



Scientists from the Mérieux Foundation and the Child Health Research Foundation Warn of Potential Typhoid Crisis After Discovering New Highly Drug-Resistant Strains

Lyon, France – November 13, 2018 – Two new highly drug-resistant forms of *Salmonella* Typhi have been discovered in Bangladesh. The bacteria are responsible for typhoid fever, a life-threatening disease that is highly endemic in parts of Asia and Africa. A new lineage of *S. Typhi* that is highly resistant to first-line antibiotics in the fluoroquinolone family has been described for the first time, along with a new strain that is highly resistant to ceftriaxone, a third-generation cephalosporin that is the most commonly prescribed treatment for typhoid fever.

This discovery has just been published in *mBio* ([Tanmoy et al.](#)) following a study led by the Mérieux Foundation and the Child Health Research Foundation (CHRF) in Bangladesh, with data analytics support from Applied Maths in Belgium.

Both of these new variants of *Salmonella* Typhi are distinct from the strain discovered in the outbreak of extensively drug-resistant (XDR) typhoid reported in Pakistan earlier this year. The authors expected to find evidence that the Pakistan strain was spreading across the region to other endemic countries. The data presented by Tanmoy *et al.* is instead proof that there are multiple and unrelated genetic mutations causing resistance in strains from diverse geographic origins. A multisource epidemic is a much more serious threat because it greatly enhances rapid, global dissemination, making it more difficult to contain than a single source outbreak.

“The emergence of these highly resistant strains in Pakistan and now Bangladesh could herald the beginning of a global pandemic of XDR strains”, said Prof. Hubert Endtz, Director of Applied Research at the Mérieux Foundation and professor of Tropical Bacteriology at Erasmus University Medical Center. “With therapeutic options disappearing, it is urgent to accelerate vaccination programs for populations at high risk”, he added.

Typhoid fever is caused by *Salmonella enterica* serovar Typhi and responsible for an estimated 17-26 million cases of typhoid fever each year worldwide. With proper treatment by an antibiotic, the death rate associated with typhoid is less than 1%. In the pre-antibiotic era, the mortality rate was 15%. If typhoid fever were to become untreatable due to a lack of effective antibiotics, a return to pre-antibiotic levels could result in up to 3.9 million deaths a year.

If typhoid is detected and treated quickly, transmission can be stopped. Without effective antibiotics, there are only two options left: improving water sanitation, which is costly and slow to implement in endemic countries, and conducting vaccination campaigns in high-risk populations. Those at highest risk are children under five. WHO has prequalified the first conjugate vaccine to prevent typhoid fever and recommended its introduction into routine immunization programs. Unlike previous typhoid vaccines, the new conjugate vaccine provides longer-lasting immunity, requires only one dose and can be given to children as young as 6 months.

The study was conducted at the Mérieux Foundation’s Emerging Pathogens Laboratory in Lyon, dedicated to applied research in the fields of global health and infectious diseases, and part of the International Center for Infectiology Research (CIRI) - Inserm U1111. This project is an example of how the foundation supports the careers of young scientists to strengthen research capacities in developing countries. The lead author, Arif M. Tanmoy, from the Child Health Research Foundation in Bangladesh, conducted the research at the Emerging Pathogens Laboratory and is also a PhD student at the Erasmus University Medical Center in the Netherlands.

About the study

Data from whole genome sequencing of 536 *S. Typhi* strains was analyzed by Mérieux Foundation scientists and bioinformaticians, in collaboration with teams at Applied Maths in Belgium and bioMérieux's Data Analytics Unit in France. The strains were collected from the Child Health Research Foundation at the Department of Microbiology, Dhaka Shishu (Children) Hospital, in Dhaka, Bangladesh. The resulting sequences were compared with data from a recent XDR *Salmonella* Typhi outbreak in Pakistan (Klemm *et al.* [mBio 9:e00105-18, 2018](#)) and laboratory surveillance of typhoid fever in Nepal (Britto *et al.* [PLoS Negl. Trop. Dis. 12\(4\): e0006408, 2018](#)).

The authors identified a new *Salmonella* Typhi H58 subtype lineage with high level resistance to fluoroquinolones. The study also identified a new strain with extended-spectrum beta-lactamase (ESBL) enzymes conferring resistance to ceftriaxone. In some cases, the two resistance mechanisms co-existed in the typhoid H58 subtype, which is the most prevalent worldwide, increasing the chances for this dual resistance to disseminate. A triple mutant strain with three different mutations conferring high-level resistance to fluoroquinolones, similar to the strains from Nepal, was also found.

The highly resistant strains observed are still susceptible to azithromycin, the only oral antibiotic left with proven efficacy against *Salmonella* Typhi. However, azithromycin-resistant strains have already been reported in South Asia (Patel *et al.* [J Clin Diagn Res. 2017 Jun; 11\(6\): DM01–DM03](#)) and its widespread use would lead to the rapid development of resistance. The only remaining treatment option after azithromycin would be very expensive intravenous drugs such as the carbapenem antibiotics, which are inaccessible in developing countries.

Study funding

The study received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No. 643476, as part of COMPARE, a project that aims to accelerate the detection of and response to disease outbreaks among humans and animals worldwide through the use of new genome technology.

Arif M. Tanmoy received a PhD scholarship (Allocation de Recherche pour une Thèse au Sud - ARTS) from the Mérieux Foundation and the French Institut de Recherche pour le Développement (IRD).

About the Mérieux Foundation - www.fondation-merieux.org

Established in 1967, the Mérieux Foundation is an independent family foundation with public interest status, chaired by Alain Mérieux. Its mission is to strengthen local capacities to fight the infectious diseases that affect vulnerable populations in developing countries, particularly mothers and children. Present in 20 countries in West Africa, Latin America, Asia and the Middle East, the Mérieux Foundation focuses on 4 objectives:

1. Increasing vulnerable populations' access to diagnostics by strengthening clinical laboratories in national healthcare systems
2. Enhancing local applied research capabilities by training researchers, developing collaborative programs and creating Rodolphe Mérieux Laboratories, transferred to local partners
3. Encouraging knowledge-sharing and public health initiatives leveraging Les Pensières Center for Global Health
4. Improving conditions for mothers and children taking a global health approach.

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