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Conference report

The Typhoid Vaccine Acceleration Consortium (TyVAC): Vaccine effectiveness study designs: Accelerating the introduction of typhoid conjugate vaccines and reducing the global burden of enteric fever. Report from a meeting held on 26–27 October 2016, Oxford, UK

James E. Meiring [a,*], Malick Gibani [a], the TyVAC Consortium Meeting Group Buddha Basnyat [a,b], Adwoa D. Bentsi-Enchill [c], John Clemens [d], Thomas C. Darton [e,f], Kashmira Date [g], Gordon Dougan [h], Denise Garett [i], Bradford D. Gessner [j], Melita A. Gordon [k,l], Robert S. Heyderman [m], Joachim Hombach [c], Karen L. Kotloff [n], Myron M. Levine [n], Stephen P. Luby [o], Vadrevu Krishna Mohan [p], Anthony A. Marfin [q], Kim Mulholland [r], Kathleen Neuzil [n], Virginia E. Pitzer [s], Andrew J. Pollard [e], Firdausi Qadri [d], David Salisbury [t], Anita Zaidi [u]

[a] Oxford University Clinical Research Unit, Patan Academy of Health Sciences, Kathmandu, Nepal
[b] Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, United Kingdom
[c] Department of Immunization, Vaccines and Biologicals, World Health Organization, Geneva, Switzerland
[d] International Centre for Diarrhoeal Diseases Research, Bangladesh (icddr,b), Dhaka, Bangladesh
[e] Oxford Vaccine Group, Department of Paediatrics, University of Oxford, and the NIHR Oxford Biomedical Research Centre, Oxford, United Kingdom
[f] The Hospital for Tropical Diseases, Wellcome Trust Major Overseas Programme, Oxford University Clinical Research Unit, Ho Chi Minh City, Viet Nam
[g] Global Immunization Division, Center for Global Health, Centers for Disease Control and Prevention (CDC), Atlanta, USA
[h] The Wellcome Trust Sanger Institute, Hinxton, Cambridgeshire, United Kingdom
[i] Sabin Vaccine Institute, Washington DC, USA
[j] Agence de Médecine Préventive, Paris, France
[k] Malawi Liverpool Wellcome Trust Clinical Research Programme, University of Malawi College of Medicine, Blantyre, Malawi
[l] Institute of Infection and Global Health, University of Liverpool, Liverpool, United Kingdom
[m] Division of Infection and Immunity, University College London, London, United Kingdom
[n] Center for Vaccine Development, University of Maryland School of Medicine, Baltimore, USA
[o] Division of Infectious Diseases and Geographic Medicine, Stanford University, Stanford, CA 94305, United States
[p] Bharat Biotech International Limited, Hyderabad, India
[q] PATH, Seattle, USA
[r] Department of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK
[s] Department of Epidemiology of Microbial Diseases, Yale School of Public Health, Yale University, New Haven, CT, USA
[t] Centre on Global Health Security, Chatham House, London, UK
[u] Enteric and Diarrheal Diseases, Global Health, Bill and Melinda Gates Foundation, Seattle, USA

[a] Oxford Vaccine Group, Department of Paediatrics, University of Oxford, and the NIHR Oxford Biomedical Research Centre, Oxford, United Kingdom

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ABSTRACT

Typhoid fever is estimated to cause between 11.9–26.9 million infections globally each year with 129,000–216,510 deaths. Access to improved water sources have reduced disease incidence in parts of the world but the use of efficacious vaccines is seen as an important public health tool for countries with a high disease burden.

A new generation of Vi typhoid conjugate vaccines (TCVs), licensed for use in young children and expected to provide longer lasting protection than previous vaccines, are now available. The WHO Strategic Advisory Group of Experts on Immunization (SAGE) has convened a working group to review the evidence on TCVs and produce an updated WHO position paper for all typhoid vaccines in 2018 that will inform Gavi, the Vaccine Alliance's future vaccine investment strategies for TCVs.

The Typhoid Vaccine Acceleration Consortium (TyVAC) has been formed through a $36.9 million funding program from the Bill & Melinda Gates Foundation to accelerate the introduction of TCVs into Gavi-eligible countries.

* Corresponding author.
E-mail address: james.meiring@paediatrics.ox.ac.uk (J.E. Meiring).

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In October 2016, a meeting was held to initiate planning of TCV effectiveness studies that will provide the data required by policy makers and stakeholders to support decisions on TCV use in countries with a high typhoid burden.

Discussion topics included (1) the latest evidence and data gaps in typhoid epidemiology; (2) WHO and Gavi methods and data requirements; (3) data on TCV efficacy; (4) cost effectiveness analysis for TCVs from mathematical models; (5) TCV delivery and effectiveness study design. Specifically, participants were asked to comment on study design in 3 sites for which population-based typhoid surveillance is underway.

