Review Article

DOI: https://dx.doi.org/10.18203/2394-6040.ijcmph20213046

Typhoid burden, drug resistance and Pakistan's stance against it

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Received: 28 May 2021 Revised: 01 July 2021 Accepted: 03 July 2021

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ABSTRACT

Salmonella typhi is a gram negative, rod shaped bacteria that features a polysaccharide capsule, flagella for motility and fimbria for adhesion to the epithelial cells of intestinal mucosa. The organism is responsible for causing enteric fever and in severe cases it leads to complications such as intestinal perforation which can lead to death. The mainstay of treatment of typhoid fever is antibiotic therapy but unfortunately the emergence of MDR (multidrug resistant) and XDR (extensively drug resistant) strains pose a major threat to the successful treatment of typhoid. Around 200,000 global deaths can be associated with typhoid and most cases are seen in low socioeconomic countries with inadequate healthcare infrastructure particularly those that are densely populated, among them Pakistan is considered as high-risk country according to WHO criteria. Prevention strategies include education of the masses regarding hand hygiene, cleanliness and consumption of clean food and water. In 2019 Pakistan encountered an epidemic of XDR typhoid and to control it, Government introduced typhoid vaccine in its nationwide vaccination program, and is hopeful that it will decrease the burden of disease on state and its citizens.

Keywords: Infectious disease, Communicable disease, Typhoid, Drug resistance

INTRODUCTION

Typhoid and paratyphoid fevers are together known as Enteric fevers and these infections have a considerable potential of epidemic spread. Over 2500 serotypes of Salmonella have been known to cause disease. Typhoid fever continues to be a major health issue in the developing countries with 21.6 million cases and 250,000 deaths annually. Newer studies, however, show that the estimated burden of typhoid fever is 10.9 million cases and 116,800 deaths per year. Although it is difficult to make an accurate estimate, 200,000 global deaths may be associated with typhoid, predominantly in various

impoverished settings where the incidence can be as high as one in five children getting typhoid fever by the age of 10.⁷⁻⁸

With the first descriptions of typhoid fever dating back to the early 1800s, Karl Eberth made the discovery of the causative pathogen, *Salmonella typhi*, in 1880.9 *Salmonella typhi* is a gram-negative, rod-shaped, and flagellated bacterium. 10 Humans are the exclusive host for Salmonella typhi and the most common source of infection is the ingestion of food contaminated with the organism. 11 Typhoid fever is a major public health issue in countries with poor socioeconomic status and in areas

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where unclean drinking water and poor sanitation system are found in abundance.¹² Typhoid fever has endemicity in the Subcontinent, Southeast Asia, Middle East, and Central and South America and it is widely prevalent in Pakistan.¹³ In Southeast Asia, the incidence of typhoid fever in children is high in urban low socioeconomic settlements which are densely populated.¹⁴

BACTERIOLOGY AND CLASSIFICATION

Salmonella typhi features a polysaccharide capsule that protects the organism against phagocytosis. 10 Various fimbrial adhesins are responsible for initiating the contact to host cells and then invasion of epithelial cells of the intestinal mucosa occurs, where the organism survives phagocytosis and is able to proliferate in salmonellacontaining vacuole. 15 The genus Salmonella comprises two species: S. enterica and S. bongori. S. enterica is further divided into over 2000 serovars, such as S. typhi which are host specialists and infect only humans and S. typhimurium which are host generalists and infect both humans and other mammalian species. 16 Salmonella typhimurium LT2, S. typhi, S. paratyphi A and S. paratyphi B are included in subspecies I of S. enterica, which colonizes mammals and birds and causes 99% of Salmonella infections in humans. 17,18 Most of the virulence phenotypes of S. enterica are encoded by genes on PAI (pathogenicity islands) and are referred to as SPI islands".15 "salmonella pathogenicity chromosomes of enteric bacteria are mosaics that are composed of collinear regions interspersed with "islands" or "loops" that often encode pathogenicity. 19,20 The acquisition of PAI by horizontal gene transfer enables the bacteria to attain complex virulence traits from other species and leads to prominent virulent phenotypes that lead to host cell invasion and intracellular pathogenesis.¹⁵

TRANSMISSION AND SOCIODEMOGRAPHICS

Orofecal route is the mode of transmission for *S. typhi*.²¹ The infection is transmitted through food and water contaminated with the organism.²² Milk borne pathogenesis has also been globally recognized as a serious public health concern and Salmonella spp. isolates have been gathered from raw milk and environmental samples.²³

In a cross-sectional observational study done in 2017, results showed that *S. typhi* predominantly affected children less than the age of 15 and males were affected more than females owing to the fact that men are more likely to eat outside the home due to work.²⁴ A study conducted in 2015 showed that the carrier state of typhoidal Salmonella serovars was very high among food handlers which is one of the reasons why typhoid fever is endemic in Karachi, Pakistan.²⁵ March, April and August are the season changing months during which the organism grows with boost and hence majority of the cases are seen in these months.²⁴

