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WHO Report

Typhoid vaccines: WHO position paper, March 2018 – Recommendations

World Health Organization

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ABSTRACT

This article presented the World Health Organization's (WHO) recommendations on the use of Typhoid vaccines excerpted from the Typhoid vaccines: WHO position paper – March 2018 published in the Weekly Epidemiological Record (World Health Organization, 2018) [1]. This position paper replaces the 2008 WHO position paper on typhoid vaccines (WHO, 2008) [2]. It re-emphasizes the importance of vaccination to control typhoid fever and presents the WHO recommendations on the use of a new generation of typhoid conjugate vaccines.

Footnotes to this paper provide a number of core references including references to grading tables that assess the quality of the scientific evidence, and to the evidence-to-recommendation tables. In accordance with its mandate to provide guidance to Member States on health policy matters, WHO issues a series of regularly updated position papers on vaccines and combinations of vaccines against diseases that have an international public health impact. These papers are concerned primarily with the use of vaccines in large-scale immunization programmes; they summarize essential background information on diseases and vaccines, and conclude with WHO's current position on the use of vaccines in the global context. Recommendations on the use of cholera vaccines were discussed by the Strategic Advisory Group of Experts (SAGE) in October 2017; evidence presented at these meetings can be accessed at: http://www.who.int/immunization/sage/meetings/2017/October/presentations_background_docs/en/.

1. Introduction

There is a continuing high burden of typhoid fever in many parts of the world and a rapid increase in the emergence and spread of antimicrobial resistant strains of Salmonella Typhi (*S.* Typhi). Currently available evidence is favourable regarding the safety, efficacy, effectiveness and/or immunogenicity, as well as cost-effectiveness of typhoid vaccines. World Health Organization (WHO) recommends programmatic use of typhoid vaccines for the control of typhoid fever. All typhoid vaccination programmes should be implemented in the context of other efforts to control the disease, including health education, water quality and sanitation improvements, and training of health professionals in diagnosis and treatment.

Among the available typhoid vaccines, typhoid conjugate vaccine (TCV) is preferred at all ages in view of its improved immunological properties, use in younger children and expected longer duration of protection. Countries may also consider the routine use of parenteral unconjugated Vi polysaccharide (ViPS) vaccine in individuals aged 2 years and older, and Ty21a vaccine for individuals aged more than 6 years. Choice of vaccination should consider costs, programmatic issues and duration of protection.

WHO recommends the introduction of TCV to be prioritized in countries with the highest burden of typhoid disease or a high burden of antimicrobial resistant *S.* Typhi. Decisions on the age of TCV administration, target population and delivery strategy for routine and catch-up vaccination should be based on the local epidemiology of typhoid fever, including antimicrobial resistance patterns, and programmatic considerations of the routine childhood immunization programme.

National decisions on the preferred vaccination strategy (universal, risk-based, or phased) should be based on an analysis of the disease burden and risk factors for transmission, availability and quality of surveillance data, cost-effectiveness, affordability, and operational feasibility. The experiences and impact of different vaccination strategies, as well as integration with water, sanitation and hygiene (WASH) or other interventions, should be monitored and documented in order to support further improvement in typhoid control.

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2. Primary vaccination

At this time, there is evidence of higher and more sustained levels of immunogenicity from one dose of injectable Vi-TT (tetanus toxoid) conjugate vaccine (Typbar-TCV®) compared with the injectable ViPS vaccine. WHO recommends TCV as a 0.5 mL single dose for infants and children from 6 months of age and in adults up to 45 years as a 0.5 mL single dose in typhoid endemic regions. WHO encourages routine programmatic administration of TCV at the same time as other vaccine visits at 9 months of age or in the second year of life [3].

When ViPS is used, a single dose of the Vi polysaccharide vaccine should be administered intramuscularly or subcutaneously from 2 years of age.

For Ty21, a 3-dose oral immunization schedule, administering the vaccine every second day, is recommended above 6 years of age.

3. Catch-up vaccination

Catch-up vaccination with TCV up to 15 years of age is recommended when feasible and supported by epidemiologic data, noting that the burden of disease and programmatic feasibility are greater in this age range than in adults. Catch-up vaccination of multiple age cohorts at the time of vaccine introduction is likely, on the basis of modelling, to accelerate the impact of vaccine use. This strategy may also increase indirect herd protection of unvaccinated individuals. In addition to the routine vaccination strategy, the decision on catch-up vaccination will also need to take into account cost, and other operational issues including vaccine transport, cold chain, and logistics.

4. Vaccine use in outbreaks and emergency settings

WHO recommends vaccination in response to confirmed outbreaks of typhoid fever. However, data on the use of typhoid vaccines for outbreak control are very limited and efforts to assess the value of both preventive and reactive vaccination campaigns for outbreaks are strongly recommended. Important considerations for the use of typhoid vaccine in outbreak control include vaccine availability, logistics, and costs as well as the characteristics of the outbreak (such as the confirmation of antimicrobial resistant *S.* Typhi strains, outbreak size, duration and age group affected). Countries experiencing typhoid outbreaks should consider introduction or strengthening of routine immunization programmes.

