exception of the N-terminus of NS4B that is formed by a signalase cleavage. The viral protease is also responsible for generating the C-terminus of the mature C protein (C_{virion}). Newly synthesized positive strand genomic RNA and the C protein form a nucleocapsid, which acquires an envelope containing the embedded prM and E proteins by budding into the ER lumen. The mature M protein is produced by cleavage of prM shortly prior to virus release by a cellular furin-like protease (9). The role of the glycoprotein NS1 in the biology of flaviviruses was unclear until recently. It appears that NS1 is essential for viral RNA synthesis (10,11), and its secreted form has been speculated to be involved in virus spread in vivo and/or disease pathogenesis and evasion of immune responses. Recent studies have demonstrated that the WN virus NS1 protein interferes with the complement system (12). In addition to the continuing molecular studies on the structure/function of viral proteins and mechanisms of viral RNA replication (1), another active area of flavivirus research is the elucidation of mechanisms of virus-host interactions, such as the role of genetic determinants in resistance of the host to flavivirus infection (13), stimulation or evasion of innate and adaptive immune responses (14), and pathogenesis of flavivirus diseases. For example, several NS proteins have been implicated in inhibiting the induction of interferons (INF) and INF signaling (14–18).

The E protein is the main functional protein of the envelope responsible for receptor binding and membrane fusion. This protein plays a dominant role in the induction of neutralizing antibodies that are the principal mediators of protective immunity (2). Virus-specific $CD8^+$ and $CD4^+$ T-cell responses, including cytotoxic T-lyphocyte (CTL) responses, against numerous T-cell epitopes scattered throughout both the structural and NS proteins are also considered essential for protective immunity (19–22).

FLAVIVIRUS DISEASES AND AVAILABLE VACCINES

The available information on the mechanisms of pathogenesis of flavivirus diseases has been reviewed (2,3,25,39). After an infectious mosquito or tick bite, virus replication occurs locally in the inoculation skin site and in draining lymph nodes. Virions then disseminate to secondary sites where further replication contributes to viremia and can cause damage to visceral organs (YF, DEN viruses), while encephalitogenic viruses (WN, JE, TBE) can invade the brain, which, in some cases, results in pathology of the CNS. Mechanisms of brain invasion are not well understood, and cell receptors that can mediate different types of flavivirus tropism have not been identified. Virus-specific neutralizing antibodies play a major role in protection from disease via preventing or slowing virus dissemination. In addition, cytolytic antibodies against viral proteins on the surface of infected cells, and antibody-dependent cell-mediated cytotoxicity (ADCC) are presumed to mediate clearance of infection. The relative contribution of T-cell immunity to controlling infection remains a matter of speculation (23). T cells could be essential for limiting virus growth by eliminating virus-infected cells or terminating virus replication by the production of antiviral cytokines.

Japanese Encephalitis Virus

JE virus causes a serious neurological disease of children in Asia, with case-fatality rate of 5% to 40%. It is estimated that more than three billion people live in regions where JE virus is endemic. In the last 25 years, the incidence has increased in many countries, and JE has extended its geographical range to areas in Asia and northern Australia that were previously free from this disease (24,25). More than 35,000 JE cases are officially reported each year by the World Health Organization (WHO), of which 5000 to 10,000 are fatal. This disease remains a serious threat to unvaccinated travelers to endemic countries. A high proportion of survivors suffer from neurological and psychological sequelae. The virus is transmitted from infected animals, mainly domestic pigs and birds, to humans by *Culex* mosquitoes. The use of a mouse brain-derived, formalin-inactivated vaccine (Biken, Japan) (Table 1) has significantly reduced disease rates in Japan, Republic of Korea, Taiwan, Sri Lanka, and parts of Thailand and Vietnam. The vaccine is 91% effective and is administered in two primary doses, one booster at one year and subsequent boosters every three years. It has been associated with 0.6% rate of allergic reactions in adults, sometimes severe, and is costly to manufacture. It may soon be replaced by a Vero cell-derived inactivated version under development. Other inactivated JE vaccines produced with virus grown in cell culture have been developed in China and Japan. A live attenuated SA14-14-2 vaccine produced in primary hamster kidney cells has been used in China, with 50 to 60 million doses administered annually (24,25). The highly attenuated SA14-14-2 vaccine has been approved by regulatory agencies in South Korea, Nepal, Sri Lanka, and India. Although multiple doses are generally employed in immunization schemes (e.g., in China), new evidence supports efficacy after a single dose (26,27).

Dengue Virus

DEN is a major public health problem of the tropics (2). The incidence and geographic distribution of the disease in tropical and subtropical regions of the world have risen dramatically in the last 40 years (4). Since 1970, the entire tropical world has become hyperendemic for DEN, meaning that all four DEN serotypes co-circulate, while prior to 1970, DEN was only hyperendemic in Asia. This has resulted in frequent and intense epidemics and increased severity of disease. Over two billion people in tropical Asia, Africa, Pacific Islands, Australia, and the Americas are at risk of DEN virus infection. Annually, up to 100 million cases of DEN fever and 450,000 cases of the more severe form of the disease, dengue hemorrhagic fever (DHF)/dengue shock syndrome (DSS) occur. The majority of severe cases occur in young children living in Asia, who suffer a case-fatality rate of approximately 5% (varying locally between 1% and 40% depending on the quality of supportive care). The virus is transmitted to humans by *Aedes aegypti* (and in some areas *Aedes albopictus*) mosquitoes. The amino acid homology between the four serotypes is 63% to 68% (and up to 77% in the E protein), compared with 44% to 51% between DEN and other flaviviruses. Infected individuals develop lifelong homotypic immunity, but cross-protection against viruses of the other serotypes is short-lived, lasting less than 12 weeks (28). As a result, people are often infected several times, each time with a different serotype of virus. Such secondary infections with a different DEN virus serotype more frequently result in DHF/DSS. These observations support the theory of immune enhancement of heterologous serotype virus infection due to antibody-dependent enhancement (ADE) of virus replication (29,30) and exacerbation of symptoms by preexisting cellular immunity (20,31). Subneutralizing concentrations of