Typhoid Data Guidance for Gavi Applications

The purpose of this document is to provide guidance for countries to collate and analyze typhoid-related epidemiological and other data for inclusion in applications submitted to Gavi for support to introduce typhoid conjugate vaccine (TCV). The document describes the steps a country should take to collect evidence of both past and current typhoid disease burden, as well as assessing other data on past and present typhoid disease risk. The principal audience for this guidance is national Ministries of Health (MOH), particularly the Expanded Programme on Immunization (EPI) and vaccine policy decision-makers assessing local typhoid disease burden or leading the development of a Gavi TCV application. The guidance herein has been prepared by Gavi's typhoid vaccine subteam which includes WHO, CDC, UNICEF, and TyVAC, among others, with additional inputs from external typhoid experts.

Overview

Typhoid fever is largely an endemic disease that occurs sporadically but may also result in outbreaks. The amount of typhoid in a given area may vary considerably over time, and only a small part of a country may experience cases at any given time despite a potential risk for typhoid transmission due to water, sanitation and hygiene (WASH) conditions favourable to the spread of typhoid in larger areas of the country. At-risk areas that do not have typhoid disease occurrence for a certain period of time may experience it at a later time. A country considering whether and how to use TCV should take into account both evidence of current and past typhoid occurrence (2-5 years), The rationale to introduce TCV and the vaccination strategy selected is most strongly supported by evidence of past or current typhoid disease, including evidence of multi or extremely drug resistant typhoid circulation. However, other evidence indicating a potential risk of typhoid (e.g., modelling data, risk factor assessments, environmental sampling etc.) may also be submitted to support TCV introduction and vaccination strategy decisions.

WHO's recommendations for TCV[1] state that countries can use TCV through a universal, risk-based, or phased approach, for both introduction into routine immunisation and implementation of one-time catch-up immunisation at the time of introduction for children up to 15 years of age. A country considering introducing typhoid conjugate vaccine should therefore conduct an assessment of typhoid risk, including in subnational level administrative areas (e.g., each province or district), if feasible. Countries may conclude that different geographic areas have varied risk of typhoid disease.

These spatial differences in typhoid disease burden or risk may drive context-specific decisions about TCV introduction and vaccination strategy in different geographic areas. A country may decide to introduce TCV into the routine immunisation programme and implement a one-time immunisation campaign for older age groups nationally, only in certain areas, or in a phased manner in which some areas introduce TCV before others. A country's assessment of typhoid risk in combination with logistical and operational feasibility and cost of delivery considerations may result in the nationwide use of TCV in the routine immunisation programme with a one-time immunisation campaign for older age groups in targeted areas.

Such conclusions and the basis for them should be clearly stated in the application for Gavi support. If additional support is needed to compile available data and/or analyze and interpret the results of the compiled data, please consult the Gavi Senior Country Manager

[1]Typhoid vaccines: WHO position paper – March 2018: https://apps.who.int/iris/bitstream/handle/10665/272272/WER9313.pdf?ua=1

who can link countries to additional technical resources, including Gavi Alliance partners to support assessment of local typhoid risk. **The consolidated information, analysis and interpretation of past, current and likely typhoid risk should be included as part of a country's submission for Gavi support to introduce TCV.**

In many instances, no single evidence or data source can be considered adequate for assessing the typhoid burden in a population. Therefore, countries are encouraged to review and provide as much data as is available among the types of evidence (and data sources) listed below and detailed in subsequent sections. In general, it is expected that:

- The types of evidence (and sources of data) listed in Step 1 are likely to provide more robust evidence of the typhoid occurrence in a population while the types of evidence (and sources of data) listed in Step 2 may provide supplemental proxy information of potential typhoid risk in a population;
- Data based on laboratory-confirmation of typhoid, and/or evidence of burden of antimicrobial resistance are more reliable indicators of typhoid disease in a population when compared to data sources not supported by laboratory confirmation;
- Data based on modelled typhoid burden, WASH assessments, or other risk factors for typhoid may be considered but are less reliable. Data from environmental sampling and serosurveys may also be considered but these methods are under development and still require validation;
- Data based on syndromic reporting of typhoid fever that is not blood-culture confirmed are not considered reliable.

It should be noted, given the diagnostic and surveillance challenges related to typhoid, that countries that do not have evidence of past or current typhoid burden (Step 1) are not restricted from submitting a Gavi application for TCV introduction. However, in the absence of these information countries need to provide the alternative data which indicate typhoid risk (Step 2) and inform introduction and vaccination strategy decisions as part of their application for Gavi support.

Step 1 – Assess Evidence of Past or Current Typhoid Occurrence

For the assessment of evidence of typhoid disease, a country should make every effort to review all sources of credible evidence of past or current typhoid disease from the previous 2-5 years if available. Please reference Table 1 for more detail.