Typhoid vaccination may be considered in humanitarian emergencies depending on the risk assessment in the particular setting. However, the main priorities for typhoid fever prevention in such settings are usually the provision of safe water and promotion of improved sanitation and hygiene measures, in particular for food handlers. WHO has published a framework for decision-making on the use of vaccines in humanitarian settings as guidance for the risk assessment of typhoid and other vaccine-preventable diseases [4].

5. Revaccination

The potential need for revaccination with TCV is currently unclear. When ViPS or Ty21a vaccine is used, revaccination is recommended every 3 years for ViPS, and every 3 to 7 years for Ty21a.

6. Vaccination of special populations, contraindications and precautions

TCV and ViPS vaccines are contraindicated for individuals with known hypersensitivity to any component of the vaccine. Ty21a should not be administered to persons who are taking antibiotics. Certain antimalarials, particularly mefloquine, may suppress the Ty21a antibody response and should not be given from 3 days before until 3 days after giving the Ty21a vaccine.

Typhoid vaccination is recommended for the following specific groups which may be at high risk of acquiring or transmitting *S.* Typhi infection.

Professional food handlers: In typhoid-endemic areas, professional food handlers could be vaccinated against typhoid. However, evidence of the real benefits of routine vaccination in this group is needed. If available, the use of a Vi negative vaccine, such as Ty21a, should be considered in order to allow for serological identification of a chronic carrier status among vaccinated persons. If Ty21a vaccine is not available, professional food handlers should be vaccinated with an alternative typhoid vaccine.

Travellers from non-endemic to endemic areas: Travellers to typhoid-endemic areas should adhere to precautions on hygienic practices to reduce their risk of infection. Typhoid vaccination should be considered for travellers, using one of the available licensed products, namely TCV, ViPS, or Ty21a. Licensed combination typhoid-hepatitis A vaccines, where available, may also be used for travellers.

Health-care workers: Clinical microbiology laboratory staff with a recognized risk of occupational exposure to *S.* Typhi should be offered vaccination against typhoid.

Vaccination of pregnant women: Data are currently lacking on typhoid vaccine use in this population, however there are no theoretical safety concerns for ViPS and TCV. Use of the live attenuated Ty21a vaccine during pregnancy should be avoided because of theoretical safety concerns about potential adverse effects in the pregnant woman or fetus.

Vaccination of HIV-infected and other immunocompromised persons: Immunocompromised persons, including those with HIV infection, should receive TCV or ViPS vaccine. Ty21a vaccine can be administered to HIV-infected, immunologically stable individuals with a CD4 percent >25% for children aged <5 years or CD4 count $\geq$200 cells/mm^3 if aged $\geq$5 years.

7. Administration and co-administration of typhoid vaccines

TCV vaccines are administered by intramuscular injection and ViPS are administered by intramuscular or subcutaneous route into the anterolateral aspect of the thigh for infants or into the deltoid muscle for older children and adults.

Typhoid vaccines can be co-administered with other killed and live vaccines using separate syringes and different injection sites. When 2 injectable vaccines are given during the same visit, they should be injected in different limbs. When 3 vaccines are given, 2 can be injected in the same limb and the third should be injected in the other limb. Injections in the same limb should be at least 2.5 cm apart so that local reactions can be differentiated. There are effective recommended methods to mitigate pain at the time of vaccination [5].

8. Interchangeability of vaccines

There are currently no data on the interchangeability and sequential use of the different typhoid vaccines.

9. Monitoring and surveillance

Introduction of TCV should include post-licensure monitoring of effectiveness and vaccine safety. This should include monitoring of any potential safety risks in special population groups (e.g. malnourished children, immunocompromised individuals and, where applicable, pregnant women).

WHO recommends (i) further safety monitoring of all TCVs through strengthening post-marketing surveillance and ensuring robust safety evaluation of TCV in planned effectiveness studies, including any potential safety risks in special population groups (e.g. malnourished children, immunocompromised individuals and, where applicable, pregnant women); (ii) the use of Brighton Collaboration case definitions and active monitoring of serious adverse events of interest; and (iii) analysis of non-specific effects of vaccination, where feasible.

Information on antimicrobial resistance patterns will be valuable in informing vaccine introduction decisions, measuring the impact of the vaccine, and adjusting antibiotic treatment recommendations in specific settings. WHO recommends that endemic countries strengthen the surveillance of typhoid fever in all age groups, and monitor the presence of antimicrobial resistant strains of *S.* Typhi in endemic and epidemic disease, before and after introduction of typhoid vaccines [6].

10. Research priorities

Priority should be given to generating data that will further support typhoid vaccination policy and immunization programmes, particularly through research in the following areas: development of tools or methods to identify populations and individuals at risk of typhoid fever; the risk of transmission from chronic carriers of *S.* Typhi and strategies to identify and treat carriers; correlate(s) of protection for typhoid vaccines; co-administration with other childhood vaccines (where not yet studied); safety and immunogenicity in special populations, including malnourished children, immunocompromised persons, and pregnant women; duration of protection for a single dose of TCV and the potential need for revaccination; whether the tetanus toxoid carrier protein of the licensed TCVs provides protection equivalent to a booster dose of tetanus vaccine; and the impact of different TCV strategies including target age ranges for routine and catch-up vaccination as well as vaccination for outbreak control.

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