DOI:10.34918/87334

Ihtisham UL HAQ[1,2,3,*], Sajida MARYAM[1], Kashif RAHIM[4,*], Israr AZIZ[1]

Chapter 8. THE UPSURGE INCIDENCE OF TYPHOID FEVER UNDER THE INFLUENCE OF THE COVID-19 PANDEMIC

8.1. Introduction

The safety and security of public health are largely threatened by infectious diseases among which typhoid fever (TF) is one of the major headaches throughout theworld, especially in developing countries [1]. TF is caused by *Salmonella typhi* which isrod-shaped gram-negative, highly pathogenic, and drug-resistant bacteria, its virulenceis increased by the presence of a polysaccharide capsule that protects from phagocytosis [2]. The consumption of food and water contaminated with the feces of infected patient led to infection of *Salmonella typhi,* which then turn into typhoid fever and infection symptoms become apparent such as chilled fever, fatigue, headache, abdominal pain, and rash [3]. Globally, approximately, 9.9 to 24.2 million people get typhoid fever and 75,000–208,000 people lost their lives due to this life-threatening infection according to the report of the World Health Organization (WHO) [4]. Typhoid fever is very prevalent in a majority of Asian countries including Pakistan and out of 16 Asian countries, Pakistani populations are higher at risk for typhoid [5]. In Pakistan, particularly in Sindh and Khyber Pakhtunkhwa (KPK) provinces reported a high prevalence of TF, Sindh province reported 22,571 cases of typhoid from the period of November 2016 to February 2020 according to the report of the National Institute of Health (NIH). Recently, an epidemiological study of TF reported a 30% prevalence among KPK populations during 2016–17 [6].

[1] Department of Biosciences, COMSATS University Islamabad (CUI), Islamabad 44000, Pakistan.
[2] Department of Physical Chemistry and Technology of Polymers, Silesian University of Technology, M. Strzody 9, 44-100 Gliwice, Poland.
[3] Programa de Pós-graduação em Inovação Tecnológica, Universidade Federal de Minas Gerais, Belo Horizonte, 30150-240, MG, Brazil.
[4] College of Life Science and Technology, Beijing University of Chemical Technology, Beijing, 100029, China.
[*] Correspondence: ihaq@polsl.pl., sajida.maryam786@gmail.com.

However, the ongoing pandemic of COVID-19 that emerged in 2019, December [7–10] has disturbed the whole lifestyle, and disease control strategies and madeit more susceptible to secondary infections. Simultaneously, in several developing countries including Pakistan, previously overstretched healthcare infrastructure has started reporting secondary infections with COVID-19 soon after declaring a pandemic [11, 12]. Majorly, typhoid prevalence has been found to increase after the pandemic of COVID-19. In Pakistan, COVID-19 cases start spreading very quickly in May 2020, and consequently on the other hand, in the first 10 days of June, approximately 20,000 people were diagnosed with typhoid and COVID-19 infections [13]. A recent study of typhoid fever conducted in Punjab Province reported 48% from March 15 to June 15, 2020. In gender-wise distribution, the highest incidence rate was observed in males and age-wise distribution, the age group 21–40 reported the highest incidence rate of 44.5% [14]. Similarly, the NIH report presented 2,883 cases in Pakistan of TF since 12 September 2020 [15]. It's become very challenging to diagnose both infections with limited financing and healthcare resources thus, it leads to a crumpling of clinical diagnosis and management strategies [14]. The prevalence of TF has been found to increase after the COVID-19 pandemic throughout the country across various provinces such as Punjab and KP. However, while keeping in mind the abrupt cases of typhoid fever across the province this study was initiated in June 2020 and completed in November 2020 with the purpose of analysis of epidemiological studies of typhoid fever in district Kohat KPK.