The conclusion of the meeting was that country-level decision making would best be informed by the respective selected sites in Africa and Asia vaccinating children aged from 9-months to 15-years-old, employing either an individual or cluster randomized design with design influenced by population characteristics, transmission dynamics, and statistical considerations.

1. Introduction

Typhoid fever is estimated to cause between 11.9 million-26.9 million cases and 129,000–216,510 deaths annually [1–3]. The burden of disease is largely within low- and middle-income countries primarily throughout Asia and Africa [4,5]. Whilst improvements in drinking water quality have been successful in reducing rates of typhoid fever in certain parts of the world [6–8], control has been hampered elsewhere and typhoid remains a significant public health problem [1,3].

In 2008 the World Health Organization (WHO) recommended the consideration of two licensed typhoid vaccines (Vi-polysaccharide and Ty21a), for programmatic use by countries with high rates of typhoid fever for controlling endemic disease, as well as for use in outbreak settings and for travelers to endemic areas [9]. However, with the expectation of second generation typhoid conjugate vaccines (TCV) becoming available in the near future Gavi, the Vaccine Alliance, deferred decisions on funding support until TCVs were licensed and prequalified by WHO [10,11].

Two Vi tetanus toxoid conjugate vaccines have now been licensed in India, with one manufacturer (Bharat Biotech) applying for WHO prequalification [12,13]. Due to these developments, the WHO Strategic Advisory Group of Experts on Immunization (SAGE) has convened a working group to 'review the scientific evidence and relevant programmatic considerations to formulate updated recommendations on the use of typhoid vaccines' [14]. Specific consideration will be given to estimates of disease burden, vaccine schedules, and economic analyses of vaccination programs. Publication of an updated WHO position paper on typhoid vaccines is scheduled for 2018 [14]. These recommendations will be highly relevant to Gavi, given their prior positive statements on support for TCV.

At this key stage in typhoid vaccine development, the Bill & Melinda Gates Foundation (BMGF) published a request for proposals to accelerate the introduction of TCVs into Gavi-eligible countries and to contribute to the data to support the use of TCVs as means of reducing the global typhoid burden. With $36.9M from BMGF, the Typhoid Vaccine Acceleration Consortium (TyVAC) was formed in 2016 comprising core partners at the University of Maryland's Center for Vaccine Development, the University of Oxford's Oxford Vaccine Group and PATH to achieve this goal [15].

A meeting of key stakeholders was held in Oxford, UK in October 2016 to discuss some of the critical issues surrounding typhoid fever and the impact on TCV effectiveness study design.

2. Typhoid vaccine acceleration consortium

In her introductory remarks, Dr. Anita Zaidi, Director of Enteric Diseases at BMGF, highlighted the motivations for this program on behalf of the foundation. Firstly, typhoid fever is primarily a disease of the poor which will require coordinated public health interventions to prevent and with the rising concern of antimicrobial drug resistance the global situation may yet get worse [16]. Secondly, with the recent development of TCVs the case for global typhoid control is compelling and there may be opportunity to demonstrate a dramatic impact through vaccination.

Following this the Director of TyVAC, Professor Kathleen Neuzil, outlined some of the key objectives for the consortium;

- To serve as a coordinating body for typhoid-related research and control activities
- To foster supportive global policies
- To ensure typhoid and TCVs are recognized as global, regional and national health priorities
- To provide data on impact, effectiveness, appropriate vaccine strategies and cost of TCV use
- To support countries in decision-making and preparation for sustained TCV introduction

Dr. Neuzil also reviewed lessons learned from other successful vaccine introduction efforts, and the need for clear goals and stakeholder involvement. Further, as TCVs are licensed, the goal of these studies will be to inform policy and financing decisions – thus the studies must be designed in light of that goal. Current funding only allows these studies to be done in a limited number of settings. Therefore, we must ensure that these settings and designs are sufficiently generalizable to inform non-trial countries in translating results to their local settings.

3. WHO perspectives

Understanding the data required by WHO to recommend TCVs is an important consideration for the consortium. Two central policy issues are currently under review by the WHO, (1) should TCV be recommended over Vi-polysaccharide (ViPS) and Ty21a vaccines for use in persons 2 years of age and older? (2) should TCV be recommended for routine use in children <2 years of age and what should be the lower age limit for use in this group? Recent ad-hoc WHO consultations to discuss the initiation of a SAGE policy pathway for TCVs identified multiple gaps in the data required to inform these policy decisions (Table 1). The design of TCV effectiveness studies should be made with these specific data gaps in mind, to provide the critical data that policy makers at global, regional and country levels will require to adopt and promote these new vaccines.

The SAGE Working Group on Typhoid Vaccines' review of the data to support TCV use will lead to consideration by SAGE for policy recommendations in October 2017.

4. Gavi

Understanding data used by Gavi before investing in TCV introduction is an important consideration for the consortium. In 2008,

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