Meeting Report

MEETING TO REVIEW DATA GAPS FOR TYPHOID CONJUGATE VACCINE POLICY AND PUBLIC HEALTH USE*

21-22 September 2015
Geneva, Switzerland

*This meeting served as the 2nd WHO expert consultation to review the adequacy of clinical data on TCVs to facilitate a decision on initiating the SAGE policy process

Initiative for Vaccine Research (IVR)
Immunization, Vaccines and Biologicals (IVB)
Background

The two types of typhoid vaccines currently licensed and recommended by WHO (in the 2008 WHO position paper on typhoid vaccines\(^1\)), are Vi polysaccharide vaccine (ViPS) and live attenuated Ty21a vaccine. Since 2008, however, uptake of these vaccines in typhoid endemic countries has been low for a variety of reasons. It is also well known that the Board of Gavi, the Vaccine Alliance announced in 2008 and reiterated in 2011, that as part of its vaccine investment strategy, Gavi would consider future funding support for the next generation of typhoid conjugate vaccines (TCVs).

In recent years, significant progress has been achieved in the development of TCVs and there is growing interest in TCVs with their potential added benefits for use in younger children and more sustained protection. Therefore WHO convened an Expert Consultation in July 2014 to review evidence in support of the use of TCVs (http://www.who.int/immunization/research/meetings_workshops/typhoidvaccines_july14/en/). Specifically the 2014 consultation aimed to assess the sufficiency of data to initiate the process for the WHO Strategic Advisory Group of Experts on Immunization (SAGE) to formulate recommendations for a global policy on TCV use and to revise the 2008 WHO position paper. The experts convened reviewed a range of evidence and concluded that while the available clinical data on TCVs were promising (at least for some of the TCV candidates), the evidence was not adequate to initiate the SAGE policy process.

In particular, the 2014 Expert Consultation noted that:

- Additional clinical data are needed for the SAGE policy review (including on immunogenicity in all age groups, memory, duration of protection and the need for boosters. Clinical efficacy data are particularly important in children under 2 years of age.
- Additional robust immunogenicity data may support provisional recommendations in children over 2 years of age (with the possibility of bridging to 9–12 months). There was concern about immunobridging to infants under 9 months without efficacy data.
- Standardization of assays for evaluation of immunogenicity is critical for comparing candidate TCV vaccines. A preliminary study to establish an international reference standard for anti-Vi PS antibody was reviewed by the WHO Expert Committee on Biological Standardization in 2014 but further work is needed to establish an international standard.
- Epidemiological data are needed to inform country decisions on a risk-based vaccination strategy and on a vaccination schedule in children less than 2 years of age.

Regarding further research, it was noted that data to support vaccine introduction should include individual and herd protection, feasibility of multiple injections, cost-effectiveness of delivery strategies, the impact of vaccination in the context of other control strategies, and the impact of long-term carriers on disease burden.

Following the consultation, other data needs to support the incorporation of TCV into EPI schedules were identified, including the need for data on vaccine performance in children under 2 years of age with different regimens, more details on age-specific disease incidence, and feasibility of TCV use with other routinely administered vaccines. In addition, programmatic considerations such as delivery strategies, necessity and timing of booster doses, product formulation and packaging, cold chain volume, vaccine vial monitors (VVMs) and use of auto-disable syringes were all highlighted. Many of these data may only be generated after a WHO policy recommendation.

Since the 2014 consultation, Phase III clinical trial data have become available for one TCV which is licensed nationally and for which a submission for WHO pre-qualification is expected in the near to mid-term. Another vaccine is undergoing national licensure while several additional candidates are in clinical and preclinical development.

**Purpose of the meeting**

Taking the above into account, WHO convened the current meeting on 21–22 September 2015 to review additional TCV clinical data and the remaining data gaps with implications for timing of the SAGE process. The specific meeting objectives were to:

1. Review the current status of clinical evidence on TCVs to inform the SAGE policy review.
2. Advise WHO on the overall roadmap for TCV policy development and TCV introduction for public health use.
3. Advise WHO on further short- to medium-term studies that will potentially generate additional data to contribute to TCV policy and introduction.

The meeting was chaired by Prof Zulfiqar Bhutta and started with a half-day open session with representatives of Bharat Biotech while the rest of the meeting was in closed session with only the invited WHO experts present. The agenda and list of participants at the meeting are provided in Annex 1 and 2 respectively.