8.2. Methodology

8.2.1. Description of the Study Area

Kohat is situated in the south of Khyber Pakhtunkhwa (KPK) which is one of the four provinces of Pakistan. Kohat city is the capital of the district and the 4th largest city ofthe KPK with an area of 2,545 square kilometers (983 sq mi) with a population of the district is approximately 228,779 [16]. The climate of Kohat is warm and semi-arid and the temperature rises above 37^{o}C after April and reached 42, and 43^{o}C in June, and July (Table 2) [17].

8.2.2. Study Type and Design

The presented epidemiological study was premeditated in the District Headquarters Hospital, Kohat Pakistan conducted from June 2020 to November 2020. Before approaching the patients, consent was taken from the hospital administration. A total of 1,165 suspected patients with the symptoms of fever, dissatisfaction headache, abdominaldiscomfort, diarrhea, malaise, and constipation referred to the laboratory by physicians were taken in this study for specimen collection. A preceding approval was taken from each patient and in the case of a child from his/her guardian according to the updated version. A pre-experienced questionnaire was used to gather information regarding their health status and issues, age, lifestyle, eating habits, and daily activities.

8.2.3. Sample Size and Laboratory Processing of Samples

A total of 4 ml fresh blood specimen was obtained from each patient in strictly sterile conditions and transferred to EDTA tubes for the detection of IgG and IgM antibodies through a typhoid test. Samples were labeled with patient name, gender,age, region, and other useful information. The collected blood samples with data like patient name, age, date/month, gender, and institute name and along with other useful information were noted and then samples were stored at -20℃ until further use. In the clinical diagnosis, all the typhoid fever suspected blood samples were evaluated for the detection of IgG and IgM *Salmonella typhi*-specific antibodies by using a typhoid test comprised of dot ELISA. Typhidot strips contain immunogenic 50 kDa outer membrane protein antigen explicit for *Salmonella typhi.* The strip was kept for 10 minutes followed by centrifugation of blood to separate the serum to apply it on the sample pad. The strip comprises 3 bands IgG, IgM, and test band, appearing color on each band indicated theirresult as described by [18].

8.2.4. Data Analysis

All the results data are determined by frequency, percentage, and graphical representation.

8.3. Results

A total of 511 patients were found positive with IgG and IgM *Salmonella typhi* antibodies among 1,165 suspected patients and the infection rate was 43.86%, males reported 313 infections while females 198 (Table 1, Graph 1). In the current study, the majority (66%) of TF cases came from urban areas. (Figure 2). Results data revealed thatthe disease incidence abruptly started in June, with the highest incidence 31.50% reportedin July followed by 28.20% in June while the lowest reported in November 3.32% as shownin Figure 3. The prevalence of typhoid fever has been found significantly increased in the present study. In past, the incidence rate did not go overhead 30% but in 2020, it surpasses 44% in this study and interestingly, Lahore reported a 48% prevalence of TF in the same years as shown in Figure 4, Figure 5 and Table 2. TF transmission is highly associated with high temperature so we accessed the temperature data of Kohat from a website as shown in Table 3 [17].

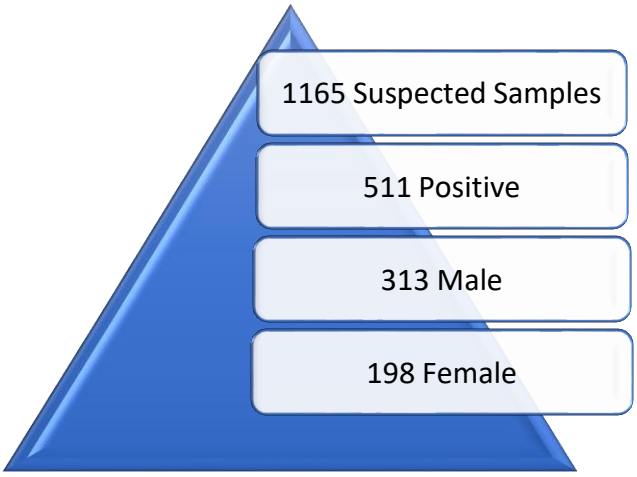

Fig. 1. Overall prevalence of typhoid fever
Rys. 1. Ogólna częstość występowania duru brzusznego

