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Conference report

WHO/IVI global stakeholder consultation on group A *Streptococcus* vaccine development: Report from a meeting held on 12–13 December 2016

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ABSTRACT

While progress towards a Group A *Streptococcus* (GAS) vaccine has been stalled by a combination of scientific, regulatory, and commercial barriers, the problem persists. The high and globally-distributed burden of disease attributable to GAS makes vaccination an imperative global public health goal. Advances across a range of scientific disciplines in understanding GAS diseases have made the goal a realistic one and focused attention on the need for coordinated global action. With a view to accelerating GAS vaccine development, the World Health Organization (WHO) and the International Vaccine Institute (IVI) convened a global stakeholder consultation on the 12th and 13th of December 2016, in Seoul, South Korea. Topics discussed included: (1) gaps in current knowledge of global GAS epidemiology, burden of disease, and molecular epidemiology; (2) contribution of pre-clinical models to candidate vaccine evaluation and new immunological assays to address GAS immunology knowledge gaps; (3) status and future of the GAS vaccine development pipeline; and (4) defining a pathway to licensure, policy recommendations and availability of a vaccine. The meeting determined to establish a GAS vaccine working group to coordinate preparation of a global vaccine values proposition, preferred product characteristics, and a technical research and development roadmap. A new global GAS vaccine consortium will drive strategic planning to anticipate requirements for licensure, prequalification, and policy recommendations.

1. Introduction and objectives

The path to a human vaccine against group A *Streptococcus* (GAS, *Streptococcus pyogenes*) has been impeded by scientific, regulatory and commercial obstacles [1,2]. This has occurred despite the longstanding and compelling case for vaccination to prevent morbidity and mortality across the full spectrum of GAS disease from superficial infections (e.g. pharyngitis, impetigo) to invasive GAS disease (iGAS, e.g. necrotizing fasciitis, toxic shock syndrome) and autoimmune complications (acute rheumatic fever, rheumatic heart disease, glomerulonephritis) [3]. Important steps have however been made towards understanding the global challenge of GAS disease, cutting through the confounding complexity of human immune protection against GAS, and plotting the trajectory and critical components of a product-agnostic GAS vaccine development pathway [4].

The WHO Product Development for Vaccines Advisory Committee (PDVAC) has previously prioritized GAS vaccine development, recognizing the significant global burden of GAS disease, the unmet need for vaccines, and the contribution that WHO engagement could have in facilitating product development [5]. With a view to accelerating GAS vaccine development, the World Health Organization (WHO) and the International Vaccine Institute (IVI) convened a global stakeholder consultation on the 12th and 13th of December 2016, with participants from academia, industry, public health agencies and funding bodies (Table 1). Topics discussed included: (1) gaps in current knowledge of global GAS epidemiology, burden of disease, and molecular epidemiology; (2) contribution of pre-clinical models to candidate vaccine evaluation and

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Table 1
List of participants.

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Mark Davies	The University of Melbourne	Melbourne, Australia
Guliz Erdem	Ohio State University	Columbus, OH
Jean-Louis Excler	International Vaccine Institute	Seoul, South Korea
John Fraser	The University of Auckland	Auckland, New Zealand
Nirmal Kumar Ganguly	Translational Health Science and Technology Institute	Faridabad, India
David Goldblatt	University College London	London, UK
Michael Good	Griffith University	Southport, Australia
Jorge Kalil	Instituto Butantan	Sao Paulo, Brazil
Ganesan Karthikeyan	All India Institute of Medical Sciences	New Delhi, India
David Kaslow	PATH	Seattle, WA
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Joshua Osowicki (rapporteur)	Murdoch Children's Research Institute	Melbourne, Australia
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Observers		
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new immunological assays to address GAS immunology knowledge gaps; (3) status and future of the GAS vaccine development pipeline; and (4) defining a pathway to licensure, policy recommendations and availability of a vaccine, including in low- and middle-income countries (LMICs) (supplementary material: meeting agenda).

2. Global burden and diversity of GAS disease

GAS is a ubiquitous human pathogen, and commensal organism. It is responsible for globally-distributed morbidity and mortality with a spectrum of mild to severe infections affecting virtually any (or every) organ at any age. Post-infective autoimmune sequelae, endemic in settings of socioeconomic disadvantage, directly contribute to the burden of chronic non-communicable conditions such as heart failure and kidney disease.

The full burden of global GAS disease remains poorly defined, as estimates derive from a patchwork of epidemiologic data available for some GAS syndromes in some populations. More comprehensive global data are required. A vaccine development pathway without strong baseline data and well-defined approaches to evaluate candidate vaccines is a potential limitation to support from funders, industry, regulators, and the public.

The complexity of the task to determine the global burden of GAS diseases is illustrated by a recent systematic review of population-based data from 2005 to 2014, updating the first comprehensive review published in 2005 [6,7]. There remain too few high-quality data for GAS-associated syndromes, especially in LMICs where burden is greatest. Conservative annual estimates are of 615 million incident cases of GAS pharyngitis, greater than 162 million prevalent cases of impetigo, 660,000 incident cases of invasive GAS infection, 470,000 incident cases of acute post-streptococcal glomerulonephritis (APSGN), and 470,000 incident cases of acute rheumatic fever (ARF) [7,8].

Newly emerging data indicate that these annual estimates significantly underestimate the true burden of GAS disease and likely reflect the 'tip of the iceberg'. Studies in low-resource settings have begun to more accurately quantify the global impact of all GAS syndromes [9,10]. These new data will be further supported by the ambitious plans for an African GAS infection registry (AFROStrep) [11]. Data from the 2015 Global Burden of Disease study showed that rheumatic heart disease (RHD) alone was responsible for 300,000 deaths annually and over 33 million prevalent cases, with an age-standardized prevalence rate two orders of magnitude greater in endemic countries (>400/100,000) than in non-endemic countries (<4/100,000). While the greatest absolute number of cases and deaths due to RHD occur in China, India, and Pakistan,

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