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Delayed-type Hypersensitivity: Probable Role in the Pathogenesis of Dengue Hemorrhagic Fever/Dengue Shock Syndrome

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The hypothesis presented proposes the involvement of a systemic form of a delayed-type hypersensitivity reaction in the pathogenesis of dengue hemorrhagic fever/dengue shock syndrome. It envisages the activation of sensitized T-lymphocytes during a secondary infection by viral antigen present on the surfaces of mononuclear phagocytic cells. These antigen-activated T cells then release a variety of biologically active chemical mediators (lymphokines), which then produce the symptoms of shock and hemorrhage seen in cases of dengue hemorrhagic fever/dengue shock syndrome.

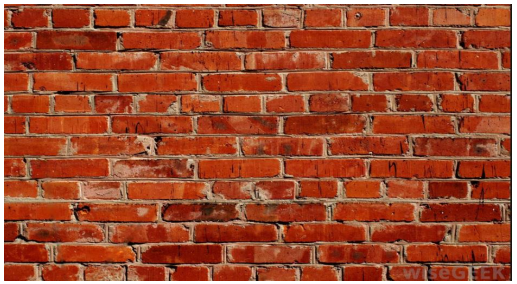
Dengue hemorrhagic fever (DHF) with accompanying dengue shock syndrome (DSS) remains a major public health problem especially in Southeast Asia and the South Pacific [1-3]. As evidence of the continued worldwide threat posed by this disease, an outbreak of DHF/DSS was thought to have occurred recently in the Caribbean [3]. However, despite the importance of this disease and intensive scientific interest in the past decade, knowledge regarding the underlying pathogenesis of DHF/DSS is far from complete. In light of this and recently available information, it is thought appropriate to propose a heretofore unconsidered mechanism for the pathogenesis of DHF/DSS. It is envisaged that cell-mediated immunity (CMI), as expressed by a systemic manifestation of a delayed-type hypersensitivity (DTH) reaction, is [1-3]). How does antibody adversely affect the outcome of dengue infection? Some investigators have suggested that DHF/DSS is a form of systemic Arthus reaction [4], while others attribute shock to immune complexes and IgE-mediated reactions [5].

More recent evidence, however, has suggested a role for "enhancing" antibodies. Several key experimental observations are relevant. The most significant was the demonstration that dengue virus showed enhanced replication in human and simian peripheral blood leukocytes [6, 7] in the presence of subneutralizing concentrations of specific antibody. Although the exact mechanism of antibody-mediated enhancement is still unclear, the cell thought most likely involved is the monocyte [1-3], and it is probable that Fc recep-

The journey from knowing to doing ….

Estimating the Full Public Health Value of Vaccines
Les Pensières, Fondation Mérieux, Veyrier-du-Lac,
France, 5-7 December 2016

Objectives of the Meeting: Climbing Over a Brick Wall



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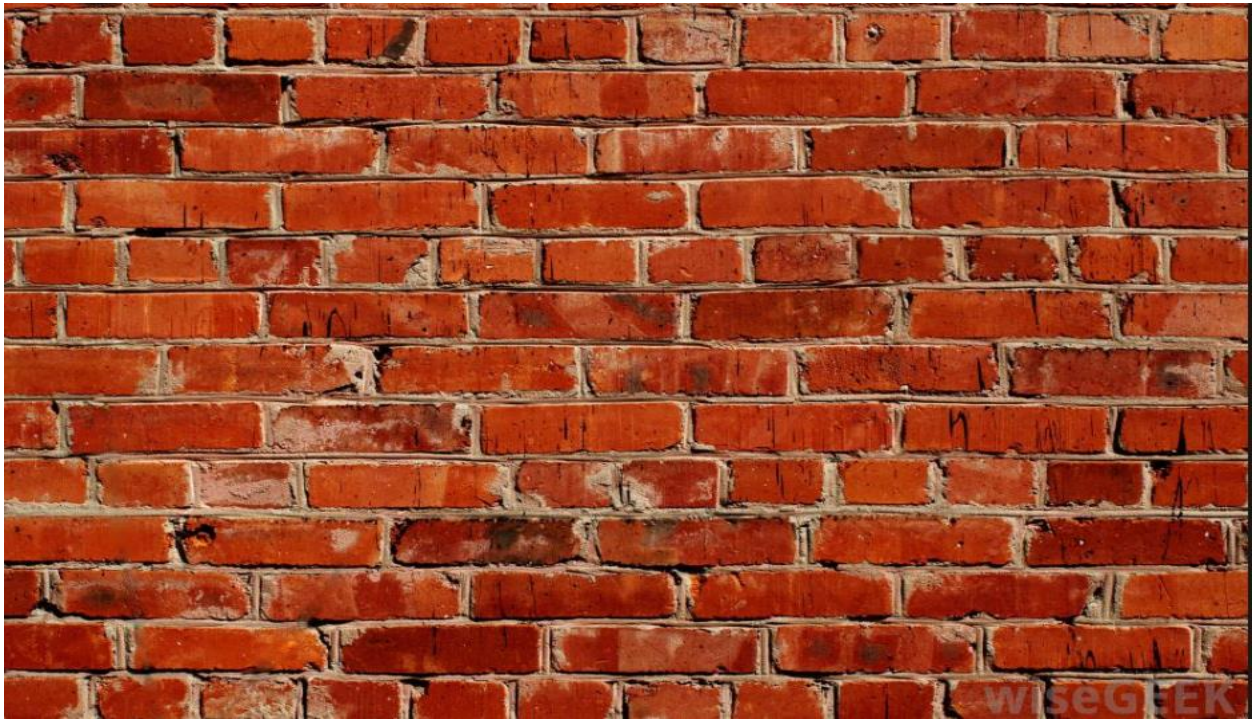
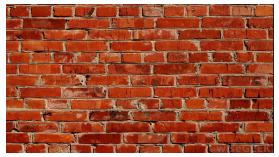
We are facing a brick wall in our current mindset on the full public health value of vaccination (FPHV).....