The growing interest in TCVs and a need to push the typhoid agenda forward was noted. Along with the progress in the TCV pipeline, there have been advances as well as work in other areas such as epidemiology and surveillance, diagnostics, risk assessment and the economic burden of typhoid. Participants were reminded of the following:

- That the aim of the meeting was to review the clinical data on TCVs in the context of policy development.
- The meeting was not a SAGE meeting but an ad hoc meeting to facilitate preparation and scheduling of a future SAGE review through the existing formal process.
- The Gavi Board was anticipated (at the time of the meeting) to review the vaccine investment strategy for typhoid in 2018.

**Bharat Biotech update on Typbar-TCV (Vi-TT) clinical data**

Bharat Biotech was requested to share updated information on available clinical data for its licensed Vi-tetanus toxoid conjugate vaccine (Typbar-TCV) as well as plans for generating additional data in post-licensure studies.
Data presented included published findings of safety and immunogenicity of this Vi-TT vaccine in healthy infants, children, and adults in a Phase III trial\(^2\) as well as unpublished data. **Unpublished data presented to the meeting and/or made available to the experts and WHO under a confidentiality agreement with WHO are not elaborated in this report.**

The multi-centre Phase III safety and immunogenicity trial included two arms: an open label trial of 327 subjects aged 6–23 months who received a single dose of Typbar-TCV, and an RCT of 654 subjects aged 2-45 years with Bharat’s Vi polysaccharide vaccine (Typbar) as the reference vaccine. The primary immunogenicity end-points were geometric mean titres (GMTs) and 4-fold rise of anti-Vi IgG response 6 weeks post vaccination. All subjects were given a similar dose of TCV, with a subset in each age group receiving a second dose after two years, and with follow-up for three years. ELISA testing was performed with a commercial test kit (Vacczyme) and with the NIH ELISA method in a subset of subjects.

**Safety:**
- In the evaluation of safety, both the open label and controlled trials indicated that Typbar-TCV was safe in all age groups and was comparable to the existing Vi polysaccharide vaccine in terms of adverse events.
- Indian regulations require a post marketing study of adverse events following immunization. A Post Marketing Study is underway to capture the adverse events following immunization in ~ 5,000 subjects by active telephone follow up daily for 7 days and monthly for the first 3 months. So far, for the 800,000 children vaccinated in India since August 2013, the main post-marketing activity has been to ask paediatricians about adverse events following Typbar-TCV, cases of typhoid and the general development of vaccinated children. No SAEs have been reported.

**Immunogenicity:**
- The TCV recipients in the open label trial had anti-Vi IgG GMTs of 1937 EU/ml (95% CI, 1785 – 2103) after 42 days and 98% seroconversion. In the controlled trial the TCV group had GMTs of 1293 EU/ml (95% CI 1153 – 1449) and seroconversion of 97% after the same period (compared to GMTs of 411 [95% CI 359 – 471] and seroconversion of 93% for the ViPS group).
- The TCV induced consistently higher antibody titres than ViPS. Across age groups, baseline seroprevalence increased with age. The TCV was equally immunogenic across the paediatric age groups, and no correlation was found between immunogenicity and baseline titres in regression analysis. The manufacturer concluded from the comparative study that Typbar-TCV was safe and more immunogenic than Typbar, and that it led to significantly higher titres and seroconversion greater than three times that following Typbar. Typbar-TCV was reported to be immunogenic in children under 2 years of age, and resulted in 200-fold higher GMTs post-vaccination.

A review of long-term immunogenicity indicated a drop in GMT titres by day 540 however, there was no significant change between days 540 and 720. The study showed stable persistence of antibodies in all age groups however, greater antibody persistence was seen in the older (> 15 years) age group. Two years after a single dose of TCV, the rise in GMTs over the baseline in all ages was ≥ 5-fold.

**Booster responses:**
- A booster dose given at day 720 to a subset of each trial arm resulted in an increase in GMTs for Typbar-TCV recipients (36-fold in the open label trial and 20-fold in the controlled trial) while Typbar vaccinees achieved GMTs similar to that at day 42 (post-dose 1).

**Quality of vaccine response**
- Data on avidity at 42, 720 and 762 days after vaccination showed that Typbar-TCV induced higher antibody avidity compared to the ViPS in all ages and that persist after a second dose. TCV immune responses were more effective than ViPS in all anti-Vi IgG sub-classes (in particular IgG3 and IgG4) at days 42 and 762. The higher GMTs at 42, 540 and 720 days post-vaccination were confirmed by ELISA using both the NIH method and Vacczyme.