Table 1

Features of typhoid fever infection based on gender, age-wise, month, area, and infectionhistory

Constraints	Categories	Positive cases	Percentage
Gender	Male	313	61.01
	Female	198	38.99
Age group	10–20	157	30.72
	20–30	208	40.70
	30–45	146	28.57
Areas	Uban	339	66.34
	Rral	172	33.66
Infection history	New	315	62.00
	With a history of TF	196	37.97
Months	June	144	28.18
	July	161	31.50
	Agust	93	18.19
	Septemer	72	14.09
	October	24	4.69
	November	17	3.32

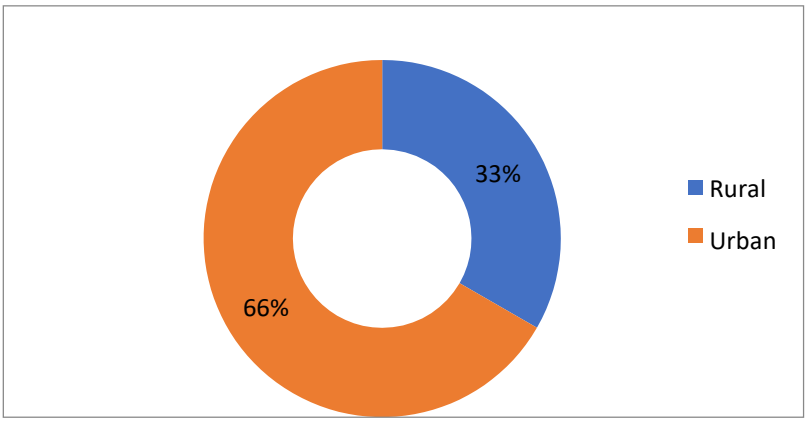

Fig. 2. Area-wise distribution of TF
Rys. 2. Rozkład występowań TF

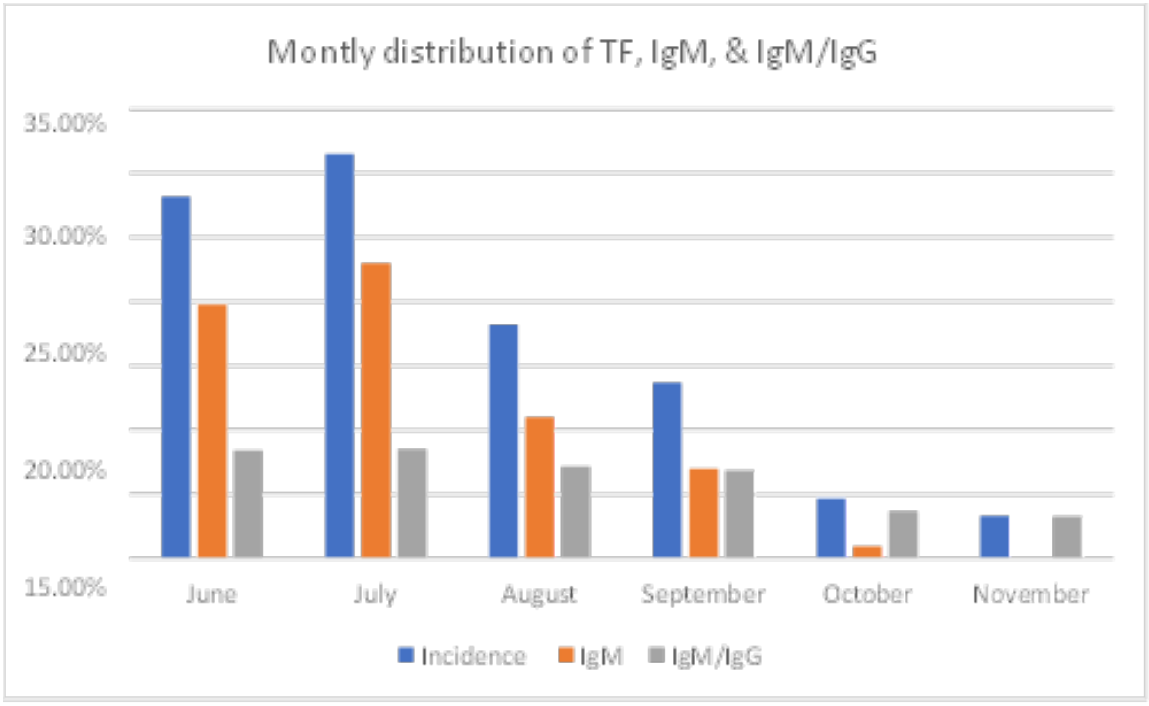

Fig. 3. Monthly distribution of TF, IgM, and IgM/IgG antibodies
Rys. 3. Miesięczny rozkład występowania TF oraz przeciwciał IgM i IgM/IgG

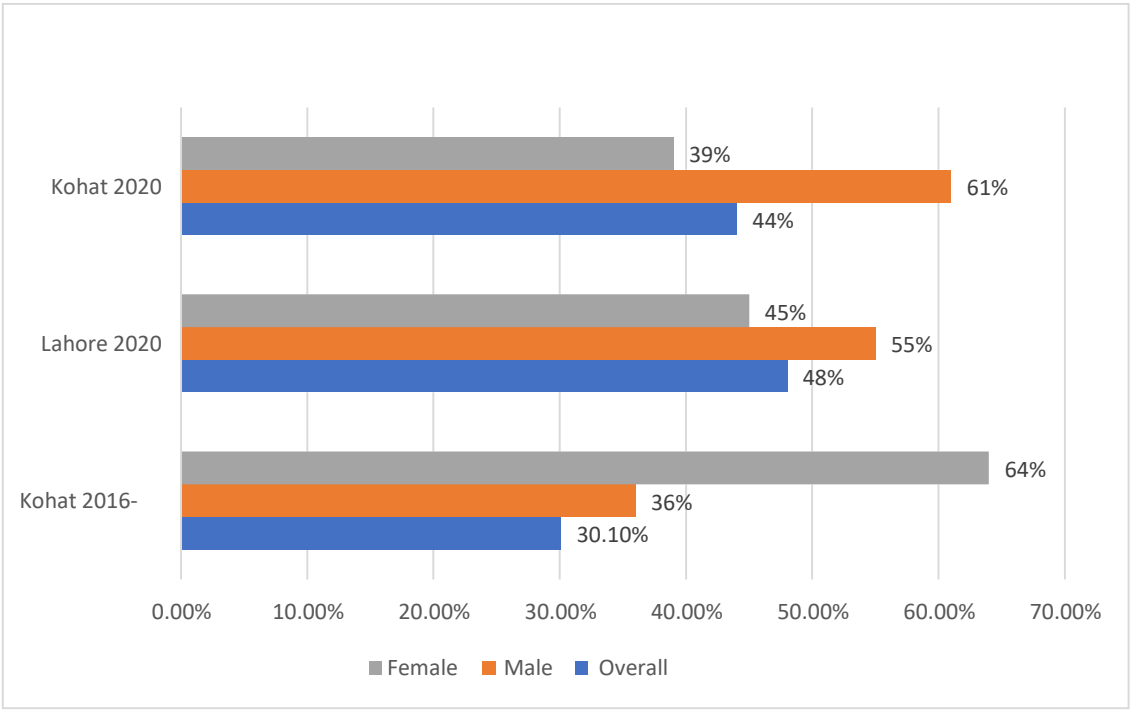

Fig. 4. Comparison of TF Prevalence with previous studies and present
Rys. 4. Porównanie występowania TF w przeszłości i obecnie

