Correlates of enteric vaccine-induced protection

Les Pensières
Fondation Mérieux Conference Center
Veyrier-du-Lac - France

21-23 March 2016

Steering Committee:

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Background

The ability to assess the protective efficacy of a vaccine by measuring the proportion of vaccinees who generate a particular immune response, without having to measure clinical outcomes, has significant advantages. The availability and quality of such substitute endpoints are important for vaccine development, licensure and effectiveness monitoring. A better understanding of the interrelationships between vaccination, the immune response, protection, and clinical outcomes is thus of interest not only to regulatory and public health authorities but also to microbiologists, immunologists, epidemiologists and statisticians [WHO/IVB/13.01].

The correlates of vaccine-induced immunity are a subject of continued interest for both theoretical and practical reasons. The latter include the need to evaluate the consistency of vaccine production; the susceptibilities of individuals and populations after vaccination; the validation of vaccines for which placebo-controlled efficacy trials are no more ethical (e.g. rotavirus vaccines), as when a priorgeneration vaccine is already licensed; and the licensure of combination vaccines.

For several enteric vaccines, the existence of correlates of protection is unclear today, for example:

Rotavirus:
Rotavirus vaccination provides the most complex and controversial puzzle with respect to definition of correlates of immunity in current vaccinology. Neutralizing antibodies, non-neutralizing antibodies, secretory antibodies, and cellular immune responses have all been proposed as correlates, and indeed, it may be that all of these play a role, depending on the situation. [Plotkin S, clinical and vaccine immunology, July 2010, p. 1055–1065].

The WHO position paper [WSR No. 5, 2013, 88, 49–64] states that : "The immune correlates of protection against rotavirus infection are incompletely defined, but the immune responses to the VP4 and VP7 proteins are generally believed to be important. Serum anti-rotavirus IgA antibody responses have been used as a measure of immunogenicity of all the live attenuated rotavirus vaccines evaluated"
Unlike serum IgA, IgA at intestinal level are predictive of protection, but the levels needed are unknown.

Hepatitis A:
The WHO position paper [WER No. 28-29, 2012, 87, 261–276] states that: "Antibody levels ranging from 10–33 IU/ml, using different assays, have been proposed as the threshold for protection from HAV infection in humans. However clinical experience suggests that protection following vaccination may be present even in the absence of anti-HAV antibodies detectable using standard immunoassays. A positive (qualitative) test for total anti-HAV antibodies is considered to signify immunity to hepatitis A."
But the limit of quantification is not standardized.

Background

Cholera:
V. cholerae is a non-invasive pathogen that does not penetrate the bloodstream. It is widely admitted that intestinal sIgAs, rather than serum antibodies, play a role in direct protection. Yet, because measurement of sIgAs is impractical in the context of large clinical trials, serum vibriocidal antibodies to V. cholerae are traditionally used as a marker of appropriate immune stimulation by cholera vaccines… although it should be kept in mind that the latter neither represent a surrogate nor a correlate of protection.[Clemens JD, et col. Cholera vaccines. In: Plotkin S, Orenstein W, Offi t PA (eds). Vaccines. 6th ed.Saunders Elsevier. Inc. USA, 2012;chapter 11:pp.141-233.]

Norovirus:
Noroviruses are a leading cause of epidemic and sporadic outbreaks of gastroenteritis worldwide [Glass RI et col. Norovirus gastroenteritis. N Engl J Med 2009; 361:1776–85], and the most important cause of foodborne illness [Ahmed SM et al.. Lancet Infect Dis. 2014 Aug;14(8):725-30].In intermediate & low income countries, The burden of disease is in young children. Norovirus has become the leading cause of Acute Gastroenteritis in young children after introduction of rotavirus vaccination [Payne et al, 2013, N Engl J Med, 368, 1121-30]. No correlate of protection have yet been identified.

Enterotoxigenic E. coli (ETEC):
ETEC is among the top 4 pathogens causing diarrhoea-associated deaths among children < 5 years old. ETEC is also the most common cause of travelers' diarrhoea, the most frequent health problem among travelers visiting developing countries. Correlates of protection have not yet been defined.
For regulatory purposes, it may not be necessary to contemplate all the factors that can influence effectiveness, but to concentrate on two: the effect of the vaccine in terms of induced immune response, and the implications of these responses for clinical protection under some standard circumstances. Despite the methodological challenges, experience is accumulating with reference to many infections and vaccines. This is considered sufficient to allow licensure on the basis of phase II immunogenicity studies and prior knowledge on effectiveness of related vaccines. Much work remains to be done.

The purpose of this workshop is to allow thorough discussions between immunologists, statisticians, epidemiologists, infectious disease and regulatory experts on the barriers for vaccine development/ improvement, and to identify cross-functional actions required to resolve these barriers.

