

Carly Ching[1], Muhammad H Zaman[1,3], Azra Parveen[2], Faisal Sultan[2], Summiya Nizamuddin[2]

[1] *Department of Biomedical Engineering, Boston University, Boston, MA, United States*
[2] *Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan*
[3] *Center on Forced Displacement, Boston University, Boston, MA, United States*

Abstract
Introduction: Pakistan has been experiencing an extensively drug-resistant (XDR) outbreak of typhoid for some years. We sought to evaluate how the COVID-19 pandemic impacted typhoid epidemiology in Pakistan, from the beginning of the pandemic in 2020 through the end of 2022, and the reduction of COVID-19 cases.
Methodology: We compared national public COVID-19 data with retrospectively obtained patient data of confirmed *S.* Typhi isolates between January 2019 and December 2022 from Shaukat Khanum Memorial Cancer Hospital and Research Centre and the hospital's extended network of laboratory collection centers across Pakistan.
Results: We observed that during the early onset of the COVID-19 pandemic and COVID-19 peaks, typhoid positivity generally decreased. This suggests that restrictions and non-pharmaceutical interventions that limited social interactions and promoted good sanitation and hygiene practices had a positive secondary effect on typhoid. This led to an overall yearly decrease in typhoid positivity between 2019 to 2021. However, the percentage of *S.* Typhi cases isolated that were ceftriaxone-resistant continued to increase, suggesting the continued dominance of XDR typhoid in Pakistan. In 2022, with the alleviation of pandemic restrictions, we observed increased typhoid positivity and COVID-19 and typhoid positivity started to follow similar trends.
Conclusions: Given the continued presence of COVID-19 along with XDR typhoid in Pakistan, it will be imperative to use differential testing to ensure that the epidemiology of each reported is accurate, the spread of each it contained, and that antibiotics are not misused. The use of approved vaccinations will lessen the burden of both diseases.

Key words: COVID-19; typhoid; drug resistance.

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Introduction

Typhoid fever is a public health concern, with the highest burden in lower- and middle- lower-income countries due to unsafe water consumption and poor, sanitation, and hygiene (WASH). Typhoid fever is a bacterial infection caused by the Gram-negative, rod-shaped serovars of *Salmonella enterica* subspecies *enterica* serovar Typhi (*S.* Typhi) and is transmitted via the oral-fecal route [1]. In Pakistan, some drivers of typhoid spread are a lack of proper sewage management systems, inadequate supply of drinkable water, high rates of rural-to-urban area migration, and insufficient health facilities. Due to the absence of a country-wide epidemiological surveillance system, inadequate data availability, and restricted laboratory capacity, it is difficult to assess the prevalence of typhoid fever in Pakistan. This underreporting is also caused by factors, such as the administration of antibiotics before confirmatory laboratory tests, and the fact that patients do not always seek healthcare treatment at hospitals or use laboratory services, due to financial constraints [2].

Recent publications have highlighted the potential impact of co-epidemics/co-infections of coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, and other infectious diseases on already overburdened healthcare infrastructures [3,4]. In Pakistan, until April 5, 2022, 1,525,775 confirmed cases of COVID-19, with 30,361 deaths were recorded in the country [5]. The situation with COVID-19 and typhoid fever is challenging since several symptoms of typhoid fever are similar to the clinical presentation of COVID-19. For instance, typhoid fever usually presents with symptoms ranging from slow onset of continuous fever, chills, liver, and spleen enlargement (hepatosplenomegaly), and abdominal pain, to rash, headache, diarrhea, or constipation, nausea, relative bradycardia, and low consciousness level. In comparison, COVID-19 symptoms include fever, headache, shortness of breath, arthralgia, sore throat, fatigue, chest pain, hypogeusia, hyposmia, and cough, amongst others [6]. Therefore, some overlaps in the clinical presentations of these two diseases can lead to underdiagnosis or misdiagnosis. Additionally, there may be a delay in diagnosis and treatment, worsening the clinical outcomes for both diseases. The diagnostic delay due to symptom similarity of COVID-19 and other infectious diseases has also been reported in other countries [7]. In addition, the lack of facilities and laboratory expendables limits the capacity of typhoid fever testing. As a result, antibiotics are often prescribed without laboratory confirmation, leading to underdiagnosis and increased antimicrobials resistance development. Indeed, there is concern that the overuse of azithromycin [8] used early in the treatment of COVID-19 may drive resistance to one of the few remaining antibiotics effective against XDR typhoid.