Over the brick wall :
Moving from vaccines to vaccination



The brick wall…..

- Candidate vaccines
- Clinical trials (PhIII/IV)
- Efficacy
- Risk-safety (individual)
- Suitability (target population, regional variations, etc.)
- Cost-benefit analysis

- Researchers/regulators

….the other side….

- Post-licensure studies (safety/efficacy/effectiveness)
- Reduce disease burden & transmission in populations
- Reduce fequency & size of outbreaks
- Programmatic & health systems impacts
- Social & economic benefits
- Equity, access, affordability, acceptance
- Recipients/community
- Policy- & decision-makers, programme managers

How? Meeting Objectives

To advance discussions on the definition, evidence and communication of the Full Public Health Value (FPHV) of vaccines:

1. To challenge the definition of what constitutes the FPHV of vaccines.
2. To review examples & case studies of public health value with existing vaccines used in outbreak settings and others used in endemic disease settings-are there lessons we can learn?
3. To propose designs, measures, and outcomes for assessing the FPHV of vaccines in phase III trials and phase IV assessments and integrated/hybrid phIII/IV strategies.
4. To apply these concepts to specific vaccines: malaria, dengue, Group B Streptococcus (GBS), Respiratory syncytial virus (RSV), Neisseria meningitidis B (NMB), and Oral Cholera Vaccine (OCV).
5. To strategize on how to communicate the FPHV of vaccines to regulatory and program policy makers.

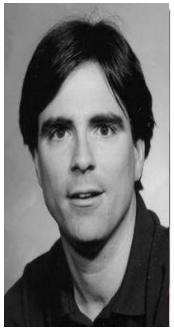
How? Meeting structure & format

- Two introductory Keynotes on key *principles* and *broader measures* of FPHV, and different ways of measuring the full public health benefits of vaccination (*social rate of returns*)
- Sessions : (1) socio-economic aspects; (2) impact on health systems of vaccination during epidemics; (3) beyond traditional efficacy measures-case studies of *endemic* and *epidemic* scenarios; (4) value of pre- and post-licensure evaluations of phase III trials; (5) policy- & decision-makers' views on FPHV
- Summary and the way forward….

Overall Messages

- We need a better, broader and more inclusive understanding (& definition) of the full public health value of vaccination (FPHV)
- A need to move beyond safety & efficacy to additional impact measures & strategies which assess reduction of disease burden and reduce inequities among populations
- Mind-set change and innovations needed to develop vaccine implementation strategies which incorporate the full public health value of preventive vaccines into the evidence-based decision-making process of vaccine licensure and public health use


This conference is about how we climb over that brick wall…



"The brick walls are there for a reason. The brick walls are not there to keep us out. The brick walls are there to give us a chance to show how badly we want something.

– Randy Pausch, The Last Lecture

Based on your experience and previous/current position/responsibilities please provide brief answers to the following questions:

1. Which three 'drivers/factors for success' do you consider most important in *realizing* the full public health value of vaccination (FPHV)?
2. Which three barriers or challenges do you consider crucial in *preventing* the full public health value of vaccination (FPHV)?
3. In your view, which three key elements of a policy/strategy is necessary to achieve the goal of FPHV, including better ways to communicate the FPHV of vaccines to regulators, programme managers, and policy- and decision-makers?