

Accelerating the control and prevention of enteric fever and invasive non-typhoidal salmonella.

Proceedings of the 8th International Conference on Typhoid Fever and Other Invasive Salmonellosis

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Foreword

In the 29 years since the First International Workshop on Typhoid Fever was held in Washington, D.C. in November 1984, the fight against typhoid fever has grown more urgent. Available vaccines are underutilized, even as growing numbers of people are at risk of the disease, and antimicrobial resistant clones are spreading around the world.

Yet the prospects for controlling this disease have never been better, and the constituency to lead that effort has grown from 31 participants at that first meeting to over 500 registrants at the “8th International Conference on Typhoid Fever and Other Invasive *Salmonellosis*”, held in Dhaka, Bangladesh in March 2013.

Today, there is a third generation of typhoid vaccines in clinical development, bivalent typhoid-paratyphoid A vaccines are on the horizon, and invasive non-typhoid *Salmonella* vaccine development has received critical support.

The “8th International Conference on Typhoid Fever and Other Invasive *Salmonellosis*” offered a timely opportunity for policy makers and the world’s leading experts on typhoid, paratyphoid and non-typhoidal *Salmonella* to share knowledge about the disease, and the public health measures needed to control and prevent it.

Executive Summary

The “8th International Conference on Typhoid Fever and Other Invasive *Salmonellosis*” held in Dhaka, Bangladesh in March 2013 brought into focus challenges to the control and prevention of enteric fever and invasive non-typhoidal *Salmonella* (iNTS). Enteric fever, a disease that devastates many of the world’s youngest and poorest people, continues to impact rapidly urbanizing populations of Asia and Africa. Awareness of iNTS and its impact on infants and young adults in Africa is growing rapidly.

The constituency to lead the effort to control and prevent enteric fever and iNTS has never been stronger and better organized. In just a few years since its founding in 2010, the Coalition against Typhoid (CaT) has grown into a global forum of over 30 member organizations and numerous individuals working in a coordinated way to expedite and sustain rational, evidence-informed policy to prevent these diseases.

Rapid progress has been made and the prospects for controlling and preventing enteric fever and iNTS have never been better. Today, after increased prioritization by key international organizations, a typhoid Vi polysaccharide (ViPS) vaccine is WHO prequalified, and long awaited typhoid Vi conjugate vaccine candidates are near licensure and plans are being drafted for their use in public sector programs, bivalent typhoid-paratyphoid conjugate and live attenuated vaccines will likely be licensed in the near future, and invasive non-typhoidal *Salmonella* conjugate vaccine development has received critical support.

Enteric fever prevention and control

Enteric fever (commonly defined as typhoid and paratyphoid fevers) is a severe bacterial infection spread through water or food contaminated with human feces. Humans are the only reservoir of infection.

The World Health Organization (WHO) conservatively estimates there are 21 million cases of typhoid fever and 216,000 deaths each year, predominantly among children of school age or younger. In addition, there are an estimated 5.4 million paratyphoid fever cases each year.

New research findings presented at the conference revealed a changing global landscape of enteric fever incidence and risk. Enteric fever is widely recognized as highly endemic in countries of South and Southeast Asia, and until now epidemiologists have estimated that 90 percent of typhoid deaths occur in Asia. However, new data underscore an unrecognized burden of enteric fever deaths and disease in sub-Saharan Africa, where a changing epidemiology and rapid urbanization has set the stage for widespread transmission.

In addition, antimicrobial resistant (MDR, resistant to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole), decreased fluoroquinolone susceptibility and fluoroquinolone resistant (DCS), and extended-spectrum cephalosporin resistant strains of *Salmonella* Typhi and *Salmonella* Paratyphi have taken hold or are emerging, making enteric fever less treatable and raising the risk of severe complications and death. Initial evidence also suggests that H58, a rapidly spreading MDR *S. Typhi* clone, has increased transmissibility and is better able to survive in the human environment.

Meanwhile, new data also challenge conventional truths about the age of greatest risk, showing that children under five years bear a much larger burden of typhoid disease than previously thought.

Against this backdrop of disease threats, presentations highlighted the opportunities to prevent and control enteric fever through a comprehensive approach that addresses safe water, basic sanitation, effective clinical care, proper hygiene including hand washing, and widespread use of vaccines. Today, international travelers are far more likely to have access to typhoid vaccines than are the billions of people at risk for typhoid in endemic areas. Presentations highlighted the urgency of both expanding access to existing vaccines and accelerating development and licensure of next-generation conjugate and live attenuated vaccines that can prevent typhoid and paratyphoid fever in infants and young children.