The World Health Organization (WHO) has defined XDR typhoid fever as typhoid fever caused by an *S.* Typhi strain that is resistant to all recommended antibiotics for typhoid fever, which include chloramphenicol, ampicillin, trimethoprim-sulfamethoxazole as the first line of treatment, fluoroquinolones as the second line of treatment as well as third-generation cephalosporins, but retains susceptibility to carbapenems and macrolides (azithromycin) [9]. Here, we refer to clinically confirmed ceftriaxone-resistant typhoid as XDR.

There have been reports of changing epidemiology, namely a decrease, in other communicable diseases and infections during the COVID-19 pandemic across the globe. First, decreases may be due to a decrease in surveillance activities as health authorities shifted attention towards controlling the COVID-19 pandemic. Second, non-pharmaceutical interventions (NPIs) such as universal masking, improved hygiene and social distancing measures practiced to control COVID-19 cases may have had a preventive effect on other communicable diseases as well. Third, panic due to the pandemic was severe and unprecedented, which may have inevitably incited a fear of hospitals and clinics in the masses, causing them to avoid them. For example, before 2020 the incidence of most foodborne diseases had not declined for many years. In the United States, during 2020, the observed incidences of infections caused by enteric pathogens decreased by 26% compared with the period between 2017 and 2019. Specifically, there was a 22% decrease in *Salmonella* infections [10]. There has also been a decrease in the incidence of repository pathogens such as influenza and *Streptococcus pneumoniae* [11,12]. However, evidence suggests that infection incidence rates (IRs) are rebounding after the easing of social restrictions (e.g., mask mandates) [11].

It is difficult to distinguish between COVID-19 and typhoid fever in some regions of Pakistan due to limited COVID-19 testing access. It is possible that these scenarios could compromise both disease treatment and epidemiological surveillance efforts as well as make COVID-19 co-infections with typhoid go overlooked. In addition, diagnostic and treatment delays can worsen the clinical picture in both cases, which may require further testing. This challenges the country's health systems and increases the burden on health facilities and human resources. Despite the potential implications of COVID-19 and typhoid, especially XDR typhoid, data on the two diseases together has not been analyzed and mapped. Thus, as Pakistan has been experiencing an outbreak of XDR typhoid and has a relatively higher burden of typhoid [13], we sought to evaluate how COVID-19 has exacerbated or alleviated typhoid epidemiologically in Pakistan, from the beginning of the pandemic in 2020 through the end of 2022 and the easing of COVID-19 cases, using national COVID-19 data, along with retrospective patient data from Shaukat Khanum Memorial Cancer Hospital and Research Centre (SKMCH&RC) and the hospital's extended network of laboratory collection centers across Pakistan. Many of the observations previously reported on communicable diseases have been yearly changes compared to years prior to COVID-19. For further insight, we sought to investigate the dynamics of the impacts of non-pharmaceutical interventions and the COVID-19 pandemic on typhoid, by comparing the pre-pandemic typhoid prevalence with prevalence during the pandemic, especially during COVID-19 peaks, and upon easing of restrictions. We also monitored the trend of antibiotic susceptibility patterns of *S.* Typhi to determine any differential trends associated with the COVID-19 pandemic.

Methodology

Sample collection

Retrospective patient data analysis was conducted at SKMCH&RC and comprised of microbiological susceptibility data of confirmed *S.* Typhi isolates collected between January 2019 and December 2022 from SKMCH&RC and the hospital's extended network of laboratory collection centers across Pakistan [14]. All data was retrieved from the online records on the in-house information system database. COVID positivity data was extracted from the national COVID website (https://covid.gov.pk/stats/Pakistan) and Twitter account (@NIH_Pakistan).

Antimicrobial susceptibility testing/Bacterial identification

All blood culture samples collected via the SKMCH&RC's laboratory network were cultured and tested for antimicrobial susceptibility as described before [14]. We calculated the positivity rates of *S.* Typhi/ XDR *S.* Typhi using the number of positive cases from the total number of blood cultures performed each month [15]. We define ceftriaxone-resistant *S.* Typhi as XDR.