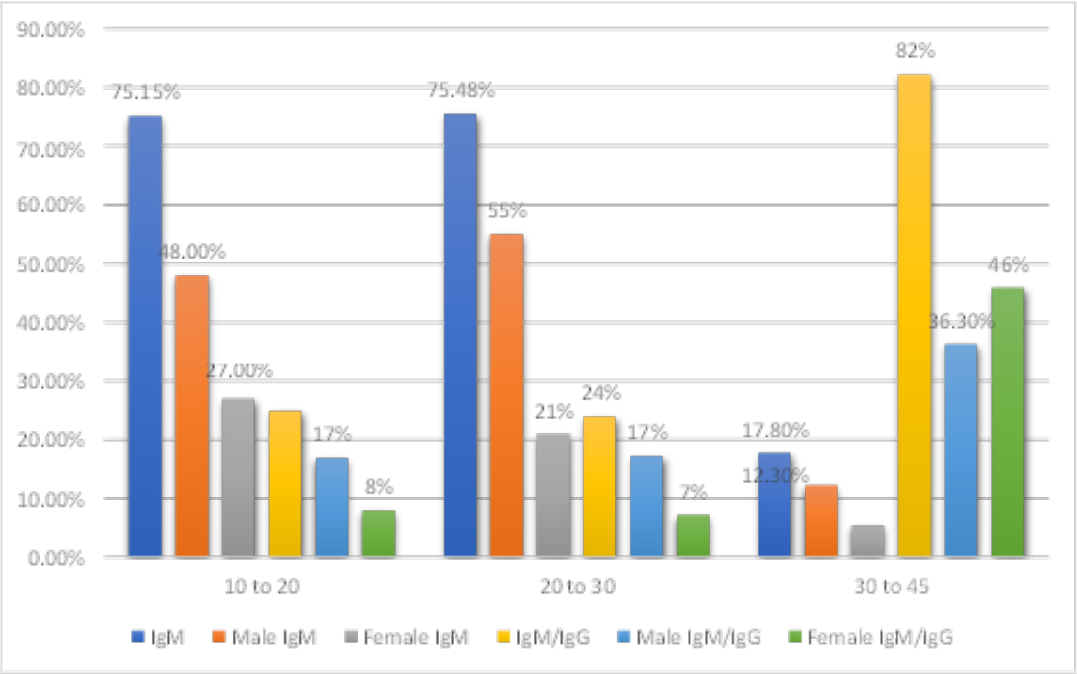

Fig. 5. The IgM and IgM/IgG antibodies prevalence among male and female patients
Rys. 5. Częstość występowania przeciwciał IgM i IgM/IgG wśród pacjentów płci męskiej i żeńskiej

Table 2

The IgM and IgM/IgG antibodies prevalence among male and female patients

Age-groups	Positive Cases	Male	Female	IgM	IgM/IgG
10–20	157	104	53	75M/43F = 118	26M/13F = 39
20–30	208	144	64	114M/43F = 157	36M/15F = 51
30–40	146	65	81	18M/8F = 26	53M/67F = 120
Total	511	313	198	301	210

Table 3

Temperature in Kohat

Months	Temperature
January	09–20°C
February	11–22°C
March	11–32°C
April	21–36°C
May	31–42°C
June	37–43°C
July	33–44°C
August	30–38°C
September	29–39°C
October	26–39°C
November	16–28°C
December	15–2°C

8.4. Discussion

Typhoid fever is a major problem in the healthcare of developing countries andis associated with high morbidities and mortalities in South-East Asian countries. Middle and lower-income countries are at higher risk for TF infection due to a lack of sanitation systems and an unhygienic environment. It is a main public health concern mainly in middle and lower-income countries including Asia. Globally, South-East Asia is the 3rd most prevalent region as most of the countries reported a high incidence of TFincluding Pakistan [19]. Currently, typhoid is considered an extensively drug-resistant infection (XDR) that infected thousands of people, recently in 2019, the first conjugate vaccine of typhoid has been familiarized by Pakistan as recommended by WHO [20]. The incidence of TF is varied as it primarily depends on the weather conditions, sporadic cases are reported throughout the year but more prevalent in summer [21–23]. The present study was led to report the updated epidemiological studies of TF. After the COVID-19 pandemic, the incidence of TF increased significantly across the province and it was stoutly recommended to report the epidemiological factors of TF to summarize the preventive and treatment strategies. The current incidence of 44% of TF has been interpreted as increased in comparison with previous studies of incidences however, it matches with the recent study conducted in Lahore in 2020 that reported a 48% incidence [6]. Incidentally, both studies reported a higher incidence in males, the current study has reported 61% at Lahore while 55% was previously reported. Our results revealed that the highest incidence was 40.70% reported in the age group 20–30, followed by 30.72% in the age group 10–20, and the age group 40–45 reported 28.57%. These figures are similar to the study of Umer Rashid and co-workers, who reported 42.33% in the age group 21–30, and 30.42% in 11–20 [6]. Similarly, Rahim et al reported a 27% incidence in the 10–20 age group [7].