MULTIDRUG RESISTANCE

A major threat to successful management of typhoid fever is the emergence of S. typhi strains which are resistant to antimicrobial agents.26 The term MDR (multi drug resistance) describes resistance to ampicillin, TMP-SMX (trimethoprim-sulfamethoxazole), and chloramphenicol while XDR (extensively-drug resistance) exhibits resistance to chloramphenicol, co-trimoxazole, ampicillin, fluoroquinolones, and third-generation cephalosporins.²⁷ The emergence of multidrug resistant and fluoroquinolone-resistant strains have shown to be associated with very severe disease and potentially adverse outcomes, posing challenges for effective management and leads to increased disease burden.²⁸ Decades of antibiotic usage have driven the evolution of multidrug-resistant and extensively drug-resistant strains of S. typhi.²⁷

PATHOGENESIS

Typhoid fever is among the leading causes of bacterial infection globally, caused by Salmonella enterica serovar typhi and Salmonella enterica serovars paratyphi A, B and C.29 While these two groups of bacteria are collectively held accountable for causing typhoid fever, both are markedly different from clinical and pathophysiological perspective, Infection caused by S. Paratyphi subgroups infects mesenteric lymph nodes and intestine in immunocompetent patient, although Salmonella typhi does infect mesenteric lymph nodes and intestine, it also spreads to liver, spleen and bone marrow colonizing and damaging them as well. 30-32 S. paratyphi causes a typical diarrheal illness with exudative intestinal inflammation and neutrophil predominance in stool sample. 33-35 Salmonella typhi has an interstitial pathology with mononuclear predominance which evades toll-like receptors (TLR) dependent interleukin-2 (IL-2) and interferon Gamma axis causing systemic dissemination and multisystem infection.³⁶

CLINICAL MENIFESTATION AND SYMPTOMS

It takes around 10 to 14 days for symptoms of typhoid fever to be clinically apparent.³⁷ Typhoid fever has a broad range of symptoms including pyrexia, decreased appetite, constipation, diarrhea, body pain and abdominal pain. Untreated patients can have severe and at times life threatening complications involving intestinal bleeding, gastrointestinal perforation, leukopenia and hepatosplenomegaly.³⁸

DIAGNOSIS

Gold standard diagnostic test for typhoid fever is isolation and detection of causative agent from blood culture, other culture for bone marrow and stool are also highly specific and sensitive.³⁸ In developing and underdeveloped countries these laboratory tests are not easily accessible

and affordable, therefore diagnosis is made on clinical and serological basis which are generally unreliable.³⁹

TREATMENT AND PREVENTION

Before the advent of antibiotics typhoid was a major concern for health care providers because of severe and at times fatal complications.²⁷ Nowadays Antibiotics are the mainstay of treatment for typhoid fever, including third generation cephalosporins as mainstay drugs and azithromycin as an alternative in low socioeconomic conditions.^{40,41} Proper knowledge and awareness about hand washing, personal hygiene, food safety and drinking water chlorination is the best approach towards prevention that we have in present circumstances, as typhoid vaccine needs large amount of government backed funding to maintain cold chain, training vaccine providers and above all long-term financial commitment which is a great barrier for countries with low socioeconomic condition.^{42,43}

REFLECTION FROM PAKISTAN

As a developing country Pakistan is suffering from typhoid endemic and its health consequences like other lower-middle income countries. When compared with other countries with typhoid endemicity, residents from province Sindh and Puniab of Pakistan are at most risk of getting infected.⁴⁴ A study conducted in low socioeconomic localities of Karachi showed estimation of typhoid infection incidents ranging from 252 to 503 per hundred thousand children, showing exceptionally high prevalence even 4 times larger than criteria specified by WHO.45 In 2019 Pakistan encountered extensively drug resistant typhoid epidemic which further demonstrates the condition in the region, in the same year Pakistan took a strong and important move by inducting typhoid conjugate vaccine in its nation-wide vaccination programme. 46,47 However additional efforts determination is required to spread awareness concerning appropriate hand washing, sanitation, safe water and food regulation laws for street food vendors as these factors are equally and at times more important to stop the spread of typhoid in general public.4

CONCLUSION

Typhoid fever is an enteric fever infecting 10.9 million people annually causing 116,800 deaths, it is endemic in countries with poor infrastructure and low socioeconomic conditions among which Pakistan is in high risk group with incidence of infection reaching at 503 per hundred thousand. Inaccessibility of vaccine and lack of awareness about personal hygiene are major infection rate aggravating factors. A big step from Pakistan in recent years is the induction of typhoid vaccine in National immunization programme, however, more efforts are required for spreading overall hygiene awareness, proper infrastructure for water and waste management with rules

and regulations for street food vendors in the direction of controlling typhoid as a nation.

Funding: No funding sources Conflict of interest: None declared Ethical approval: Not required

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Cite this article as: Ali NM, Nasr R, Rehman M, Mahmood SU. Typhoid burden, drug resistance and Pakistan's stance against it. Int J Community Med Public Health 2021;8:4082-5.