These types of evidence can include:

Laboratory-confirmed typhoid cases confirmed by blood cultures in that country, including any antimicrobial resistance testing results

AND / OR

Laboratory-confirmed typhoid cases confirmed by molecular testing, such as polymerase chain reaction, using a known or validated protocol, such as in a research study

AND / OR

Laboratory-confirmed typhoid outbreaks, including blood culture confirmed typhoid cases or non-traumatic terminal ileal perforations[2] with blood-culture confirmation of *S.* Typhi[3]

[2] If the ileal site (e.g., terminal) is unknown for all cases, you may give the total number of ileal perforation cases, and the proportion of cases documented to have perforations in the terminal ileum

[3] Laboratory-confirmed typhoid outbreaks means a minimum of two cases are confirmed by blood culture as caused by *S.* Typhi. (Source: *WHO Surveillance Standards for Typhoid and other invasive salmonellosis* (2018) https://www.who.int/immunization/monitoring_surveillance/burden/vpd/standards/

Sources for this evidence include:

In-country surveillance data[4] and/or research study or survey data of laboratory-confirmed typhoid cases (not including cases confirmed with only a positive Widal test)

AND / OR

In-country surveillance data on laboratory-confirmed typhoid outbreaks, which may be identified through blood culture testing or non-traumatic terminal ileal perforations with laboratory confirmation of *S.* Typhi

AND / OR

In-country data (surveillance, survey, clinical laboratories) of proportion(s) of *S.* Tyhpi blood culture confirmed non-traumatic terminal ileal perforations (e.g., presented as a proportion of patients presenting with fever from the community with *S.* Typhi blood stream infection, proportion of all acute non-traumatic abdominal emergencies with laboratory confirmation of *S.* Typhi)

Studies are ongoing to further determine the value of serosurveys in assessing typhoid infection rates in a population. Please consult the Gavi Senior Country Manager who can link countries to additional technical resources to assist in reviewing serological data where available or feasible to collect.

[4] *WHO Surveillance Standards for Typhoid and other invasive salmonellosis* (2018) https://www.who.int/immunization/monitoring_surveillance/burden/vpd/standards/

It should be noted that surveillance data on suspected typhoid (or enteric fever) cases or cases classified as typhoid solely on the basis of positive Widal tests are not considered credible evidence of past or current typhoid disease.

Table 1: Country Assessment of Surveillance Data Sources on Typhoid Disease Burden

DATA SOURCE	Yes/ No	NOTES/QUESTIONS TO CONSIDER (IF APPLICABLE)
In-country surveillance of laboratory-confirmed typhoid within the past 5 years		• For data on individual laboratory-confirmed cases (blood culture or molecular testing), specify: ○ If from surveillance, specify whether active or passive[5] ○ The proportion of bloodstream infections that are community-onset versus hospital-acquired ○ The age groups of cases ○ The month, year, and geographic area that cases occurred in ○ For each geographic area, population covered in location(s) identified / % of the total country population ○ The number of cases confirmed by each method, specifically blood culture and molecular testing. ○ Annual incidence of laboratory-confirmed typhoid disease based on country determined denominator (e.g. healthcare facility catchment area) ○ *Salmonella* Typhi antimicrobial resistance testing results by year[6] ○ Proportion of febrile patients with *S*. Typhi bloodstream infections ○ If available, where *Salmonella* Typhi falls in the rank order of causes of community-acquired bloodstream infections at a site or in national data
Research study data demonstrating laboratory-confirmed typhoid (e.g., blood) within the past 5 years		
Surveys/Records of in-country laboratory facilities that perform blood cultures		
In-country laboratory-confirmed typhoid outbreaks, which may be identified through clusters of non-traumatic terminal ileal perforations		• For laboratory-confirmed typhoid outbreak data, specify: ○ The month and year of the start of each laboratory-confirmed typhoid outbreak (i.e. one or more blood culture confirmed cases) ○ Number of total cases (suspect and confirmed) in each laboratory-confirmed typhoid outbreak ○ Antimicrobial resistance testing results, particularly by year of those results ○ How each laboratory-confirmed typhoid outbreak was identified, for example, through increased occurrence of blood-culture confirmed typhoid cases, increased occurrence of antimicrobial resistant typhoid, or increased occurrence of non-traumatic terminal ileal perforations

[5] *Passive case detection means that health facility staff detect and report cases from among patients presenting to the specific facility/facilities, while active surveillance means that designated surveillance staff are directly involved in detecting cases. For example, surveillance staff may do a regular review of facility registers and have regular contact with clinicians regarding potentially missed cases. Compared to passive methods, active surveillance is more resource-intensive and expensive; it is often used for VPDs in the elimination or eradication phase, to characterize VPD epidemiology or vaccine impact in discrete populations or sentinel sites, or in specific situations such as in outbreak response.*