The increased incidence of typhoid fever indicates the impact of COVID-19 onTF. A letter to the editor of the report characterized COVID-19 and *Salmonella typhi* co-epidemics as a real problem in Pakistan [6]. It is very difficult to report the actual prevalence of TF in the absence of an organized clinical diagnosis, sufficient sample size, and most primarily due to symptoms similar to COVID-19. Physicians face problems in the differentiation of both infections due to symptoms similarity, which is the major issue in the diagnosis of typhoid [6]. It has been reported that the prevalence of TF is high in summer and low in winter, but accidentally our study was started in June 2020 and completed in November 2020, and gradually the disease incidence starts to decline after August, and no single cases were reported in December [1]. The present

study reported a significant variation in the epidemiological studies of TF in comparison with previous studies that found deviated such as reporting of higher infection cases in urban areas. Moreover, in our study, the patients with a history of TF were fewer and the new infections reported high, which indicated that the population across the districtbecome highly susceptible to TF. It seems that TF susceptibility is increased with the ongoing pandemic of COVID-19 that affected every individual, most of the patients recovered quickly but their immune systems weakened. The weak immune system makes people more susceptible to TF in the presence of unhygienic water, food, and theenvironment. Its transmission increases due to contaminated water, poor sanitation, low hygienic environment [24], and no vaccination all these factors contributed to the susceptibility of the entire communities [25]. The transmission risk can be reduced by the implementation of preventive and treatment strategies such as providing clean waterto the public and installation of organized sanitation to dispose of the fecal material without exposure to the environment. Besides these, vaccination against typhoid in the susceptible population can play a major role in the prevention of disease that must be prioritized [25]. Timely diagnosis is necessary for parallel analysis of COVID-19 and typhoid, which is difficult in current poorly equipped healthcare facilities. COVID-19 and typhoid have become a headache for Pakistan however, the previous year Pakistan responded well to the COVID-19 pandemic and typhoid epidemics as well. The third wave of COVID-19 has started in Pakistan with alarming circumstances and concerned authorities must be determined the attenuation of the COVID-19 pandemic and typhoid epidemics.

8.5. Conclusion

Results concluded that typhoid prevalence has increased significantly in 2020 in comparison with the past studies but in parallel, various other studies of Lahore and NIH have also reported the increased prevalence of typhoid fever across the country in 2020. Interestingly, there is no significant variation of infection observed in different age groups. All the age groups revealed similar susceptibilities except the age group 20–30, which shows the highest incidence rate of 40%. Diagnostic facilities and clinical management should be improved to differentiate both infections and timely diagnosis. To combat the co-epidemics of COVID-19 and typhoid fever in the third wave of the pandemic accurate and rapid diagnosis is stoutly recommended for its better management.

Acknowledgments

All the authors of the manuscript thank and acknowledge their respectiveuniversities and institutes.

Conflict of interest: There is no conflict of interest.

Author Contributions: Conceptualization, I.U.H., literature collection and analysis, S.M.; I.U.H.; writing-original draft preparation I.U.H.; writing review and editing, S.M. K.R. All authors have read and agreed to the published version of the manuscript.

Funding: We confirm that there was no funding for this study. It was self-financed by the authors.