**Measles interference study**
- This study is underway to evaluate non-interference in immune response of Typbar-TCV when administered concomitantly with measles vaccine to children at 9 months of age. Preliminary data in both co-administration and single administration groups were presented.
- Bharat reported that evidence so far indicates that TCV is compatible with measles vaccine. Co-administration with measles-containing vaccine (given in the 9- to 18-month window) was seen as an opportunity for a one-dose or two-dose schedule with a potential booster at school age. The exact schedule for a second dose of Typbar-TCV is also being assessed as well as any possibility of interference of MMR (given at 15 months of age) on the TCV response.

Other relevant points/data reported:
- Noting that the Vi-rEPA field efficacy studies showed protective efficacy for 4 years in the 2–5-year age group, with seroprotection lasting for 8–10 years, and in the absence of an internationally accepted anti-Vi IgG standard serum, the estimated protective titre suggested by NIH was taken as the best correlate available. Thus in the Typbar-TCV studies, immunogenicity was compared with Vi-rEPA using the NIH ELISA method.
- The target age group for Typbar-TCV immunization in India is primarily a single dose at 6 months and above. [Note: The Indian Academy of Pediatrics recommends single dose vaccination of TCV at 9-12 months of age with an interval of at least 4 weeks with measles/MMR vaccine and a booster dose of either ViPS or TCV at 2 years of age.]
- Results from in-house Typbar-TCV studies on vaccine stability when maintained in a controlled temperature chain (CTC) at 40°C and 55°C were reported to be highly encouraging. Further temperature studies were due to begin in October 2015.
Points raised in discussion by the expert group included the following:

- There was speculation about the possibility of ongoing stimulation of antibody response (boosting of memory B cells) through continuous natural exposure, considering that almost everyone in the trial populations was exposed to typhoid.
- An observation was made that to show a memory effect there needs to be a comparison of a known naïve group with a non-naïve group. Therefore, ideally a study with naïve subjects, perhaps at an earlier age, would be needed to investigate the “booster” response observed. Currently it is difficult to interpret the booster data fully without a naïve group, however the group also acknowledged the challenge to find a truly naïve group in an endemic setting. Further it was noted that other immune data suggested that a memory response had occurred.
- Data on avidity 1 year post-booster dose would be of interest, however Bharat reported those data are not yet available.

**Bridging of Bharat Vi-TT and NIH Vi-rEPA data**

A comparison of the immunogenicity and efficacy data for Vi-rEPA and currently available data for the Bharat Vi-TT was presented for discussion and included the following points:

- The only currently available evidence on efficacy for a TCV is provided for the NIH Vi-rEPA (95% efficacy, [95% CI 77.1-96.6] for 2 doses in 2-5 year olds) which makes the data critical for comparison with Typbar –TCV.
- NIH estimated a protective level of ≤ 7 ELISA units (EU) of anti-VI IgG from the initial Vi-rEPA trials, subsequently lowered to 3.52 EU based on the results of longer-term follow up of trial subjects which showed no significant difference in efficacy. Further work permitted the conversion of the protective level of 3.52 EU to 4.34 µg/ml. Finally, additional analysis published in 20147 established a protective threshold >10 µg/ml at 6 months post vaccination for long term protection (at least a 4 year period).
- Importantly the Vi-rEPA trial in infants (with co-administration of routine EPI vaccines) showed 90% of vaccinees had antibody levels above the protective level (at that time) of 3.52 EU 7 months after vaccination, while 50% were above the same protective level 13 months post-vaccination.
- Nonetheless, using a “strawman analysis” approach, if several assumptions and pieces of data are accepted from the original Vi-rEPA studies (i.e., the original correlate of protection of 3.52 EU, the new IgG anti-Vi reference standard serum, recalibration of the original standard to µg/ml, and reanalysis of the correlate of protection with a µg/ml

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6 Lanh MN et al. Persistent Efficacy of Vi Conjugate Vaccine against Typhoid Fever in Young Children. NEJM 2003; 349:1301.

7 Thiem VD et al. The Vi conjugate typhoid vaccine is safe, elicits protective levels of IgG anti-Vi, and is compatible with routine infant vaccines. Clin. Vaccine Immunol 2011; 18:730-5.


readout where >10 µg/ml six months after vaccination = long term protection), then one could use the correlate to predict efficacy of similar conjugate vaccines evaluated by immunogenicity assuming (i) a similar assay is used and bridged for the analysis, (ii) similar populations (age) are studied, and (iii) efficacy is linked to the assay readout (circulating IgG).

