Epidemiological Alert
Salmonella enterica serovar Typhi haplotype H58

10 October 2018

Given the emergence in Africa and Southeast Asia of *Salmonella* serovar Typhi haplotype H58 with extensive resistance to fluoroquinolones and third-generation cephalosporin, the Pan American Health Organization / World Health Organization (PAHO/WHO) encourages Member States to strengthen surveillance and laboratory diagnostic capacity for early detection of typhoid fever cases with extensive drug resistance, adequate treatment, and identification of sources of infection.

Background

Typhoid fever, which is caused by *Salmonella enterica* serovar Typhi, is a systemic bacterial disease whose clinical picture varies from mild illness with low-grade fever to severe clinical disease with complications. It is estimated that the median rate for *S.* Typhi disease in the Americas is 10 per 100,000 population (95% UI 2-32) and mortality rate of 0.07 (95% UI 0.01-0.2) per 100,000 population.

Severity of *S.* Typhi infection is influenced by factors such as strain virulence, quantity of inoculum ingested, duration of illness before adequate treatment, age, and vaccination history. The estimated case-fatality rate ranges from 1% to 4% in patients who received appropriate antimicrobial therapy but can rise to 10% to 20% in untreated cases or in case treated with inappropriate antibiotics.

The symptoms of acute or mild illness, even the sub clinical infections, may follow by the carrier state in which the host can excrete *S.* Typhi for prolonged periods of time. Humans are the only known reservoir of *S.* Typhi. Transmission of typhoid fever is due to the ingestion of food and water contaminated with feces or urine of patients or carriers, therefore the risk of transmission is increased in populations lacking access to safe water and adequate sanitation. Children are the most affected by typhoid fever with higher incidence long known to occur in children aged 5 to < 15 years old.

Fluoroquinolones are the drugs of choice in adults. The rapid emergence of decreased susceptibility to these antibiotics could change the empirical treatment of choice for typhoid fever, as described previously during an outbreak of *S.* Typhi haplotype H58, where third-generation cephalosporins were used due to resistance to fluoroquinolones with the consequent selection of strains producing extended-spectrum β-lactamases. The increasingly complex pattern of resistance detected highlights the value of antibiotic susceptibility tests in understanding the local resistance patterns to enable the selection of appropriate antibiotics and management of cases.

The emergence and spread of a novel extensively drug resistant *S.* Typhi associated with the haplotype H58 is of concern as this strain is resistant to first-line drugs, such as

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ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole, as well as to fluoroquinolones and third-generation cephalosporins. Since November 2006 Pakistan reported an outbreak of extensively drug resistant typhoid fever related to *S.* Typhi haplotype called H58. The circulation of this extensively drug resistant strain poses a risk to public health due to the reduction of antimicrobials available for treatment of typhoid fever. To date, a single remaining oral antimicrobial, azithromycin, has been identified as an option for the treatment of this type of strain.

Situation summary in the Americas

In 2018, **Canada** reported the isolation of *S.* Typhi from a pediatric patient sample, which contains conjugative plasmids carrying resistance genes including ampicillin, extended-spectrum cephalosporins, fluoroquinolones, chloramphenicol, and trimethoprim-sulfamethoxazole.

In 2018, the **United States of America** reported two cases of extensively drug resistant typhoid fever in travelers from Pakistan, where there is currently an outbreak of *S.* Typhi haplotype H58.

According to data provided by the Latin American Antimicrobial Resistance Surveillance Network (ReLAVRA), during 2016 a limited number of isolates of *S.* Typhi were reported in Latin America and the Caribbean. Briefly, no isolates of *S.* Typhi were reported by Argentina, Bolivia, Chile, Costa Rica, the Dominican Republic, Honduras, Mexico, Nicaragua, Panama, Paraguay, Uruguay, and Venezuela. Fewer than ten isolates per country were reported by Brazil, Cuba, and Peru, all of them susceptible to fluoroquinolones and third-generation cephalosporins.

Ecuador reported 8 isolates, 4 of which had decreased susceptibility to ciprofloxacin and one to third-generation cephalosporins. Guatemala reported 13 isolates, two with decreased susceptibility to fluoroquinolones and none susceptible to third-generation cephalosporins. Finally, Colombia reported 204 isolates and El Salvador 298 isolates of *S.* Typhi with high percentages of decreased susceptibility to fluoroquinolones (12.7 and 40% respectively) but without being susceptible to third-generation cephalosporins.

In summary, up to now, the circulation of *S.* Typhi resistance to both fluoroquinolones and third-generation cephalosporin has not been reported in Latin America and the Caribbean.

Advice to national authorities

In light of the emergence of extensively drug resistant *S.* typhi haplotype H58, the Pan American Health Organization / World Health Organization (PAHO/WHO) recommends Member States increase efforts for early detection of *S.* Typhi resistant to both fluoroquinolones and third-generation cephalosporins and implement urgent prevention and control measures to contain the spread of antimicrobial resistance.

Provided below are the main guidance for health authorities.

Antimicrobial resistance surveillance

Surveillance is a key component of prevention and control of antimicrobial resistance and should be strengthened, along with laboratory capacity, to support the detection of

asymptomatic infections and treatment failures, as well as to identify high-risk communities and populations.

Laboratory capacity

- Strengthen national laboratory capacity through quality assurance, training, provision of standards and regulations.
- Monitor the decrease of susceptibility of first and second line antimicrobials, especially fluoroquinolones and third generation cephalosporins. When an extensively drug-resistant pattern is detected, the strain should be sent to a laboratory with molecular technique capacity, in order to characterize the circulating lineage, and detect the emergence and spread of new resistance mechanisms in the Region.
- Improve surveillance and knowledge through the implementation of new technologies, participation in national or regional molecular studies, and the determination of resistance mechanisms to first and second line antimicrobials.

Clinical Management

- Consider the differential diagnosis of typhoid fever with other febrile syndromes caused by viruses, bacteria or protozoa, especially in endemic areas for malaria, rickettsiosis, leptospirosis, brucellosis, and dengue.
- Treatment decision should be based on the local epidemiology of antimicrobial resistance patterns. Clinicians must constantly be updated on treatment recommendations as these evolve due to very dynamic changes in antimicrobial resistance patterns.
- Treatment of *S.* Typhi infections with extended resistance to fluoroquinolones and cephalosporins require an individualized clinical decision based on the patient's clinical history and the severity of infection.

Prevention Measures

As *S.* typhi is transmitted through ingestion of food and water contaminated with feces or urine from patients and carriers, collaboration between different sectors, including water and sanitation as well as food safety authorities, is critical to effectively address prevention measures. Typhoid fever is common in places with poor hygiene and lack of drinking water, therefore access to safe water and adequate sanitation, and good hygiene among food handlers are the main prevention measures.

The following advice should be given to the general population:

- Ensure foods are well cooked and served hot.
- Drink boiled or pasteurized milk and dairy products.
- Avoid ice unless it is made of safe water.
- When safe water is not available, treat water by boiling or chemically.
- Emphasize hand washing as a routine practice after defecation and before preparing, serving, or eating food.
- Wash fruits and vegetables, especially if eaten raw. If possible, vegetables and fruits should be peeled by consumer.

Sources of Information

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