

Global policy support for typhoid conjugate vaccine

On the global health agenda, typhoid has often been overlooked as a priority. Perhaps this is because for many in the United States and Western Europe, typhoid is a disease of the past, largely eliminated with infrastructure investments to provide piped water, and sewer and waste disposal systems. However, for too many families in low- and middle-income countries (LMICs), typhoid remains a prevalent threat but does not receive the prioritization or resources needed for adequate prevention and control. Growing concerns about drug resistance, climate change, and rapid urbanization underscore the urgency to address typhoid. The good news is that beginning in 2017, there have been new global policies for effective and efficient typhoid prevention and control. With the global policies and resources in place, decision-makers and stakeholders in typhoid-endemic countries have the opportunity to align with the global standards and prioritize typhoid control in their own countries.

Typhoid

Typhoid is a serious and potentially life-threatening enteric fever spread through food and water contaminated with the bacteria *Salmonella enterica* serovar Typhi. While largely eliminated in high-income countries, it remains a substantial public health issue that disproportionately affects children and adolescents in LMICs: in 2019, there were an estimated 9 million cases of and more than 110,000 deaths from typhoid, the vast majority of them in Southeast Asia and sub-Saharan Africa.¹

Diagnosing typhoid presents many challenges due to the non-specific symptoms of the disease and limitations of available diagnostic tests. The tendency to initially misdiagnose typhoid as malaria, flu, or other febrile illnesses often leads to delayed treatment, which can cause complications such as intestinal perforation and bleeding. Appropriate antibiotics are the only way to treat typhoid and avoid these potentially fatal complications.

Alarming, in high-burden communities, resistance to first-line antibiotics and fluoroquinolones is growing, leading to the global spread of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains of typhoid. When newer, more expensive antibiotics are not available, as is the case in many LMICs, drug-resistant typhoid

becomes untreatable. Prevention through vaccination is key to taking on drug-resistant typhoid: by preventing new cases of typhoid, the need for antibiotics is reduced.



Typhoid conjugate vaccines (TCVs)

Recent global policy breakthroughs regarding TCVs enable national decision-makers to reconsider vaccination as an effective tool in the fight against typhoid. Since 2017, the World Health Organization (WHO) and Gavi, the Vaccine Alliance (Gavi) have come out in support of TCV, opening the door to introduction at the national level. WHO prequalified TCVs can be administered to children as young as six months of age, allowing for vaccination as part of the routine childhood immunization schedule, protecting the age groups most vulnerable to typhoid, and offering more efficient, effective, and longer-lasting protection than other typhoid vaccines. Without a large-scale push for improved water and sanitation infrastructure, programmatic vaccination with TCV offers the best chance to reduce the burden of typhoid in endemic countries. Results from three large efficacy studies conducted in Bangladesh, Malawi, and Nepal show that TCVs are safe and protective in both Asia and Africa.

Global policies

The current policy landscape overwhelmingly endorses TCVs as safe and efficacious tools to prevent and control typhoid.



World Health Organization Strategic Advisory Group of Experts on Immunization meeting report²

In October 2017, the WHO Strategic Advisory Group of Experts (SAGE) on Immunization, the principal advisory body to the WHO on vaccination, carefully reviewed the available information and data regarding TCV efficacy and safety, and concluded the importance of TCV introduction and programmatic vaccination for controlling typhoid in endemic settings. In particular, the report recommends prioritizing TCV introduction efforts in countries where there is a high burden of disease or a growing threat of drug-resistant typhoid strains.



Gavi, the Vaccine Alliance, opens a funding window for TCV introduction³

Based on the SAGE recommendation, and in anticipation of a forthcoming WHO prequalification of a TCV candidate, Gavi announced in November 2017 that it was opening a funding window for TCV. The Gavi board approved US\$85 million to support TCV introduction in eligible countries, and committed to funding the vaccine itself along with co-funding the costs of introduction. This marked the first time a typhoid vaccine became eligible for Gavi funding support, clearly designating typhoid and TCVs as a priority on the global health stage and creating a route to increase access to the vaccine where it is most needed.



World Health Organization prequalification

In December 2017, after a rigorous data review process, the WHO prequalified Typbar TCV^{®4}, the first typhoid conjugate vaccine to receive this designation. The WHO stated, "Typbar TCV is the first typhoid vaccine clinically proven to be administered to children from 6 months of age to adults and confers long term protection against typhoid fever". In December 2020, WHO prequalified TYPHIBEV[®]. Clinical studies show that its immune response profile is similar to that of Typbar TCV.⁵

What you need to know

- » The WHO formally **recommends integration of TCVs** as part of routine childhood immunization programs alongside catch-up campaigns for children up to 15 years of age, prioritizing countries with a high burden of disease and/or evidence of drug-resistant typhoid.
- » **TCVs possess many advantages** compared to earlier vaccines, as confirmed in the WHO position paper: longer-lasting protection, safe for use in children six months and older, and only require one dose for years of protection.
- » Data from TCV introduction trials have been reviewed by GACVS to assess vaccine safety and potential adverse events, with the conclusion that **Typbar TCV is safe for use** as recommended by the WHO.
- » The WHO emphasizes that expanding access to **TCVs can reduce the need for antibiotic treatment** and slow the spread of drug-resistant typhoid strains.
- » According to the WHO, programmatic **vaccination efforts should be combined** with improvements in WASH services, strengthened surveillance, health and disease education, and appropriate use of antibiotics to reduce the burden of typhoid in endemic countries.