- Caveats raised about this approach included that the original NIH correlate of protection was based on 76 serum samples, and the new reference standard was made using only 8 vaccinees and the sera were analysed in one laboratory only. Further the recalibration effort was undertaken by a single laboratory.
- It was only possible to compare vaccinees in a 2-4 year range (Typbar-TCV) to those in a 2-5 year range (Vi-rEPA).
- Further it was not possible to compare data directly (between Typbar-TCV and Vi-rEPA) for children less than two years old. However the IgG levels for Typbar-TCV vaccinees in this age range were comparable at all time points with older Typbar-TCV vaccinees.
- The overall conclusion from the comparative analysis presented to the group was that “all things being equal” the Typbar-TCV immunogenicity was similar to Vi-rEPA immunogenicity, and further that as the latter has been shown to be efficacious in 2-5 year olds (with long-term persistence) the Typbar vaccine should be similarly efficacious. Nonetheless, the caution was that this interpretation should take into account unanswered questions such as whether the assays are comparable, whether the serum antibody readout is the correct one and whether efficacy in 2-5 year olds will automatically translate into efficacy for infants.
- Additional questions were highlighted for further consideration: whether the IgG anti-Vi antibodies are the true effector molecules mediating protection against S. Typhi or a proxy for some other immune response that mediates protection, whether a test of functional antibody is required to augment the available data, and whether the IgG anti-Vi antibodies measured following Vi-rEPA are equivalent in function to those measured after Typbar-TCV.

There was a call for the WHO standards team to lead a process to develop a precise definition of bridging for analyses such as this.

**Standardization of assays**

The expert group highlighted the critical need for development of a standardized assay for assessment of anti-Vi IgG responses.

A brief update on progress in the work to establish international reference standards was tabled by the WHO standards team (absent from the meeting due to other conflicting meetings). It was noted that further work, led by NIBSC, is ongoing following their preliminary report on a collaborative study to evaluate a candidate international standard to the WHO Expert Committee on Biological Standardization in October 2014.

It was also noted that the ELISA test developed by NIH has been performed by many laboratories with quite a lot of variation. NIH has developed a set of standard operating procedures which were issued in 2015. However, it was unclear what the current availability and use of these SOPs is. The current work at NIBSC involves an in-house assay.
The expert group concluded that the standardization of assays is urgent, however it acknowledged that the work might need to involve a great deal of collaboration over a long period as in the case of pneumococcal conjugate vaccine (see next section). It was suggested that WHO could try to bring the relevant people together to agree on an assay and reference reagents and to develop standard operating procedures for their use. A panel of sera would need to be provided and the reference reagents specified with each participating laboratory to run the assay in order to assess its performance.

The group further encouraged that WHO ensure that there is a process in place on how to use available anti-Vi serum reference to develop a further pool for future studies. For reference, an example from PCVs was cited to note that in 2005 there remained about 2 to 5 years’ supply of the standard serum pool for PCV ELISAs that had been in use since 1990. Since that reference standard had been used to evaluate PCV7, the link to clinical efficacy would be severed if stocks of that reference standard were completely depleted. Further, demonstration of immune responses comparable to those elicited by PCV7 has been used to evaluate new PCV products for so a replacement reference standard was required. Steps were undertaken to develop a new reference standard for longer term use (at least 25 years).

Another issue raised was that while an assay can be developed for vaccine efficacy, it is not clear how this might translate to protection. It was suggested that the field needs better understanding of the role of functional antibodies. For example, the point was made that FDA and EMA have put more emphasis on functional antibodies to approve vaccines based on immunogenicity data only. However, the validity of functional assays was raised and varying opinions were expressed about the relative value of avidity data compared to data on antibody response.

Policy development for pneumococcal conjugate vaccines: lessons for TCV

The expert group considered experience from the collaborative effort to establish the efficacy of the pneumococcal conjugate vaccine (PCV) as a background to the current discussion on TCVs. PCV was noted to be more complex than TCV as it contains multiple serotypes

Starting with PCV7, the approach used for PCV development and licensure required a significant global collaboration – including vaccine developers, regulators and academics over an approximate eight-year period – to ensure standardization and validation for the evaluation of immunogenicity to all PCV vaccines, specifically to ensure consensus on the use of a reference assay and also to establish a method for assessing assays using agreed performance criteria. To support this, two WHO pneumococcal serology reference labs were established to provide training and other technical support to PCV developers on the use of the standard assays. As a result, a training manual was produced on the qualification of materials and analysis of assay performance. The resultant recommendations for evaluation of PCV were subsequently adopted by the FDA and EMA and were critical to PCV head-to-head studies and licensure. Furthermore the reference established has continued to be used to date. The point was therefore emphasized that it is critical to accelerate the efforts to
standardize assays to facilitate evaluation and comparison of TCV candidates. The expert group recommended that lessons should be taken from the PCV model and applied to TCV.

