



22 May 2024

**Subject: Advisory for Prevention and Treatment of Typhoid Fever including XDR Typhoid**

**Background:**

Typhoid fever is a bacterial infection caused by the *Salmonella Typhi* and *Salmonella Paratyphi* pathogens. The disease if not treated properly may be a life-threatening infection. It is endemic in most of the Asian, African, Latin American and Caribbean countries. Pakistan is also among the countries, with highest burdens of typhoid fever. Lack of access to safe drinking water, inadequate sanitation and poor hygiene practices, low immunization coverage, and limited disease surveillance make country at high risk of increased disease burden. Cases of Extensively Drug Resistant *Salmonella Typhi* (XDR S. Typhi) in the country have been reported since 2016 from different parts of the country, especially during summer and monsoon season. This XDR S. Typhi is resistant to commonly used antibiotics such as ampicillin, chloramphenicol, trimethoprim-sulfamethoxazole, fluoroquinolones and third generation cephalosporins. The XDR S. Typhi is sensitive only to carbapenem (Meropenem) and macrolide (azithromycin).

**Purpose:** Keeping in view the seasonal trend of XDR Typhoid, it is important to take necessary measures to limit its transmission through preventive measures; early detection, using recommended diagnostic tools and prompt treatment. This advisory aims to alert the health authorities for timely actions for preparedness for prevention and control of typhoid fever including XDR Typhoid. Moreover, the health departments must involve other line departments such as WASA, Public Health Engineering, District and Local Administration for preparedness and response.

**Case Definition:**

**Suspected Case:** Any person with a history of fever of at least 38°C for 3 or more days with abdominal symptoms like diarrhea or constipation, abdominal tenderness, and prostration.

**Confirmed Case:** A suspected/ probable case that is laboratory confirmed by isolation of S. Typhi from blood/ stool or urine.

**Classification of Typhoid Fever Cases by Drug Resistance in Pakistan (WHO-2018):**

**Non-resistant Typhoid fever:** Typhoid fever caused by S. Typhi and/or *Salmonella Paratyphoid* A, B or C strain which are sensitive to first-line drug and third generation cephalosporins, with or without resistance to second-line drugs.

**Multi-drug resistant (MDR) Typhoid fever:** Typhoid fever caused by S. Typhi and/or *Salmonella Paratyphoid* A, B or C strain which are resistant to the first-line recommended drugs for treatment, with or without resistance to second-line drugs.

**Extensive Drug Resistance (XDR) Typhoid:** Typhoid fever caused by S. Typhi strain which are resistant to all the recommended antibiotics for typhoid fever.

**Clinical Presentation:** Typhoid fever and paratyphoid fever are systemic illnesses that have an insidious onset characterized by prolonged fever (>38°C), headache, constipation or diarrhea, body aches, abdominal pain, fatigue, loss of appetite and vomiting. A transient, rash of rose spots may be present on the trunk. Severe cases may include encephalopathy, gastrointestinal bleeding, or



intestinal perforation, which typically occur after 2–3 weeks of illness.

**Mode of Transmission:** Typhoid infection occurs through feco-oral route and infection spreads through contaminated food, milk, frozen fruits, raw/fresh fruits or vegetables and water or through close contact with already infected persons. The contamination of food and water usually occurs due to poor sanitation and mixing of sewerage water with drinking water.

**Incubation period:** It depends on the inoculum size and host factors; 3 days to more than 60 days with a usual range of 8 to 14 days for *S. Typhi* and 1 to 10 days for *S. Paratyphoid*.

**Diagnosis:**

- *S. Typhi* can be isolated from blood during the first week of illness or from stool and urine after the first week of illness.
- **Widal and Typhidot have No diagnostic value due to limited sensitivity, specificity and cross reactivity and must be stopped immediately by all labs.**

**Treatment:** Suspected patients compatible with case definition(s) should immediately seek medical advice from registered medical practitioner. Samples should be collected for culture & sensitivity before starting the empirical therapy from all the suspected cases. The prescription of antibiotics for treatment should be based on culture report. Unnecessary use of antimicrobial agents should be discouraged to treat the patients presenting with fever. To limit the antimicrobial resistance (AMR), antibiotics should be prescribed based on the results of culture and sensitivity tests. The XDR Typhoid cases and lab culture report must be notified to the concerned district health authorities, DG Offices of the respective province and NIH.

- Use of **Azithromycin** and **Meropenem** should be restricted and only be given to XDR cases of typhoid fever based on prescription by registered medical practitioner.
- In case of other infections such as upper and lower respiratory tract infections, other available drug options should be used instead of oral azithromycin which should be spared/ reserved for lab confirmed XDR Typhoid cases and other serious medical conditions.

**Preventive measures and Vaccination:**

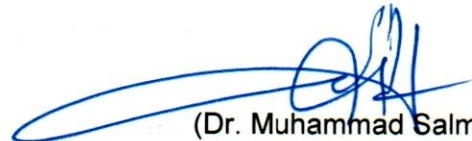
The treatment options for typhoid becoming more limited, following preventive measures are urgently needed, including improved sanitation and vaccination campaigns:

- Raising community awareness on the following:
  - Thorough hand washing with soap and water is highly recommended after changing baby's diaper, after using toilet, before and after attending patient, before handling, cooking, and eating.
  - Drink treated, boiled, or bottled water. Use ice, prepared from clean drinking water preferably boiled. Wash fruits and vegetables properly before eating. Eat freshly cooked, hot served, and home-made food.
  - Avoid eating street vendors foods, raw fruits or vegetables, market prepared or leftover food. Use pasteurized milk.
- Vaccination is recommended for all age groups especially high risk group of people and those who are exposed to the disease. Typhoid fever vaccines do not provide 100% protection however they will reduce the severity of the illness.
- Typhoid conjugate vaccine (Typbar-TCV@) is a new conjugate vaccine with longer immunity. WHO has prequalified the first conjugate vaccine in December 2017 to prevent typhoid fever.

