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Epidemiological Alert

Emergence and spread of *Shigella sonnei* with extreme resistance to antibiotics. Potential risk for Latin America and the Caribbean

6 June 2022

Given the emergence and spread of *Shigella sonnei* with extreme resistance to antibiotics in Europe, the Pan American Health Organization/World Health Organization (PAHO/WHO) emphasizes the importance of surveillance and appropriate microbiological diagnosis for its detection. Likewise, it suggests the implementation of infection prevention and control measures for its containment.

Background

Shigella spp. it is one of the leading causes of severe infectious diarrhea worldwide. The shigellosis is seen mostly in children and is mainly caused by the consumption of contaminated food and water. In some countries, shigellosis is primarily reported in travelers returning from endemic areas or among high-risk populations, including men who have sex with men (MSM) (1).

It can be transmitted by the oro-faecal route by direct contact with infected people (predominant mode of transmission), indirect contact through vectors such as flies, fomites, consumption of contaminated food or water, and by sexual transmission through oro-anal practices or indirect contact after anal intercourse, through fingers, condoms, or contaminated sex toys.

Since 1970, shigellosis has been considered a sexually transmitted disease when the same pattern of gastrointestinal infection was identified in MSM (2). In 2015, the first outbreak of an unusual *S. flexneri* 3a serotype was reported through a genomic epidemiology study that analyzed shigellosis cases from 29 high- and low-risk countries, between December 1955 and June 2014, identifying intercontinental spread of this serotype in regions considered low risk, and the acquisition of multiple antibiotic resistance determinants in MSM (3).

The *Shigella* genus is made up of nonmotile, facultatively anaerobic, non-sporulating, gram-negative rods belonging to the family *Enterobacteriaceae*, which cause bacillary dysentery. The genus includes four subgroups with multiple serotypes: *Shigella dysenteriae* (subgroup A), *S. flexneri* (subgroup B), *S. boydii* (subgroup C), and *S. sonnei* (subgroup D). This is a virulent pathogen with a low infective dose, which means that only a small number of bacteria (10 to 100 microorganisms) are needed to cause disease (4). The most common symptoms include watery, bloody diarrhea, abdominal pain, cramps, fever, nausea, vomiting, loss of appetite, headache, and malaise. The incubation period is generally 1 to 4 days, and the transmissibility period extends from the acute phase until the bacteria is no longer present in feces. Asymptomatic carriers can transmit the disease (1).

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In January 2022, an approximately five-fold increase in cases of gastrointestinal infections among MSM by *S. sonnei* with extreme antibiotic resistance (XDR)—implying no sensitivity to penicillins, third generation cephalosporins, tetracycline, sulfonamides, quinolones, and azithromycin—was reported in the United Kingdom (5). Similar cases of shigellosis due to *S. sonnei* were also reported in several European countries (Austria, Belgium, Denmark, France, Germany, Ireland, Italy, Norway, and Spain) between 2020 and 2022, confirming the dissemination of this bacterium in Europe (6).

In the light of these findings, in March 2022 the WHO Regional Office for Europe generated an alert due to the increase in cases of gastrointestinal infections by *S. sonnei* XDR among MSM (7).

Situation Summary in the Region of Americas

In the United States of America, shigellosis is the third most common cause of enteric infection, with approximately 500,000 cases per year. Due to high rates of resistance to ampicillin and trimethoprim/sulfamethoxazole (SXT), the most commonly used antibiotics for the treatment of this disease are ciprofloxacin, ceftriaxone, and azithromycin. However, cases of resistance to these antibiotics have been reported, mainly in shigellosis in MSM (8,9). In Canada, an increase in the number of cases of shigellosis due to *S. flexneri* has been reported since 2014 (10), and the circulation of *Shigella* spp. with decreased sensitivity to azithromycin mainly in MSM (11).

According to data compiled by the Latin American Antimicrobial Resistance Surveillance Network (ReLAVRA, per its acronym in Spanish), in the period 2014-2020, in the countries of the Region of the Americas participating in the network, *Shigella* spp. the most frequently recovered from acute diarrheal illness were *S. flexneri* (49%), *S. sonnei* (30%), and *S. dysenteriae* (0.3%). *S. sonnei* presented high levels of resistance to SXT (58-100%) and ampicillin (10-92.6%). In addition, some countries reported resistance to ciprofloxacin (8-62.7%), azithromycin (12-30%), ceftriaxone (25%), and ceftazidime (17%) (12). There are no data on shigellosis transmitted by sexual contact in Latin America.

So far, cases of shigellosis due to *S. sonnei* have only been reported in countries with high surveillance capacity and high water, sanitation and hygiene (WASH) standards. However, the prolonged transmission time of this bacterium after infection, the potential role of asymptomatic carriers, and the low infectious dose are factors that could favor the spread of XDR strains (7).