Several similarities were noted between PCV and the current considerations for TCV in that the licensed products available (PCV7 and ViPS) were not ideally suited to high-burden countries, new products needed to be bridged to the existing vaccine, new vaccine products are based on different carrier proteins that may affect the immune response, and policy recommendations required (PCV), or may require (TCV), extrapolation from existing vaccines at some stage. However, unlike PCV (for which data were extrapolated from the licensed PCV7 and unlicensed PCV9 with efficacy data), TCV is preceded by a polysaccharide vaccine with a different immunological profile, efficacy data are not available for all the target groups (i.e. young children), and TCV with efficacy data (Vi-rEPA) is not available for head-to-head comparison of immunogenicity.

For PCV, it was noted that even after the initial reference standard was established, work continued on standardizing the functional antibody assays, as did exploration of nasopharyngeal carriage as an additional marker. Further, work is still ongoing on issues such as standardizing definitions for radiological pneumonia. As new and reduced dose schedules are being considered, the “established” criteria are under constant discussion to determine their validity. While the challenges for TCV do not seem to be as great as those for PCV, there may still be a need for further data and continued monitoring of TCVs in the future.

**Status of additional relevant TCV data or reviews to be considered for the SAGE process**

**Human challenge studies**
The history and future prospects for assessing typhoid immune responses in human challenge studies was shared with the expert group. Early typhoid vaccine trials with controlled human challenge were conducted in the 1950s to 1970s. An overview of previous challenge studies with the S. Typhi Quailes strain and immune responses was presented.

More recently the Oxford Vaccine Group at the University of Oxford has established a controlled human infection model to study the early inflammatory and immune responses to S. Typhi infection and to identify novel diagnostic markers. The Oxford team is undertaking challenge studies using the Bharat Biotech Typbar-TCV. Adult volunteers will be screened and enrolled to be vaccinated with control MenACYW or Vi polysaccharide or Typbar-TCV (approximately 33 subjects in each group). They will be challenged one month later followed by antibiotic therapy. The study will examine relative efficacy, correlates of protection, persistence and shedding. The study is expected to complete enrolment in July 2016. The expert group was informed that the Oxford team also has a paratyphoid challenge model using an isolate from the Kathmandu strain and are awaiting availability of Phase I material and data for LPS conjugates before planning an efficacy study.
The presentation was well received and the expert group supported the value of the data from challenge studies which can be anticipated to contribute significantly to the evidence for recommendations on TCV use.

**Other Candidates in the TCV pipeline**

A brief presentation on the pipeline of TCV products was presented showing that there is a significant time gap between the currently licensed TCVs and other candidates. In the context of potential to target the global market, four candidates were noted to be at the late preclinical stage with their Phase I trials projected to start in early 2016. One candidate was noted to be in Phase II trials (but not currently anticipated to target a global market).

**Prequalification**

The expert group was informed by the WHO Secretariat that there are three submission dates for prequalification applications to WHO each year. WHO screening of the application normally takes about one month (may take up to four months if concerns arise). The next step would then be an evaluation of the product summary file and dossier. If both of these are satisfactory, a site audit will begin. The full prequalification process takes approximately nine months on average, however if WHO has questions or concerns the process will last as long as it takes for the manufacturer to reply satisfactorily. Bharat Biotech has indicated interest to apply for prequalification in 2016. One issue highlighted by WHO was that the prequalification process requires a comparison to be made between the candidate vaccine and a prequalified vaccine. For the Bharat Typbar-TCV, those data are currently not available. WHO anticipates that a prequalification application dossier will include data from the Phase III comparative study with the Bharat ViPS (Typbar), however the latter is not a prequalified vaccine. A previous study comparing Typbar to the GSK ViPS (Typherix) could have some value for the future prequalification review of the Typbar-TCV although Typherix is also not a prequalified vaccine.

**Other considerations for future use of TCVs - Experience from large-scale typhoid vaccine trials**

Additional critical questions for global TCV policy and public health recommendations were highlighted in this session.

The Vi effectiveness trials carried out by the Diseases of the Most Impoverished (DOMI) typhoid fever programme carried out in the early to mid-2000s to assess the protective impact of a licensed ViPS vaccine when administered under programmatic public health conditions were noted as some of the largest cluster randomized vaccine trials ever mounted in Asia. These large-scale effectiveness trials (covering more than 200,000 persons) were conducted in slum areas of Kolkata (India) and Karachi (Pakistan) and were standardized in the two sites with exception of the target populations (subjects enrolled

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were 2 years and above in Kolkata compared with 2-16 years in Karachi). The results showed overall total protection against typhoid of 27% in Karachi (no protection in children 2-4 years) while in Kolkata the overall protection was 60%, (82% protection in children aged 2–4 years). Differences in age of the target populations and coverage levels achieved (61% in Kolkata versus 52% in Karachi) contributed to the differences in effectiveness observed. Karachi also had large migration patterns of around 20%.