Throughout two days of presentation and discussion, research findings created new awareness of enteric fever's role as a major source of infant and child mortality and of the epidemic and pandemic potential of MDR, DCS and extended-spectrum cephalosporin resistant strains of *S. Typhi* and *S. Paratyphi*. Long-standing dogmas about enteric fever were overturned, highlighting the urgency of preventing and controlling this long-neglected disease.

Major findings included:

- **Emerging African epicenter.** The burden of typhoid fever in Africa appears to be seven times higher than previously thought, making it comparable to or higher than rates in some Asian countries. Outbreaks and epidemics are increasingly reported across sub-Saharan Africa.
- **Major source of under-five morbidity and mortality.** Infants and toddlers in many areas are at equal or greater risk from typhoid fever than older children and adults, making typhoid an important and overlooked cause of infant and child morbidity and mortality, on par with other vaccine preventable diseases such as pneumonia, diarrhea, and meningitis.
- **Pandemic potential of MDR and DCS clones.** The emergence and swift spread of MDR, DCS and extended-spectrum cephalosporin resistant clones of *S. Typhi* and *S. Paratyphi*, abetted by lack of access to safe water and basic sanitation in rapidly growing cities, has poised enteric fever for epidemic and potential pandemic spread as the disease becomes more lethal and difficult to treat.
- **Vaccines make control and elimination possible.** The development of next-generation conjugate vaccines, effective in infants and young children and offering high levels of long-lasting protection, will be a critical component of enteric fever control and prevention. WHO is now establishing standards for regulatory evaluation and licensure of next generation typhoid conjugate vaccines which will form the scientific basis for potential WHO prequalification and UNICEF procurement. GAVI Alliance financial support for typhoid conjugate vaccines is already prioritized. Until these vaccines become available, existing vaccines can provide a front-line of defense. WHO has prequalified a typhoid ViPS vaccine and use of current vaccines in more than a dozen countries has shown them to be safe and effective in preventing typhoid and controlling outbreaks.
- **Urgent need for new diagnostics.** Diagnosis confirmed by blood culture is the “practical standard” for typhoid and paratyphoid, but it has a sensitivity of only 30 percent in highly endemic areas. The lack of sensitive, easy to use diagnostics is a major barrier to the control of enteric fever. Better diagnostics would improve case management, save lives, improve surveillance, and greatly accelerate the development of new vaccines and therapeutics. More effective diagnostics, based on breakthroughs in genomics, immunology and technology, are in development.
- **Global health policies lag behind the urgent need to control typhoid now.** While some global and national entities recognize the burden of enteric fever and have prioritized a comprehensive approach to its control, others have not. Placing enteric fever on ‘the back-burner’ of global, national and even local/municipal health agendas not only leaves millions to suffer and heightens the risk of deadly outbreaks, but also ignores a dangerous gap in knowledge as the bacteria –

especially MDR, DCS and extended-spectrum cephalosporin strains – continue to mutate and spread.

The Coalition against Typhoid (CaT), an international organization with over 25 member institutions, presented the basic elements of a public health strategy to prevent and control enteric fever, which includes:

- **Vaccination.** Advance public sector vaccination to realize the full potential of existing and next generation vaccines against the major forms of enteric fever.
- **Clinical care.** Increase timely access to clinical care and effective use of antimicrobials to reduce enteric fever case fatality rates from as high as 30 percent to 1 percent or lower.
- **Surveillance and diagnostics.** Integrate enteric fever surveillance with existing febrile illness surveillance systems and improve diagnostics to identify at-risk populations and expedite effective treatment and prevention of disease.
- **Water, sanitation and hygiene.** Place a greater priority on clean water supply and basic sanitation systems in urban development, as well as on education to promote proper hygiene including hand washing.

The World Health Organization (WHO) is taking an approach to typhoid control based on the latest evidence. In 2008 WHO updated its 2000 position paper to recommend that countries consider programmatic use of typhoid vaccines for controlling endemic disease, as well as for controlling outbreaks. As of 2012, WHO has also committed to expediting the availability of next generation typhoid conjugate vaccines through the development and dissemination of standards for the regulatory evaluation and WHO prequalification of these vaccines, and by coordinating the development of international and Vi antigen standards.