WHO prequalification signifies that the vaccine meets globally held standards of quality, safety, and efficacy, and allows the WHO, the United Nations Children's Fund, and other United Nations procurement agencies to purchase the vaccine. Prequalification also officially enables eligible countries to apply for funding assistance through Gavi to support introduction of the vaccine, a critical step to increase access to TCVs in LMICs with the greatest burden of typhoid.

In non-Gavi-eligible countries, prequalification can expedite licensure of the vaccine, allowing government regulators to more quickly approve the vaccine for widespread use in their country. The prequalification of a TCV affirms the value of the vaccine for typhoid control and represents a commitment to increasing access to the vaccine globally.



World Health Organization typhoid vaccines position paper⁶

The WHO issued its formal recommendation in support of TCV introduction in March 2018, replacing the previous typhoid vaccine position from 2008. The paper reflects the updated formal stance of the WHO—that TCVs are preferred over other available typhoid vaccines in all age groups due to “improved immunological properties, suitability for use in younger children, and expected longer duration of protection”. Echoing the SAGE recommendation, the position paper emphasized that TCV introduction should be prioritized in countries with the highest burden of disease and/or with high burden of drug-resistant typhoid.

The position paper also cited disease modeling studies that predicted routine vaccination, especially when coupled with catch-up vaccination campaigns, is likely a cost-effective method to reduce typhoid incidence in many countries. The report clearly recommends TCV introduction as a control strategy in response to confirmed typhoid outbreaks as well as for routine use. Additionally, the report emphasizes the value of an integrated approach to typhoid control, stating: “All typhoid vaccination programmes should be implemented in the context of other efforts to control the disease, including health education, water, sanitation and hygiene (WASH) improvements, and training of health professionals in diagnosis and treatment”.

The release of a new position paper—the WHO official policy on typhoid and TCV—signals to member states that typhoid control deserves prioritization, and that TCV introduction alongside other typhoid control strategies should be considered in endemic countries.



Global Advisory Committee on Vaccine Safety confirms safety of Typbar TCV⁷

Following the review of TCV introduction studies conducted in Malawi, Nepal, Bangladesh, Pakistan, and India, which include data on more than 340,000 children and adolescents vaccinated, the Global Advisory Committee on Vaccine Safety (GACVS) confirmed that Typbar TCV is safe for widespread introduction, and that no safety concerns or signs of adverse events associated with the vaccine had been reported. The report reiterates the safety of TCVs, specifically in the LMIC context, reassuring that introduction of the vaccine is safe, effective, and important for typhoid control. As studies of Typbar TCV continue to yield additional data on the safety profile and efficacy of the vaccine, the GACVS will continue to review information and update its reports.



World Health Organization Strategic Advisory Group of Experts on Immunization meeting report



World Health Organization prequalifies Typbar TCV



Global Advisory Committee on Vaccine Safety confirms safety of Typbar TCV

OCTOBER 2017

NOVEMBER 2017

DECEMBER 2017

MARCH 2018

DECEMBER 2018

DECEMBER 2020



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World Health Organization typhoid vaccines position paper



World Health Organization prequalifies TYPHIBEV

Recommendations

Now is the time for decision-makers in typhoid-endemic countries to adapt these global policies for local action and impact, including TCV introduction.

Policy makers and other government leaders can:

- » **Contact TyVAC for additional information** about typhoid burden in their country and learn about the support TyVAC offers during the new vaccine introduction decision-making process by visiting www.takeontyphoid.org.
- » Speak with pediatricians, health care workers, and parents to **learn about the impact typhoid** has had on their work and lives.
- » **Identify ongoing research** and TCV introductions in neighboring countries to learn about new evidence that can inform decision-making. TyVAC is also available to supply this information.
- » **Commit to prioritizing** typhoid prevention and control in their country. This may include tabling TCV introduction at key meetings, or adding TCV into key child health, immunization, and other relevant policies.
- » Learn more about how to **apply for funding support** for TCV introduction from Gavi [here](#).

Advocates, including pediatricians, researchers, scientists, program managers and implementers can:

- » **Review current policies** to identify the specific actions and commitments government leaders have already made to address typhoid in the local context and compare them to the global policy recommendations presented here. Are there child health, immunization, or WASH policies that specifically call for typhoid prevention and control, including TCV?
- » **Carry out stakeholder mapping** to identify the key players who will be involved in conversations and decisions related to typhoid control policy and TCV introduction.
- » **Attend relevant child health and vaccine technical working group meetings** to provide information and highlight current policies and commitments to relevant stakeholders, including parliamentarians, ministry heads (finance, education, infrastructure), subnational leaders, health professionals, and community members.

References

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- ⁷ WHO. Global Advisory Committee on Vaccine Safety, 5-6 December 2018. *Weekly Epidemiological Record*. 2019;4(94):45-52. Available at: <https://apps.who.int/iris/bitstream/handle/10665/279829/WER9404.pdf?ua=1>