IVI’s Vi-based Vaccines for Asia (VIVA) initiative carried out a school-based vaccination demonstration programme in collaboration with the government of Pakistan in two towns near Karachi (Gulshan and Jamshed). Some 1,600 schools were targeted, with a target population of 200,000 children aged 5 to 15 years. Vaccination coverage levels of 39% in Gulshan and 60% in Jamshed were achieved, and there was a 10% reduction in typhoid burden in the two towns during this pilot programme.

Differences in study results between sites in both DOMI and VIVA studies and observations from other studies have shown that a range of non-vaccine factors must be taken into account for studies evaluating typhoid vaccination in real world settings. These include disease burden distribution by age, characteristics of the health system, care-seeking/household behaviours, patterns of antimicrobial use and resistance and environmental factors. TCV demonstration project(s) will need to include a range of these factors in their design. Methodological considerations should include the role of clinical endpoints, diagnostics and current treatment strategies.

**Future research agenda to address TCV policy gaps**

The expert group considered a range of possibilities to address the question of what near-to-medium-term research agenda should be considered to support an updated global policy and decision on TCV introduction. It was noted that different audiences (or purposes) would have different data needs. However, there was agreement that not all these data needs would be critical for the SAGE policy process. Data will be needed for SAGE recommendation/global policy formulation, national licensing authorities, WHO prequalification, Gavi commitment and vaccine subsidy, and country awareness and demand generation. The expert group also took note of studies that are ongoing to address some of these data needs.

The proposed data needs outlined for a near-to-medium term research agenda are summarized in Table 1.

Specific points highlighted in the discussion by the group included:

- In regards to policy development, as yet there are no clear data on the priority age targets for TCV use. While a high typhoid burden in school-aged children is clearly established and the current WHO guidance focuses on this age group, further evidence on age distribution of typhoid, in particular in young children, will be critical to guide a TCV immunization strategy.
- Countries will need impact data and epidemiological data on risk factors (e.g. age and geographical risks) in order to inform their vaccine introduction decisions.
- The Oxford University controlled human infection model is a means of generating confidence in a vaccine in order to further research.
As clinical trials are developed for the next generation of TCVs there should be guidance in areas such as trial endpoints, study design and specific age targets for vaccination. Additional data should be generated on immune memory (including duration of protection and the need for boosters), to understand the role of circulating versus functional antibodies, and clinical efficacy especially in children under 2 years of age. It was suggested that WHO should take a lead role in building consensus for the requirements for licensure.

It was noted that the Oxford Vaccine Group and a group of partners have initiated a study incorporating genomics, modelling and immunity, plus surveillance activities. The study, which has sites in Bangladesh, Malawi and Nepal, includes serological testing for 100,000 population and demographic surveillance of 12,000 population.

There are currently little data on cost-effectiveness of typhoid vaccines, however a number of studies are under way. Yale University is carrying out a TCV cost-effectiveness project which aims to (1) identify predictors and patterns of typhoid incidence, (2) extend analysis of the potential impact of typhoid vaccination strategies to all GAVI-eligible countries and incorporate cost-effectiveness analyses, (3) examine the sensitivity of incremental cost-effectiveness ratios to population factors, delivery strategy and vaccine characteristics, and (4) conduct budget impact analyses and explore the potential for public-private-donor funding schemes for high-burden countries. The project has already made significant progress on objective 1. The focus in 2016 will be assessments of health impact and cost-effectiveness, while budget impact analyses will begin in 2017.

The meeting was informed that the Bill & Melinda Gates Foundation was developing a typhoid strategy which was assessing, among other issues, potential possibilities to include typhoid control through vaccination within the context of other interventions such as those relating to water and sanitation. Efforts are also under way to understand fully the relative importance of transmission pathways, the role of carriers and natural immunity as well as efforts to define effective interventions that combine vaccination with other activities and to examine the impact of targeted interventions. Work on improving local epidemiology is also under way, including standardized models for local rapid surveillance and diagnostics to enable rapid surveillance to take place. These pieces of work will eventually feed into an optimal intervention package for which funding and political will have to be generated.

