Vaccine 28 (2010) 8073–8076

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Review

Is it time for a new yellow fever vaccine?

Edward B. Hayes*

Barcelona Centre for International Health Research, Rosselo 132, 08036 Barcelona, Spain

ARTICLE INFO

Article history:
Received 17 June 2010
Received in revised form 7 September 2010
Accepted 7 October 2010
Available online 3 November 2010

Keywords:
Yellow fever
Yellow fever vaccine
Global health
Traveler's health
Flavivirus vaccine

ABSTRACT

An inexpensive live attenuated vaccine (the 17D vaccine) against yellow fever has been effectively used to prevent yellow fever for more than 70 years. Interest in developing new inactivated vaccines has been spurred by recognition of rare but serious, sometimes fatal adverse events following live virus vaccination. A safer inactivated yellow fever vaccine could be useful for vaccinating people at higher risk of adverse events from the live vaccine, but could also have broader global health utility by lowering the risk-benefit threshold for assuring high levels of yellow fever vaccine coverage. If ongoing trials demonstrate favorable immunogenicity and safety compared to the current vaccine, the practical global health utility of an inactivated vaccine is likely to be determined mostly by cost.

Contents

Acknowledgment 8075
References 8075

Yellow fever is one of the great infectious scourges of humankind, ranking in historical impact with plague and smallpox. It is a fearsome disease and, unlike smallpox, has never been fully controlled. Yellow fever virus is endemically transmitted in forests and savannas of South America and Africa, periodically emerging from enzootic cycles to cause epidemics of hemorrhagic fever with case fatality rates ranging from 20% to 50% [1]. Thousands of cases of yellow fever are reported to WHO each year from tropical areas of Africa and South America, and rare sporadic cases occur among travelers to endemic areas.

The 17D live attenuated yellow fever virus vaccine was developed in the 1930s through work that was recognized with a Nobel Prize awarded to Max Theiler in 1951. The vaccine was used in field trials in 1937, and over the intervening 73 years has been given to more than 500 million people and considered one of the most effective and safe vaccines ever developed [2]. A single dose of 17D yellow fever vaccine confers long-term immunity, and costs less than one U.S. dollar for use in endemic countries [1]. All that seems hard to beat, so do we need another yellow fever vaccine?

In 2001 three articles first described a new type of serious adverse event after yellow fever vaccination [3–5]. The vaccine recipients developed an illness that closely resembled wild type yellow fever and had a similarly high fatality rate. This multi-organ system failure after vaccination was later named yellow fever vaccine-associated viscerotropic disease (YEL-AVD). Initial investigations focused on the possibility that the live vaccine virus had reverted to virulence but found no conclusive evidence this had occurred [6]. The 17D vaccine is genetically heterogeneous, but the consensus genetic sequences obtained from people with YEL-AVD have shown remarkable stability and concordance with reference vaccine strain sequences [1,6,7]. Cases of suspected YEL-AVD have been retrospectively discovered from as early as 1973 [8,9]. To date, the most plausible conclusions about YEL-AVD are that it has probably occurred rarely and without detection throughout the years of 17D vaccine use, and that it is most likely a consequence of injecting a live yellow fever vaccine into a person who, because of inherited or acquired susceptibility, fails to control the proliferation of the vaccine virus. YEL-AVD is relatively rare; the estimated frequency in the United States is 0.4 per 100,000 vaccine doses, and limited data suggest that it is has also been rare during vaccination campaigns in Africa [10,11]. However, during a recent vaccination campaign in Peru the incidence was 7.9 per 100,000 doses [7]. To put this in context with a severe adverse event from another commonly used live vaccine, the reported frequency of vaccine-associated paralytic poliomyelitis (VAPP) after first doses of live oral polio vaccination from 1990 to 1999 in the United States, including

* Tel.: +34 93 227 1852.
E-mail address: ned.hayes@cresib.cat

0264-410X/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.vaccine.2010.10.015

cases among contacts of vaccine recipients, was 0.11 per 100,000 doses [12].

Two other rare but severe adverse events after 17D vaccination are anaphylactic reactions and yellow-fever-vaccine-associated neurologic disease (YEL-AND). Anaphylaxis occurs at a frequency of about 1.8 per 100,000 doses and is thought to be mostly attributable to allergy to proteins from eggs or gelatin used in vaccine production [1,10,13]. YEL-AND can manifest as encephalitis, meningitis, neuropathy, Guillain-Barre syndrome, acute disseminated encephalomyelitis, or spinal myelitis. The case fatality rate of YEL-AND appears to be relatively low; of 28 cases in one review, 1 fatality was reported in a man with underlying human immunodeficiency virus infection [1]. Estimates of the frequency of YEL-AND have ranged from 0.4 to 9.9 per 100,000 doses depending on the study and case definition used [1,10,14]. Overall, the risk of any severe adverse event after yellow fever vaccination of travelers in the United States is about 4.7 per 100,000 but is higher among vaccine recipients 60 years of age or older (8.3 per 100,000 doses) [10]. In the face of a yellow fever outbreak this adverse event risk is very low, and most severe adverse events, apart from YEL-AVD, are not generally as threatening as yellow fever. Nevertheless, the risk of severe adverse events among older travelers is concerning when compared to the risk that a traveler to endemic areas in South America will acquire yellow fever (roughly estimated at 5 per 100,000 travelers for a 2 week trip) [1,15].