Results and Discussion

Overview of COVID restrictions and peaks

The COVID-19 pandemic in Pakistan was part of the ongoing global COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Pakistan's first case was confirmed in late February 2020 [16,17]. By then the government and the Ministry of Health held formal consultations and formulated strategies to strengthen the pandemic response. By the end of March, positive cases had been registered in all four provinces and territories of the country, and soon after lockdowns were implemented in parts of the country. With the rapidly changing initial responses from the developed countries, Pakistan imposed a series of non-pharmaceutical interventions (NPIs), including the closure of educational institutions, bans on large gatherings, sealing of borders, and closure of some non-essential businesses. The country also strengthened its surveillance system and implemented standard operating procedures, mandatory mask use, and a trace, test, and quarantine approach [16-19]. The five COVID-19 waves and dominant variants in Pakistan are summarized in the literature [20-23].

Typhoid and COVID-19 positivity rates throughout the pandemic

We observed how COVID-19 positivity (country-wide) and *S.* Typhi positivity moved in relation to each other, and how specific interventions impacted *S.* Typhi epidemiology month-by-month from March 2020 to December 2022. These types of analyses allow resolution that allows correlation to specific peaks and NPIs, compared to looking at the change from one pre-COVID-19 timeframe to one post-COVID-19 timeframe. We first noted blood cultures received did not notably decrease between March 2020 and December 2022 (Figure 1) and maintained similar yearly seasonal patterns.

We observed that *S.* Typhi positivity decreased during the first three COVID-19 peaks, after the introduction of critical NPIs (Figure 2). Typhoid is a disease that spreads through the fecal-oral route. For example, many contract typhoid from contaminated food or drinks from local eateries or roadside stalls. Thus, during the time of peaks and lockdowns, movement in and between cities was restricted, and people were not able to socialize and consume food and drink as they pleased, which in turn controlled the spread of typhoid. During the first peak from April to June 2020, COVID-19 positivity increased by 116.7%, while *S.* Typhi decreased by 65.6%. During the second peak from October to December 2020, COVID-19 positivity increased by 203.1%, while *S.* Typhi decreased by 43.4%. During the third peak from February to April 2021, COVID-19 positivity increased by 179.0%, while *S.* Typhi decreased by 51.6%. Conversely, during the fourth peak, from June to August 2021, COVID-19 positivity increased 171.1%, while *S.* Typhi remained similar (6.4% increase). This may be due to the circulation of a more transmissible variant (Delta [20-23]) which was more infectious

Figure 1. Blood cultures between January 2019 and December 2022.

