Available online at www.sciencedirect.com
ScienceDirect
Comparative Immunology, Microbiology & Infectious Diseases 31 (2008) 239–252
COMPARATIVE IMMUNOLOGY MICROBIOLOGY & INFECTIOUS DISEASES
www.elsevier.com/locate/cimid

Towards a dengue vaccine: Progress to date and remaining challenges

Bruno Guy, Jeffrey W. Almond*

Sanofi pasteur, 1541 Avenue Marcel Merieux, 69280 Marcy L'Etoile, France

Accepted 12 July 2007

Abstract

The increased incidence and extended geographical reach of *Dengue virus* over the past two decades have made the development of an effective vaccine an international urgency. Various strategies are being pursued, including live, vectored and killed/recombinant preparations. For all approaches, the challenge is to induce a broad durable immune response against all four serotypes of *Dengue virus* simultaneously whilst avoiding the possible exacerbation of risk of developing the severe forms of disease through incomplete or modified responses. This review presents the current state of knowledge and discusses the challenges of further clinical development.

Keywords: Dengue; Vaccine; Clinical trials; Antibodies; Cellular immunity; Vaccine safety

Résumé

La fréquence croissante ainsi que l'extension géographique des virus de la dengue lors de ces deux dernières décennies ont fait du développement d'un vaccin efficace une urgence internationale. Différentes stratégies sont actuellement poursuivies, incluant notamment des vaccins vivants atténués ou vectorisés, des vaccins ADN et des formulations sous unitaires inactivées. Pour toutes ces approches, le défi est d'induire simultanément une réponse immunitaire large et durable contre les quatre sérotypes du virus de la dengue, tout en excluant

*Corresponding author. Tel.: +33437379453.
E-mail address: jeffrey.almond@sanofipasteur.com (J.W. Almond).

0147-9571/$ - see front matter
doi:10.1016/j.cimid.2007.07.011

un risque potentiel d'immunopathologie qui serait lié à des réponses incomplètes ou inadaptées. Cette étude présente l'état actuel de connaissances et examine les défis à relever lors de futurs développements cliniques.

Mots clés: Dengue; Vaccins; Essais cliniques; Anticorps; Immunité cellulaire; Sécurité de vaccin

1. Introduction

Dengue virus exists as four closely related but antigenically distinct serotypes (DEN1–4) and is a member of the genus *Flavivirus*. The virus infects humans via blood feeding by infected *Aedes* mosquitos (*Aedes aegypti* and *Aedes albopictus*). Dengue infection thus occurs only in tropical and subtropical areas where insect vectors are present. Over the past two decades the number of dengue infections has continued to grow in the endemic areas of South-east Asia, Central and South America and the South Pacific regions. Up to 80 million dengue infections and 24,000 deaths are now estimated annually with children bearing the bulk of the disease burden. Over 100 countries are affected with >3 billion people at risk (Fig. 1).

Infection with any of the four serotypes of *Dengue virus* is often asymptomatic but can produce clinical manifestations ranging from a self-limiting dengue fever (DF) to

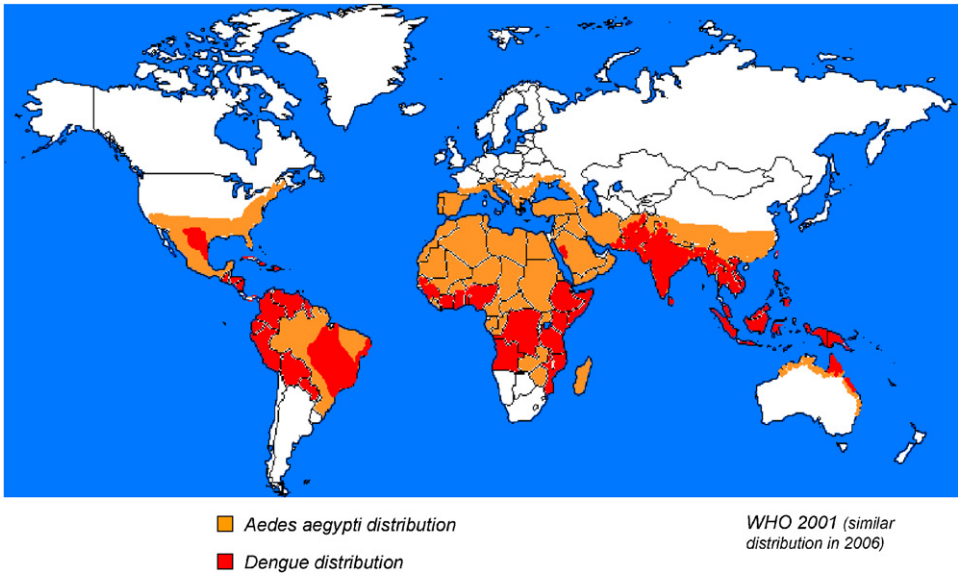

Fig. 1. Worldwide distribution of *Aedes aegypti* and dengue fever as reported by WHO in 2001. A similar distribution has been observed through 2006. Dengue fever has the potential to spread throughout the zones where *Aedes aegypti* is present.