Bibliography

1. A. Fusheini, S.K. Gyawu, Prevalence of Typhoid and Paratyphoid Fever in the Hohoe Municipality of the Volta Region, Ghana: A Five-Year Retrospective Trend Analysis. *Annals of Global Health.* (2020) **86**(1).
2. J. Akram, A.S. Khan, H.A. Khan, S.A. Gilani, S.J. Akram, F.J. Ahmad, R.Mehboob. Extensively drug-resistant (XDR) typhoid: evolution, prevention, and its management. *BioMed Research International*. (2020).
3. J.A. Crump. Progress in typhoid fever epidemiology. *Clin Infect Dis.* (2019) 68:S4–S9.
4. M. Antillón, J.L. Warren, F.W. Crawford, et al. The burden of typhoid fever in low- and middleincome countries: A meta-regression approach. *PLoS neglected tropical diseases.* (2017) **11**(2): 0005376.
5. M.K. Rasheed, S.S. Hasan, Z.U.D. Babar, S.I. Ahmed, "Extensively drug-resistant typhoid fever in Pakistan," *The Lancet Infectious Diseases* (2019) **19**(3): 242–243.
6. K. Rahim, I. Ul Haq, F. Hussain, W. Ashraf, A. Basit, M.M. Jalees, M.A. Gonda, M. Shuaib. The prevalence rate and epidemiological study of Typhoid fever in KhyberPakhtunkhwa, Pakistan. *Bioscience Research* (2021) **18**(1): 221–228.
7. I. Ul Haq, K. Krukiewicz, H. Tayyab, I. Khan, M. Khan, G. Yahya, S. Cavalu. Molecular Understanding of ACE-2 and HLA-Conferred Differential Susceptibility to COVID-19: Host-Directed Insights Opening New Windows in COVID-19 Therapeutics. *Journal of Clinical Medicine*. (2003). **12**(7), 2645.
8. C. Egbuna, S. Chandra, C.G. Awuchi, S. Saklan, I. Ulhaq, M. Akram, K.C. Patrick--Iwuanyanwu, J. Khan. Myth surrounding the FDA disapproval of 594 hydroxychloroquine sulfate and chloroquine phosphate as drugs for coronavirus disease 2019. In Coronavirus Drug Disc. Elsevier (2022) **595**, 153–168.

9. I. Ul Haq, K. Krukiewicz, G. Yahya, M. Ul Haq, S. Maryam, R.A. Mosbah, S. Saber, M. Alrouji. The breadth of bacteriophages contributing to the development of the phage-based vaccines for COVID-19: An ideal platform to design the multiplex vaccine. *International Journal of Molecular Sciences*. (2023). **24**(2), 1536.
10. S. Maryam, I. Ul Haq, G. Yahya, M. Ul Haq, A.M. Algammal, S. Saber, S. Cavalu. COVID-19 surveillance in wastewater: An epidemiological tool for the monitoring of SARS-CoV-2. *Frontiers in cellular and infection microbiology*. (2023). **12**, 978643.
11. A. Haqqi, U.A. Awan, M. Ali, M.A.N. Saqib, H. Ahmed, M.S. Afzal. COVID-19 and dengue virus co-epidemics in Pakistan: a dangerous combination for overburdened healthcare system. *J Med Virol*. (2020) 26144.
12. R. Ozaraszaras, R. Cirpin, A. Duran, et al. Influenza and COVID-19 co- infection: report of 6 cases and review of the literature. *J Med Virol.* (2020). https://doi.org/10.1002/jmv.26125.
13. B.T. Shaikh, N. Ali. COVID-19 and fiscal space for health system in Pakistan: It is time for a policy decision. *Int J Health Plann Manage*. (2020).
14. NEWS A. Doctors report increasing typhoid cases in Punjab than COVID-19. Accessed 19 June 2020. https://arynews.tv/en/doctorsreport-increasing-typhoid-cases-punjab/.
15. National Institute of Health Islamabad, Weekly field epidemiology report. https:// www.nih.org.pk/wp-content/uploads/2020/09/37-FELTP-Pakistan-Weekly-Epi demiological-Report-Sep-05-12-2020.pdf, 2020. [Accessed 13 December 2020].
16. PAKISTAN: Provinces and Major Cities. *PAKISTAN: Provinces and Major Cities*. citypopulation. de. Retrieved 4 May 2020.
17. www.accuweather.com.
18. K. Yadav, S.K. Yadav, G. Parihar. A Comparative Study of typhidot and widaltest for Rapid Diagnosis of Typhoid Fever. *Int. J. Curr. Microbiol. App. Sci (2015)*4(5): 34–38.
19. F.J. Siddiqui, F. Rabbani, R. Hasan, S.Q. Nizami, Z.A. Bhutta. Typhoid fever in children: some epidemiological considerations from Karachi, Pakistan. *International Journal of Infectious Diseases* (2006) 10(3):215–222.
20. World Health Organization. Pakistan first country to introduce new typhoid vaccine into routine immunization programme. Accessed 19 June 2020. http://www.emro.who.int/pak/pakistan-news/pakistan-first-country-tointroduce-new-typhoid-vaccine-into-routine-immunization-programme. html