Policymakers representing the most affected populations are also taking action. Throughout South and South East Asia and the Pacific Islands there are several examples of successful typhoid vaccination programs at the municipal and provincial levels and this experience is being shared in meetings and peer-exchanges. Typhoid vaccination is consistently prioritized for '*immediate*' introduction by local technical experts and in 2012 regional policymakers prioritized typhoid vaccines for introduction.

Invasive non-typhoidal *Salmonella*

Non-typhoidal *Salmonella*, a global cause of foodborne illness, commonly results in self-limited diarrhea. However, in Africa, invasive NTS (iNTS) can cause febrile and often fatal disease. iNTS is increasingly identified among young children and young adults in Africa, especially where HIV, malaria and malnutrition are common.

Preliminary estimates of iNTS disease burden indicate there are as many as 3.4 million cases globally each year, with 80 percent of illness in sub-Saharan Africa. Case fatality rates are as high as 20 percent and can be up to 50 percent when left untreated.

Confounding febrile illnesses such as malaria, combined with limited access to and poor quality of clinical microbiology services including blood culture, contribute to a lack of awareness and the resultant low prioritization of iNTS research, surveillance and general control and prevention efforts. However, there is hope. A public-private partnership has been funded to discover and develop iNTS conjugate vaccines.

The opportunity to eliminate typhoid

Among the more than 60 presenters at the “Conference on Typhoid Fever and Other Invasive *Salmonellosis*”, the preponderance of research findings pointed to growing global risks posed by enteric fever and iNTS. Leading experts and policy makers stressed both the need to control typhoid and enteric fever and the potential to eliminate it through a comprehensive approach that includes vaccination with next generation conjugate vaccines; timely access to effective clinical care; expanded standardized surveillance and improved diagnostics; safe water and basic sanitation; forward-thinking policies; and adequate funding.

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The conference was held on 1-2 March 2013 at the Pan Pacific Sonargaon Hotel in Dhaka, Bangladesh.

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Conference materials are available online at: <http://www.TYPHOIDCONFERENCE.org/>

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The Coalition against Typhoid (CaT)

The Coalition against Typhoid (CaT) is a global forum of health and immunization experts working to expedite and sustain rational, evidence-informed policy at the global, regional, national and local/municipal levels regarding the use of typhoid vaccines to prevent childhood enteric fever. CaT also works to define barriers to the adoption of typhoid vaccines in communities that would benefit most and the key activities that are needed to overcome them. The Sabin Vaccine Institute serves as the CaT Secretariat and is supported by a grant from the Bill & Melinda Gates Foundation. The CaT objectives are accomplished through the activities of its membership.

Participation in CaT is open to any institution interested in contributing to the control of enteric fever and invasive non-typhoidal Salmonella. Currently, there are over 30 CaT member organizations:

- Aga Khan University, Pakistan
- Agence de Médecine Préventive (AMP), France
- ATV D-Team, Russia
- Bharat Biotech International Ltd. (BBIL), India
- Bill & Melinda Gates Foundation, USA
- Center for Vaccine Development at the University of Maryland, USA
- Crucell, Switzerland
- Eunice Kennedy Shriver National Institute of Child Health & Human Development, US National Institutes of Health, USA
- Finlay Institute, Cuba
- Fogarty International Center, US National Institutes of Health, USA
- Foundation Mérieux, France
- GAVI Alliance, Switzerland
- Global Immunization Division, US Centers for Disease Control and Prevention, USA
- Incepta, Bangladesh
- International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b)
- Institute of Tropical Medicine, Antwerp, Belgium
- International Vaccine Institute (IVI), Korea
- Lao-Oxford-Mahosot Hospital-Wellcome Trust-Research Unit (LOMWRU)
- National Enterics Laboratory Diagnostics & Outbreak Team (NELDOT), Enteric Diseases Branch, US Centers for Disease Control and Prevention, USA
- National Institute of Cholera and Enteric Diseases (NICED), Kolkata, India
- Novartis Vaccines Institute for Global Health, Italy
- Oxford Vaccine Group at the University of Oxford, UK
- Oxford University Clinical Research Unit at the Hospital for Tropical Diseases, Vietnam
- PATH, India and USA
- Sabin Vaccine Institute, USA
- Sanofi-Pasteur, France
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