In the Region of the Americas, millions of people still lack an adequate source of drinking water and safe facilities for the disposal and elimination of feces. In 2017, it was estimated that some 28 million people lacked access to an improved water source, some 83 million did not have access to improved sanitation facilities, and some 15.6 million still practiced open defecation (13). For this reason, if *S. sonnei* XDR is introduced into countries with limited resources where water, sanitation and hygiene conditions are not optimal, the probability of infections by this microorganism increases and there is a risk of a major outbreak of diarrheal diseases with a high rate of infection and potential lethality in the main risk groups, including children under 5 years of age.

Also of concern is the possible contribution of *S. sonnei* XDR to the spread of antibiotic resistance in the community through horizontal transfer of mobile genetic elements such as plasmids to other bacterial species.

Recommendations for health authorities

Given these findings, Pan American Health Organization / World Health Organization (PAHO/WHO) recommends Member States implement and strengthen the early detection of *S. sonnei* XDR for timely action to prevent the transmission and spread of this microorganism in the community.

Provided below are key guidance for health authorities.

Surveillance and epidemiological investigation.

National authorities are advised to strengthen surveillance and epidemiological investigation of *S. sonnei*, to detect possible introductions in new areas and prevent community transmission. To this end, PAHO/WHO recommends:

- Increase the participation of national public health laboratories in surveillance activities for the timely detection of cases or outbreaks, to provide early guidance on the antimicrobial treatment of patients and implement prevention and control measures.
- According to the risk assessment through the application of Annex 2 of the International Health Regulations (IHR 2005), Member States should notify cases or outbreaks of *S. sonnei* XDR, following the protocols and notification flows of the country/territory, and share information with relevant services and clinics dealing with sexually transmitted infections to alert health workers and decision makers at all levels.
- Strengthen the surveillance of diarrheal disease in vulnerable populations due to *S. sonnei* or other *Shigella* species prevalent in the region, warning about the modes of transmission and prevention measures.

Detection by microbiology laboratories

Microbiology laboratories are essential for the detection of the etiological agent and its resistance profile. Therefore, PAHO/WHO recommends:

- To follow the guidelines of the WHO manual (14) to take samples.
- Strengthen the identification capabilities of *S. sonnei* in clinical laboratories.
- Carry out susceptibility tests and monitor the decrease in susceptibility of first- and second-line antibiotics, especially fluoroquinolones, azithromycin, and third generation cephalosporins (including the detection of extended spectrum β -lactamases).
- Strengthen the capacity of national reference laboratories to carry out molecular epidemiology techniques to characterize the mechanisms present in XDR isolates.

Infection prevention and control

The prevention of bloody diarrhea caused by *Shigella spp.* is based primarily on measures that prevent the spread of the bacteria within the community, including person-to-person transmission. These include:

- Continue efforts to provide access to safe water and adequate sanitation to populations.
- Strict attention to hand washing with soap and water, especially after using the bathroom and before preparing, serving, or eating food.
- People affected by shigellosis should not handle or prepare food in catering establishments and private homes until the person recovers or stool culture is negative for *Shigella spp.*
- People affected by shigellosis should avoid water activities for at least one week after the resolution of the illness.
- Consistently use condoms, maintain barrier protection methods in sexual practices that may facilitate direct contact with feces.

To prevent and control outbreaks of *Shigella spp.* in health care settings, in addition to standard precautions, PAHO/WHO recommends:

- Contact isolation measures for patients with suspected or confirmed *Shigella spp.* infection.
- Where possible, place the patient in a single room with an exclusive bathroom for suspected or confirmed cases of *S. sonnei* XDR. If this is not possible, cohort infected patients.

Prevention of sexual transmission of *Shigella spp.* (particularly at risk groups such as MSM), and to minimize the risk of infection (15), should adopt the following practices:

- Sexual abstinence during symptoms and for 7 days after complete resolution of symptoms.
- Avoid oro-anal exposure for 4-6 weeks, taking into account the transmission period.
- Use barrier protection methods during sexual activity.
- Washing the body, hands and sex toys before and after sexual intercourse, especially after removing condoms.

Antimicrobial treatment

Antimicrobial treatment is necessary in patients with severe or invasive disease, patients requiring hospitalization, with risk factors, and children under 5 years of age. It decreases the risk of serious complications and death, the duration of symptoms, and the time of

transmission/spread, and therefore can be recommended by public health authorities for outbreak control.

Empirical treatment should be based on host factors, severity of infection, results of local susceptibility testing, and history of possible acquisition in travelers to endemic areas. Taking these factors into account, treatment options may be azithromycin, furazolidone, ceftriaxone, cefixime, or ciprofloxacin (16).

Antimicrobial resistance profiles with sufficient epidemiological information will allow early detection and investigation of treatment failures and will serve as the basis for national and international treatment guidelines.

Due to the multi-resistance to antimicrobials reported in cases of shigellosis, mainly in MSM in Europe, the importance of performing sensitivity tests in risk groups is emphasized in order to select the best treatment and reduce the spread of XDR strains.

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