Two recent reports raise further concern about 17D vaccine safety. In January 2010, the Centers for Disease Control and Prevention (CDC) reported transmission of 17D virus through accidental transfusion of blood products from recently vaccinated donors [16]. This risk had been recognized on theoretical grounds but had not been previously demonstrated. In February 2010, the CDC published a report of encephalitis in an infant in Brazil who acquired yellow fever vaccine virus through breastfeeding [17]. The risk of 17D virus transmission through breastfeeding had also been recognized on theoretical grounds, but this is the first confirmation that such transmission can cause illness in an infant [17]. Although congenital infection with the 17D vaccine can apparently occur, thus far the vaccine has not been shown to adversely affect infants of mothers who were vaccinated during pregnancy [1,18]. The risks of non-intentional vaccine transmission are inherent to 17D because it is a live vaccine. Theoretically, the newly developed chimeric vaccines against Japanese encephalitis, dengue and West Nile virus disease that use a 17D virus strain as their backbone could carry similar risks of non-intentional transmission, although the level of viremia elicited by these vaccines appears to be comparatively low [19].

Because of a higher risk of YEL-AND in young infants (the estimated risk ranges from 0.5 to 4 per 1,000 vaccinations) [1], the 17D vaccine is contraindicated for infants less than 6 months of age, and is not generally recommended for infants less than 9 months of age, thus leaving an important age gap in protective utility of the vaccine [1,33]. In addition, the 17D vaccine is contraindicated for people who are immunocompromised. While the vaccine has been safely administered to people with asymptomatic HIV infection who have adequate CD4 counts, it is contraindicated for people with symptomatic HIV infection, representing a public health barrier to protection against yellow fever in endemic areas where HIV infection is prevalent. According to the Joint United Nations Programme on HIV/AIDS, in 2007, there were over 9 million people living with HIV infection in African countries considered by CDC to have endemic yellow fever (http://www.unaids.org/en/KnowledgeCentre/HIVData/Epidemiology/latestEpiData.asp and http://wwwn.cdc.gov/travel/yellowBookCh4-YellowFever.aspx#668).

An inactivated yellow fever vaccine could circumvent many of the safety concerns regarding 17D vaccine. A safe and effective inactivated vaccine might be considered for use either as an alternative to live attenuated vaccine, or as a priming vaccine, and could be targeted to persons who are at higher risk of adverse events from the live vaccine or offered more universally. In 1928, Hindle [20] described development of an inactivated vaccine made from liver and spleen taken from a monkey who had died of yellow fever. The infected tissue was macerated and treated with formaldehyde in one preparation and with phenol in another. Both preparations appeared to protect monkeys against yellow fever, but subsequent investigations of efficacy were inconclusive [1,20]. The techniques and immunologic knowledge for preparing these and other early inactivated vaccines were rudimentary, and these efforts soon yielded to the development of live attenuated vaccines [1]. The recent safety concerns regarding 17D have spurred renewed efforts to develop inactivated vaccines from attenuated vaccine strains with modern methods.

In 2008, Gaspar et al. [21] described pressure inactivation of 17DD vaccine virus. The product caused no mortality in 20 mice following intracerebral inoculation compared to 100% mortality among 20 mice inoculated with live 17DD vaccine virus, suggesting that the inactivated preparation did not contain residual live virus. The inactivated vaccine elicited lower levels of neutralizing antibody than the live virus vaccine but did protect mice from intracerebral challenge with live 17DD virus.

In 2010, Monath et al. [22] described development of an inactivated whole virion vaccine using 17D virus that was inactivated with beta-propiolactone and adsorbed to aluminum hydroxide. Loss of infectivity was demonstrated by plaque assay. Inoculated rats developed inflammation at injection sites, lymph nodes and the spleen, but had no serious toxicity that would impede plans to test the vaccine in humans. All the rats developed neutralizing antibodies. The inactivated vaccine was also immunogenic in mice and hamsters. The hamsters developed neutralizing antibody titers similar to or higher than titers after live 17D vaccination and were protected against challenge with wild-type yellow fever virus. One dose of the vaccine elicited high neutralizing antibody titers at day 21 after inoculation in two of three monkeys, and two doses elicited high levels of antibody at day 21 in three other monkeys. Neutralizing antibody persisted at day 42 in all monkeys. A trial of the vaccine in humans is under way [22].

To borrow a phrase from John Irving's novel The Cider House Rules, would an inactive yellow fever vaccine "be of use"? An inactivated vaccine would be appealing for vaccination of travelers, particularly those over 60 years of age, since their exposure to yellow fever is generally transient, and their risk of severe adverse events after vaccination for some itineraries can approximate their risk of acquiring yellow fever. But would an inactivated vaccine be of any global public health use? The pros and cons of inactivated vaccine compared to live vaccine have been extensively debated in the context of global efforts to control polio [23,24]. The estimated risk of VAPP that provoked cessation of live polio vaccine use in the United States was lower than the current estimated rate of YEL-AVD [10,25]. While VAPP can cause severe disability, the case-fatality rate of YEL-AVD is notably higher [1,26]. However, the policies in favor of use of inactivated polio vaccine are also influenced by the risk of person-to-person transmission of vaccine-derived polioviruses [24,25]. Apart from the rare instances of non-intentional transmission mentioned above, live yellow fever vaccination does not raise this concern. An inactivated yellow fever vaccine would most likely be injectable so there would be little difference between an inactivated vaccine and the 17D vaccine regarding ease of inoculation. Thus, the principle determinants of the relative usefulness of a new inactivated yellow fever vaccine are reduced to three factors that must be compared against the current 17D vaccine: effectiveness, safety, and cost.