Scientific programme

Monday 21 March 2016

15:30 - 16:15	Registration	
16:15 - 16:30	Welcome address	Fondation Mérieux
16:30 - 17:05	Key-note address 1: Correlates of protection induced by vaccines with emphasis on enteric vaccines	Stanley Plotkin
17:05 - 17:15	Discussion	
17:15 - 17:50	Key-note address 2: The links between mucosal and systemic immunity: what is known and what is not known	Jan Holmgren
17:50 - 18:00	Discussion	
18:00 - 18:20	Results from the GEMS study	Karen Kotloff
18:20 - 18:35	Discussion	
18:35 - 18:55	Correlates of protection against enteric infections: What can be learned from polio vaccination?	Nicholas Grassly
18:55 - 19:10	Discussion	
19:30	Welcome dinner	

Tuesday 22 March 2016

Session 1

Workshop: novel approaches to correlate mucosal immune responses with protection in humans

Chair: Cecil Czerkinsky

08:30 - 08:45	Introduction to the workshop: intestinal B and T cells "homing"	Cecil Czerkinsky
08:45 - 09:00	Discussion	
09:00 - 09:20	Mucosally derived antibody-secreting B cells	Anu Kantele
09:20 - 09:35	Discussion	
09:35 - 09:55	Th1, Th17 and T follicular helper cell responses to oral vaccination	Anna Lundgren
09:55 - 10:10	Discussion	
10:10 - 10:30	Coffee break	
10:30 - 10:50	Heterotypic B cell immunity to rotavirus- new insights	Harry Greenberg
10:50 - 11:05	Discussion	

Scientific programme

Session 2

Case studies I: correlates of protection: cholera, ETEC, typhoid and shigella Chair: David Sack and Roger Glass		
11:05 - 11:25	Immune protection in cholera and immune response to oral cholera vaccination: knowledge from challenged volunteer model	Myron Levine
11:25 - 11:40	Discussion	
11:40 - 12:00	Correlates of protection induced by cholera vaccines and suggested studies for licensure of new vaccines	John Clemens
12:00 - 12:15	Discussion	
12:15 - 12:45	Protective immunity against ETEC and immune response to vaccination	Ann-Mari Svernnerholm
12:45 - 13:00	Discussion	
13:00 - 14:30	Lunch	
14:30 - 14:50	Mucosal immune response and correlates of protection against ETEC	Firdausi Qadri
14:50 - 15:05	Discussion	
15:05 - 15:25	Immune response and correlates of protection against typhoid	Marcelo Sztein
15:25 - 15:40	Discussion	
15:40 - 16:15	Coffee break	
16:15 - 16:35	Immune response and correlates of protection against shigella	Dani Cohen
16:35 - 16:50	Discussion	
16:50 - 17:05	Correlates of protection from campylobacter: the known unknowns	Beth Kirkpatrick
17:05 - 17:20	Discussion	

Session 3

Case studies II: correlates of protection: rotavirus, norovirus and hepatitis A Chair: Harry Greenberg and Roger Glass		
17:20 - 17:40	Current status of rotavirus vaccine and the value of a correlate of protection	Umesh Parashar
17:40 - 17:55	Discussion	

Scientific programme

17:55 - 18:15	Immune response and protection against rotavirus: lessons from a birth cohort studies	Gagandeep Kang
18:15 - 18:30	Discussion	
18:30 - 18:50	Rotavirus immune responses and correlates of protection	Manuel Franco
18:50 - 19:05	Discussion	
19:30	Dinner	

Wednesday 23 March 2016

Session 3 Continued

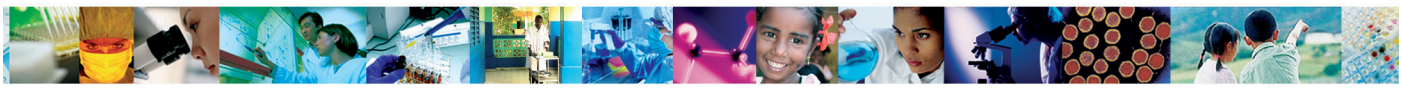
08:30 - 08:50	Mechanisms of protective immunity to hepatitis A	Stephen Feinstone
08:50 - 09:05	Discussion	
09:05 - 09:25	Immune response and correlates of protection from norovirus: lessons from challenge studies and clinical trials	Robert Atmar
09:25 - 09:40	Discussion	
09:40 - 10:00	Norovirus diversity and immune-driven evolution: mechanisms of protection and implications for vaccine design	Lisa Lindesmith
10:00 - 10:15	Discussion	
10:15 - 10:40	Coffee break	

Session 4

Regulatory aspects and further development of vaccines against enteric infections

Chair: Anita Zaidi

10:40 - 11:00	WHO's approach to immune correlates of protection in the draft clinical vaccine evaluation guidelines	Vasee Moorthy
11:00 - 11:15	Discussion	
11:15 - 11:35	Vaccine development pipeline for enteric vaccines	Duncan Steele
11:35 - 11:50	Discussion	



Scientific programme

12:00 - 13:30	Lunch	
13:30 - 15:00	General Discussion: 1- summary of key points from each session by chairpersons; 2-Identification of research gaps in correlates of protection; and 3-how to go forward	Facilitators: David Sack, Harry Greenberg and Anita Zaidi with participation of the speakers
15:00 - 15:15	Concluding remarks	David Sack
15:15	End of meeting