21. L. Cao, S. Fu, Z. Lv, C. Tang, S. Cui, X. Li, W. Lei. West Nile virus infectionin suspected febrile typhoid cases in Xinjiang, China: West Nile virus and febrile tyhoid coinfection. *Emerging microbes & infections* (2017) 6(1): 1–4.
22. A.L. Wagner, M.Y. Mubarak, L.E. Johnson, J.M. Porth, J.E. Yousif, M.L. Boulton. Trends of vaccine-preventable diseases in Afghanistan from the Disease Early Warning System, 2009–2015. *PLoS One* (2017)12(6): e0178677.
23. H. Gu, W. Fan, K. Liu, S. Qin, X. Li, J. Jiang, Q. Jiang. Spatio-temporal variations of typhoid and paratyphoid fevers in Zhejiang Province, China from 2005 to 2015. *Scientific reports (2017)* 7(1): 5780.
24. V. Mogasale, B. Maskery, R.L. Ochiai, et al. Burden of typhoid fever in low- income and middle-income countries: a systematic, literature-based update with risk-factor adjustment. *The Lancet Global health.* (2014) 2(10): 570–580. https://doi. org/10.1016/S2214-109X(14)70301-8.
25. S. Ahmad, et al. A skeleton in the closet: The implications of COVID-19 on XDR strain of typhoid in Pakistan. *Public Health Pract* (2021) 100084.

THE UPSURGE INCIDENCE OF TYPHOID FEVER UNDER THE INFLUENCEOF THE COVID-19 PANDEMIC

Abstract

Typhoid fever is one of the most persistent bacterial infections in developing countries causes. The current study was designed to analyze the epidemiological studies of typhoid feverin the recent pandemic of COVID-19. In this study, a total of 1,165 suspected patients with typhoid symptoms were screened for typhoid. Results revealed a significant upsurge in typhoid cases. Overall, the prevalence was 44%, which is comparatively high but aligns with the recentstudies of typhoid fever reported during an ongoing pandemic. The high number of IgM antibodies in typhoid patients indicated the higher prevalence of new infections. It shows that TF susceptibility has increased with the present pandemic of COVID-19 as co-epidemics of COVID-19 and typhoid have remained a major public health issue in Pakistan. COVID-19 weakened the immune system, which makes people more susceptible to typhoid coupled with an unhygienic environment and lack of scheduled vaccination. The transmission risk can be reduced by the implementation of preventive measures such as the installation of

organized sanitation to dispose of the fecal material. Vaccination can play a major role in the prevention of typhoid. Timely diagnosis is necessary for parallel analysis of COVID-19 and typhoid, whichis difficult in poor healthcare facilities and turned into a headache for Pakistan. Such alarmingcircumstances warn the concerned authorities to develop preventive strategies for the future typhoid epidemics.

Keywords: Typhoid, COVID-19, co-epidemics, epidemiology, prevalence, Pakistan