[6] *Increasing antimicrobial resistance may alter estimated case fatality ratio of typhoid fever. TCV's estimated cost effectiveness may increase in this scenario and further support introduction of TCV*

DATA SOURCE	Yes/ No	NOTES/QUESTIONS TO CONSIDER (IF APPLICABLE)
Proportion (s) of *S.* Typhi blood culture confirmed cases with non-traumatic terminal ileal perforations		• Please specify: ○ Proportion(s) of *S*. Tyhpi blood culture confirmed cases with non-traumatic terminal ileal perforations and why considered high (e.g., comparison with literature or increasing rates in the same site(s)). ○ Proportion of ileal perforation cases with lab confirmation of *S.* Typhi. ○ Proportion of all acute non-traumatic abdominal emergencies requiring surgery

Step 2 – Assess Evidence Which Indicates a Potential Risk of Typhoid Occurrence

For the assessment of evidence of potential risk of typhoid disease, a country should attempt to review all sources of credible information predictive of future risks. Please reference Table 2 for more detail (next page).

These types of evidence include:

Modelled burden or prediction of typhoid disease based on country-specific data

AND / OR

Data on risk factors for typhoid disease OR outbreaks or high burden of other WASH related diseases such as cholera (e.g. lack of access to improved water and adequate sanitation, paved roads, housing density)

AND / OR

Laboratory-confirmed *Salmonella* Typhi from **environmental sampling**

Neighbouring country or country with similar risk factor profile data should only be used as context (e.g. surveillance data on laboratory-confirmed typhoid cases/outbreaks or modelled burden)

Sources for this information include:

Published and unpublished typhoid modelling studies

AND / OR

Water and sanitation assessments

OR

Assessment of other risk factors for typhoid OR other WASH related diseases such as cholera

AND / OR

Surveys of any groups conducting environmental surveillance for *Salmonella* Typhi

Table 2: Country Assessment of Alternative Data Sources on Typhoid Disease Burden

DATA SOURCE	Yes/No	NOTES/QUESTIONS TO CONSIDER (IF APPLICABLE)
Published and unpublished modeled burden of typhoid fever based on country-specific data		• Some global modeling examples to consider: ○ Antillón M et al. (2017)*The burden of typhoid fever in low- and middle-income countries: A meta-regression approach*.PLoS Negl Trop Dis 11(2): e0005376. doi:10.1371/journal.pntd.0005376 ○ IHME GBD data visualization tool: http://www.healthdata.org/gbd/data-visualizations) • Please specify: ○ The group that completed the modelling ○ The date the modelling was performed ○ The age group(s) and areas covered by the modelling ○ The projected burden of typhoid disease or risk of typhoid disease for an area
Risk factors for typhoid fever, e.g., lack of access to improved water and adequate sanitation		• Please specify: ○ Description of the risk factor(s) being assessed ○ Specific location where the risk factors are present; group that performed assessment ○ Date(s) and geographic area(s) of the assessment ○ The findings of the assessment
Laboratory-confirmed *Salmonella* Typhi from environmental sampling		• Please specify: ○ The group that performed the assessment ○ Date(s) and geographic area(s) of the assessment ○ The findings of the assessment ○ Any link with clinical typhoid cases if applicable

Step 3 – Key Considerations for use of evidence for Decision Making

Data and evidence on risk and burden of typhoid disease should be carefully analysed to inform various decisions including; whether and when to introduce TCV, vaccination strategy – campaign, routine, universal, risk-based, or phased. The scenarios illustrated below provide an overall decision framework for evidence-based decision-making, but key contextual factors, including epidemiological and operational considerations should be taken into account; Note, WHO recommends that countries experiencing typhoid outbreaks should consider TCV introduction into the routine immunization schedule with concurrent strengthening of the routine immunization programme to ensure high coverage.

TCV introduction nationally: evidence points towards nation-wide risk or risk for a greater part of the country, with nation-wide data, research and/or surveys available. Countries lacking nation-wide data may additionally consider national routine introduction to ensure equity where cases are not being detected.

TCV introduction sub-nationally: evidence points towards a higher risk of typhoid disease for a certain region, and minimal or no risk for the rest of the country. Countries should strongly consider if evidence of no disease or risk is sufficient to target routine use of TCV. In non-large federated countries, the operational feasibility of subnational routine introduction should also be considered.

Catch-up immunisation at time of TCV routine introduction: evidence of typhoid fever endemicity e.g., over the last 2-5 years should guide towards TCV introduction into the routine immunization schedule, while evidence of typhoid incidence in older age groups in recent outbreak(s) could guide towards one-time catch-up immunisation at the time of introduction in the identified areas of risk.