Conclusions

The expert group concluded on a number of points:

- Immunobridging of the licensed Typbar-TCV (Bharat) data to the NIH Vi-rEPA vaccine (with prior efficacy data) gives a reasonable level of confidence about the protective effect of the former. However the group expressed the need for further data, particularly clinical efficacy data in children under 2 years of age since manufacturers are considering their products for inclusion in routine EPI immunization. Data on the duration of protection and the need for boosters are also required for such analysis.
- The burden of disease for typhoid is quite well established and endemic countries do not need to be convinced of the burden. The general consensus was that there is almost no burden in the 0-1 year age group, however there is a need for more in-
depth analysis of burden in children < 2 years and a SAGE Working Group should be asked to advise on optimal age scheduling.

- The need for robust post-marketing safety data for Typbar-TCV was emphasized in view of the limited safety data. The expert group took note of the plans for post-marketing safety data to be generated as presented by the manufacturer and reiterated that safety data should be sought consistently for TCVs that are licensed and on the market.

- There will be a need to balance the longer duration of immunity provided by TCVs versus existing vaccines against the fact the latter are less costly. Research on cost-effectiveness is therefore required to guide any recommendations for wide adoption of TCVs.

- Clearly-defined demonstration projects should be carried out in a variety of endemic settings to assess the demand for, and acceptability of, TCVs. TCV demonstration project(s) will need to include a range of factors in their design, including disease burden distribution by age, characteristics of the health system, care-seeking/household behaviours, patterns of antimicrobial use and resistance, and environmental factors. The role of clinical endpoints, diagnostics and current treatment strategies will also need to be considered.

- There was also a call for WHO guidance to accelerate the work initiated and achieve consensus on development of standardized assays and reference reagents in order to provide timely guidance to manufacturers of the next generation of TCVs, and to facilitate immunobridging. Manufacturers should be required to validate their products against the approved standards. The antibody threshold for establishing non-inferiority must be clearly defined. A global reference laboratory (or laboratories) may also need to be designated.

- Guidance should also be provided to developers of the next generation of TCVs to encourage the generation of the most useful data to further inform future policy recommendations, including data to allow comparison among TCV products.

- Finally, the expert group recommended to WHO that a proposal should be made to SAGE to schedule a review of draft recommendations for TCV use at its meeting in October 2017. In the meantime, a SAGE Working Group on TCV would be established to review the evidence to be submitted to SAGE to support those recommendations.
Table 1: Proposed data gaps for near-to-medium term research agenda to guide TCV policy and use

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<th>Critical 2-5 year research agenda</th>
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<td>Typhoid fever control strategies</td>
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<td>1. Assay &amp; reagents development and standardization – immediate</td>
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<td>4. Diagnostics – different types (Point-of-care, surveillance, environmental)</td>
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### Annex 1: Agenda

**Meeting to Review Data Gaps for Typhoid Conjugate Vaccine Policy and Public Health Use**

Starling Hotel - Geneva, Switzerland
21-22 September 2015

### MONDAY 21 SEPTEMBER 2015

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<td>09:10-09:20</td>
<td>Recommendations from July 2014 expert consultation &amp; Expected outcomes of this meeting</td>
<td>A Bentsi-Enchill</td>
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<td>09:20-10:20</td>
<td>Update by Bharat on Tybar-TCV clinical data (Presentation + discussion)</td>
<td>BBIL Representative</td>
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<td>*Bharat participation till 13:30 on Day 1</td>
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<td>10:20-10:50</td>
<td><strong>Coffee/Tea break</strong></td>
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<td>10:50-11:20</td>
<td>Update by Bharat on Tybar-TCV and questions/discussion (contd.)</td>
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<td>11:20-11:30</td>
<td>Introduction of critical questions on TCV clinical data in context of global policy and public health recommendations for use. Are the available clinical data sufficient to guide global policy, in relation to: - protective efficacy, duration of protection, need for booster dose(s) and immune memory? - age-stratified considerations for policy recommendations (in particular in children aged &lt;2 years)? - defining the optimum vaccination schedule and delivery strategies?</td>
<td>Chair</td>
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<td>11:30-12:30</td>
<td>Expert reviewer comments on Bharat Vi-TT clinical data and immunobridging to NIH Vi-rEPA vaccine (Presentation + discussion)</td>
<td>D Goldblatt</td>
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<td>12:30-13:30</td>
<td><strong>LUNCH</strong></td>
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| 13:30-14:30 | Brief review of other relevant TCV data and/or review expected before SAGE process:  
- Human challenge studies  
- Update on progress of other TCV candidates  
- Status and future prospects for anti-Vi assay standardization; other written and physical standards  
- Expected PQ timelines | A Pollard  
A Bentsi-Enchill  
A Bentsi-Enchill on behalf of TSN  
O Lapujade |
14:30-15:15 Roundtable discussion of critical questions on TCV clinical data (as introduced above and emerging from the discussions).