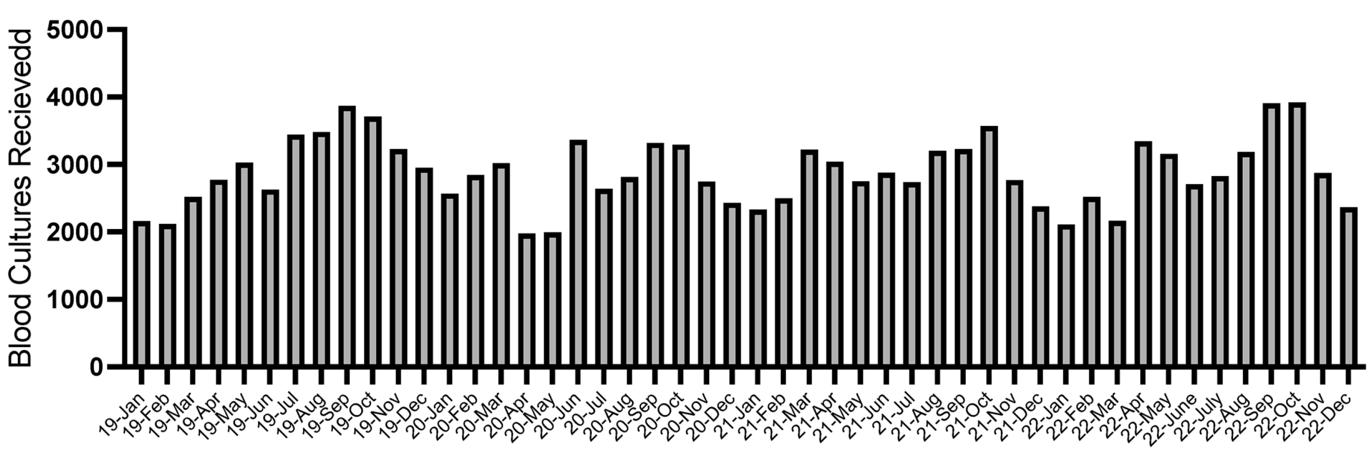
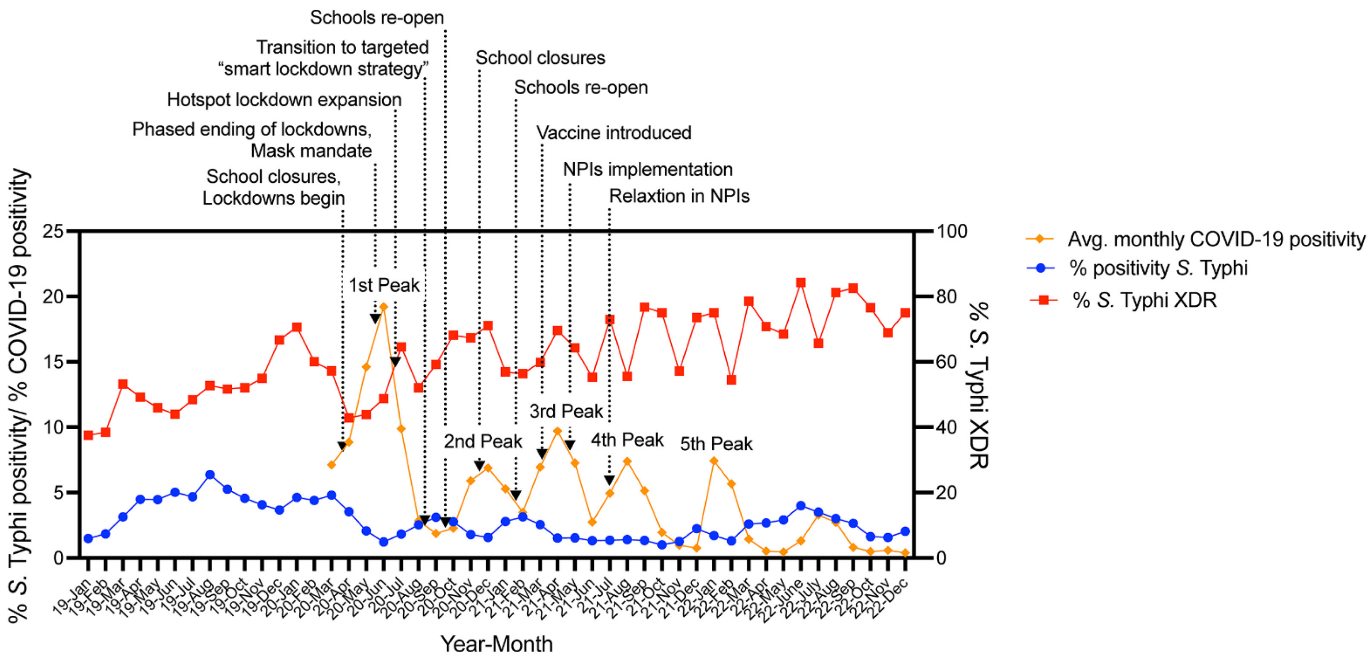


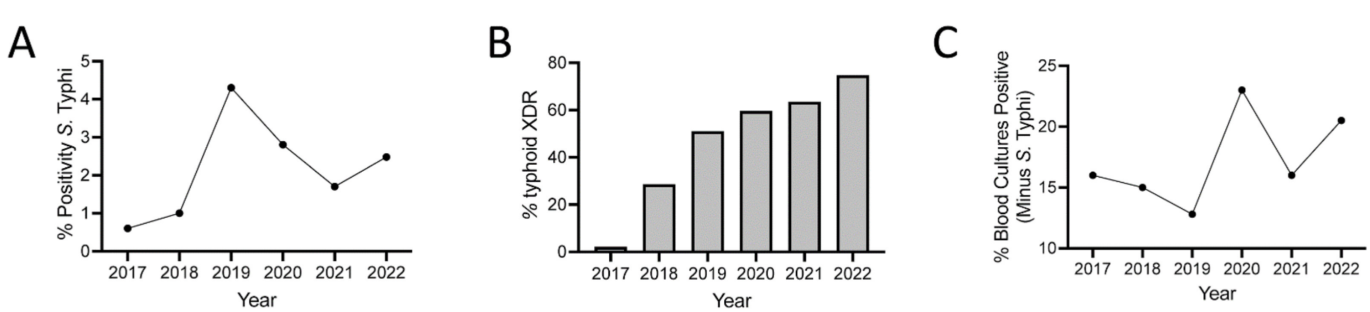
Figure 2. Average monthly COVID-19 positivity, % positivity *S.* Typhi, and % *S.* Typhi that is extensively drug-resistant (XDR) from January 2019 to December 2022. NP: non pharmaceutical interventions.