**Laboratory Diagnosis and NIH Support:**

- Patients with typhoid typically have bacteremia; blood culture is therefore the preferred method of diagnosis.
- Depending on the blood culture system used, cultures might need to be held and observed for up to 7 days before reporting a negative result.
- Although bone marrow culture is more invasive (and therefore less commonly performed), it increases the sensitivity to ≈80% of cases and is relatively unaffected by previous or concurrent antibiotic use.
- Stool culture is not usually positive during the first week of illness and has less diagnostic sensitivity than blood culture.
- Lab tests for Typhoid fever should be recommended to those who fulfill criteria of suspected case definition.
- For any further assistance in this context, the Center for Disease Control (CDC-NIH) (051 — 9255237 and Fax No. 051-9255575) and Virology Department of Public Health Laboratories Division (051-9255082), NIH may be contacted.

The above 'Advisory' may please be circulated widely to all concerned.

  
(Dr. Muhammad Salman)  
Chief Executive Officer

Distribution overleaf



**Distribution List:**

1. Secretary, Health Department, Government of the Punjab, Lahore
2. Secretary, Health Department, Government of Sindh, Karachi
3. Secretary, Health Department, Government of KPK, Peshawar
4. Secretary, Health Department, Government of Balochistan, Quetta
5. Secretary, Health Department, Government of AJK, Muzaffarabad
6. Secretary, Health Department, Government of Gilgit-Baltistan, Gilgit
7. Chief Executive Officer, Islamabad Healthcare Regulatory Authority, Islamabad
8. Chief Executive Officer, Punjab Healthcare Commission, Lahore
9. Chief Executive Officer, Sindh Healthcare Commission, Karachi
10. Chief Executive Officer, KPK Healthcare Commission, Peshawar
11. Director General Health Services, Government of the Punjab, Lahore
12. Director General Health Services, Government of Sindh, Hyderabad
13. Director General Health Services, Government of KPK, Peshawar
14. Director General Health Services, Government of Balochistan, Quetta
15. Director General Health Services, Government of Gilgit-Baltistan, Gilgit
16. Director General Health Services, Government of AJK, Muzaffarabad
17. Director General, NEHS, Islamabad
18. Director General, Federal Directorate of Immunization (FDI), Islamabad
19. Animal Husbandry Commissioner, M/o National Food Security & Research, Islamabad
20. Executive Director, Pakistan Institute of Medical Sciences, Islamabad
21. Executive Director, Federal Government Polyclinic Hospital, Islamabad
22. Executive Director, Capital Hospital CDA, Islamabad
23. Executive Director, Federal Government TB Hospital, Rawalpindi
24. Executive Director, National Institute of Rehabilitation Medicine (NIRM), Islamabad
25. Director General Health Services, Capital Development Authority, Islamabad
26. Director General, PAEC Hospital, Islamabad
27. Director General, KRL Hospital, Islamabad
28. Director General, NESCOM Hospital, Islamabad
29. Director, Border Health Services-Pakistan, Islamabad
30. District Health Officer, ICT, Islamabad
31. Director, Nuclear Oncology & Radiotherapy Institute (NORI), Islamabad
32. Commandant, PAF Hospital, Islamabad
33. Commandant, Naval Complex Hospital, (PNS Hafeez), Islamabad
34. Medical Superintendent, Social Security Hospital, Islamabad
35. Director, Federal General Hospital, Park Road, Islamabad
36. Executive Director, Shifa International Hospital, Islamabad
37. Executive Director, Quaid-e-Azam International Hospital, Islamabad
38. Executive Director, Maroof International Hospital, Islamabad
39. Commandant, Combined Military Hospital (CMH), Rawalpindi
40. Commandant, Military Hospital (MH), Rawalpindi
41. Medical Superintendent, Cantonment General Hospital, Rawalpindi
42. Medical Superintendent, District Headquarter Hospital, Rawalpindi
43. Medical Superintendent, Fauji Foundation Hospital, Rawalpindi
44. Medical Superintendent, Holy Family Teaching Hospital, Rawalpindi
45. Medical Superintendent, Benazir Bhutto Hospital, Rawalpindi
46. Medical Superintendent, WAPDA Hospital, Rawalpindi
47. Medical Superintendent, Railway Hospital, Rawalpindi
48. Medical Superintendent, IHITC, Islamabad
49. In-charge, Federal Disease Surveillance Unit (FDSRU), NIH Islamabad
50. Officer In-charge, Provincial Disease Surveillance & Response Unit (PDSRU) at Provincial Health Directorates, Lahore, Hyderabad, Peshawar, Quetta, Gilgit and Muzaffarabad
51. Deputy Commissioners with the request to direct all concerned departments at district level.
52. Provincial Coordinator, EPI, Punjab, Sindh, KPK, Balochistan, GB and AJK

**C.c:**

1. Chief Secretary, Govt of Punjab, Sindh, KPK, Balochistan, GB and AJK.
2. Surgeon General Pakistan Army, GHQ Rawalpindi
3. Chief Commissioner, ICT Administration Islamabad
4. WHO Country Representative, Islamabad
5. SPS to Federal Minister of Health, M/o NHR&C, Islamabad
6. SPS to Secretary, M/o NHR&C, Islamabad
7. PS to Director General Health, M/o NHR&C, Islamabad