What are the remaining critical gaps for TCV clinical data and how should they be addressed for (a) short-term SAGE policy and (b) longer term recommendations?

15:15-15:40 **Coffee/Tea Break**

| 15:40-16:20 | What can be learned from the policy process/introduction of PCV (or other conjugate vaccines)? *(Presentation + discussion)* | T Cherian |
| 16:20-17:00 | Review of other critical questions (not directly dealing with vaccine performance) for global TCV policy and public health recommendations for use: What is the current state of evidence (or expected in the short term)? *(Presentation + discussion)* | Z Bhutta |
| 17:00 | Wrap up for Day 1 | Chair |

**TUESDAY 22 SEPTEMBER 2015**

| 09:00-10:30 |Moderated discussion on research agenda to address TCV policy gaps (including efficacy trials, demonstration studies) - what is the minimum feasible (near-to-medium-term) research agenda to be considered to support (a) an updated global policy/revised WHO Position paper, and (b) national decision-making on TCV use? | D Steele |
| 10:30-11:00 | **Coffee/Tea break** |
| 11:00-11:30 | Discussion on research agenda *(contd.)* |
| 11:30-12:00 | Conclusions and recommendations for SAGE pathway and research agenda | Chair/WHO |
| 12:00-13:00 | **Meeting adjournment (Lunch)** |
Annex 2: List of participants

EXPERT GROUP

Professor Zulfiqar Ahmed Bhutta, Co-Director, Center for Global Child Health, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada

Professor David Goldblatt, Professor and Head, Immunobiology Unit, University College London Medical School, Institute of Child Health, London, UK

Professor Mike Myron Levine, Director, Center for Vaccine Development, University of Maryland School of Medicine, School of Medicine, Baltimore, MD, USA

Dr Mark Miller, Associate Director for Research, Director, Division of International Epidemiology and Population Studies, Fogarty International Center, National Institutes of Health, Bethesda, MD, USA

Professor Andrew J. Pollard, Professor of Paediatric Infection and Immunity, Director of the Oxford Vaccine Group, Department of Paediatrics, University of Oxford, Oxford, UK

Dr Shousun Chen Szu, Scientist, Chief, Center for Vaccine Evaluation, Zwings Inc., Bethesda, MD, USA

PARTICIPANTS

Ms Megan Carey, Associate Program Officer, Enteric and Diarrheal Diseases, Bill & Melinda Gates Foundation, Seattle, USA

Ms Zoey Diaz, Senior Program Officer, Vaccine Delivery, The Bill and Melinda Gates Foundation, Seattle, USA

Dr Hope Johnson, Head, Outcomes and Impacts, Monitoring and Evaluation Policy & Performance, Gavi, the Vaccine Alliance, Geneva, Switzerland

Dr Deepali Patel, Senior Programme Officer, Policy & Performance, Gavi, the Vaccine Alliance, Geneva, Switzerland

Dr Duncan Steele, Deputy Director and Strategic Lead for Enteric Vaccines, The Bill and Melinda Gates Foundation, Seattle, USA

OBSERVERS

Dr Radhika Bobba, Vice President, Medical Affairs, Bharat Biotech International Limited, Genome Valley, Hyderabad, India

Dr Krishna Mohan, Executive Director, Bharat Biotech International Limited, Genome Valley, Hyderabad, India

Dr Vineeth Varanasi, Assistant Medical Director, Medical Affairs, Bharat Biotech International Limited, Genome Valley, India

WHO SECRETARIAT

Dr Adwoa Desma Bentsi-Enchill, Medical Officer, Initiative for Vaccine Research, World Health Organization, Geneva, Switzerland

Mr David Bramley, WHO Consultant/Rapporteur, Prangins, Switzerland
Dr Thomas Cherian, Coordinator, Immunization, Vaccines and Biologicals, World Health Organization, Geneva, Switzerland

Dr Adam Cohen, Medical Officer, Expanded Programme on Immunization Plus, World Health Organization, Geneva, Switzerland

Dr Kai Gao, Scientist, Technologies Standards and Norms, World Health Organization, Geneva, Switzerland (Not available, inputs provided in advance)

Dr Joachim Hombach, Senior Adviser, Initiative for Vaccine Research, World Health Organization, Geneva, Switzerland

Dr Ivana Knezevic, Team Leader, Technologies Standards and Norms, World Health Organization, Geneva, Switzerland (Not available, inputs provided in advance)

Dr Olivier Lapujade, Scientist, Prequalification Team, Essential Medicines and Health Products, World Health Organization, Geneva, Switzerland

Dr Carsten Mantel, Medical Officer, Expanded Programme on Immunization Plus, World Health Organization, Geneva, Switzerland