(40% to 60% more transmissible than the previous dominant Alpha variant [24]), even though masking and social distancing was more common to prevent spread of typhoid fever. We observed that while typically measures to contain peaks decreased typhoid incidence, once restrictions were eased and COVID-19 numbers started to decrease, typhoid positivity would start to increase after the first two peaks. The decrease in typhoid after the third peak was maintained until November 2021, which may be explained by now more commonplace masking (and increased availability of masks, PPE, and hand sanitizer, which was limited early on) and social distancing measures during the new variant outbreaks. From November 2021 to December 2021 there is a small increase in typhoid positivity from 1.3% to 2.2% (76.4% increase). However, the fifth wave of COVID-19, which began in December 2021 due to dominant Omicron variants [20-23], saw an 877.6% increase in COVID-19 cases between December 2021 to January 2022, and a 52.4% decrease in typhoid positivity. After this wave, the positivity rates started to follow each other (Figure 2). This may be because masking and social distancing are now less common and exposure to both is similar, and instead follows seasonal trends based on social activity.

Overall, typhoid positivity decreased from 2019 to 2021, during the onset and height of the COVID-19 pandemic (Figure 3A). This suggests that lockdown and non-pharmaceutical interventions that limited social interactions and promoted good sanitation and hygiene practices had a secondary effect on other infectious diseases. However, the percentage of *S.* Typhi cases isolated that were ceftriaxone-resistant continued to increase (Figure 3B), suggesting its continued

Figure 3. Positivity rates for **A.** *S.* Typhi from Shaukat Khanum Memorial Cancer Hospital and Research Centre, calculated as % of total number of blood cultures performed each year that were positive for *S.* Typhi. **B.** % of all S. Typhi isolates from blood culture samples that were ceftriaxone resistant (XDR). **C.** Blood cultures other than *S.* Typhi.



dominance in Pakistan. We observed that in 2022 typhoid positivity started to rise again, with another increase in the percentage of S. Typhi cases isolated that were ceftriaxone resistant (Figure 3A,3B). Blood culture positivity rates for all bacterial infections (minus those reported positive with *S.* Typhi), presented a somewhat different picture (Figure 3C). The overall rate of bloodstream infections showed a decreasing trend from 2017 to 2019, however, a sharp rise in overall positivity was noted between 2019 and 2020. Like *S*. Typhi positivity, total blood culture positivity decreased between 2020 and 2021 and increased again in 2022. This dip and reversal may be explained by loosened restrictions, and increased social interactions in 2022, but also under-diagnosis in the height of COVID-19 (although there was not a noticeable decrease in blood cultures received).

When analyzing the impact of school reopening on COVID-19 cases during the school closures spanning March 2020 to mid-September 2020 and from November 2020 to late January 2021 [18,19], we note that school re-openings tended to precede increases in COVID-19 cases and peaks (Figure 2). Indeed, a recent analysis on the impact of school closures and re-openings on COVID-19 in different cities in Pakistan noted that school closures were associated with a significant reduction of daily COVID-19 cases across different major cities while re-opening was associated with a significant increase in daily cases [18]. However, this study also notes the negative social costs that school closures can have. Thus, to allow schools to reopen and remain open, it is imperative that safety measures be implemented and adhered to, given that the spatially restricted environments of schools can contribute to the spread of infectious diseases.

Given the continued presence of COVID-19 along with typhoid in Pakistan, and the easing of restrictions and social behaviors, it will be important to use differential testing to ensure that the epidemiology of each reported is accurate, the spread of each it contained, and that there is no misuse of antibiotics. Additionally, high usage rates of approved vaccinations against each will remain critical to lessen the burden of both diseases. Overall, we observe the effect that increased vigilance can have in reducing the burden of typhoid and emphasize the need for continued good hygiene and sanitation practices.

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Corresponding author

Dr. Summiya Nizamuddin
Section of Microbiology, Department of Pathology
Shaukat Khanum Memorial Cancer Hospital and Research Centre,
7A, Block R3, Johar Town, Lahore, Pakistan
Tel: +92-42-35905000
Fax: +92-42-35945198
Email: summiyan@skm.org.pk

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