has been emphasized since 2016 by many authors [2–5]. First, the time since vaccination appears to be a key factor in the waning of neutralizing antibody responses. Second, in a subgroup of vaccine recipients, neutralizing antibodies decrease rapidly below protective levels in the first few years after vaccination [2]. One hypothesis for the latter phenomenon is the high variability of postvaccination viremia in primary vaccinees, modulating the subsequent protective immune response. Based on research with other whole-virus vaccines associated with long-lived immune response, such as the Measles-Mumps-Rubella vaccine, it has been suggested that a certain antigenic threshold must be reached in order to induce long-duration immune protection [6]. It is thus conceivable that, in a subgroup of primary vaccinees, the postvaccination viremia is insufficient, remaining below the antigenic threshold. In children vaccinated before the age of 2 years, intrinsic peculiarities of the innate and adaptive immune system include a Th2 shift and weak plasma cell and germinal center B-cell responses [7]. Whether an additional dose of yellow fever vaccine after age 2 to ensure long-term seroprotection would be effective is unknown. In immunocompromised adults, despite the heterogeneity of this population in term of mechanisms of immune pathways affected, this systematic review was able to show that seroprotection appeared to decline more rapidly than in healthy adults. Accordingly, we reported the same finding in people with human immunodeficiency virus (HIV) in a recent systematic review [8].

But is revaccination (or booster) the answer? By the authors' own admission, the data available and presented in this systematic review are so scarce that they do not allow to answer this question, either in children or in healthy or immunocompromised adults.

The critical aspect required to guide yellow fever international vaccination strategies is thus no longer the lack of data on the persistence of long-term immune protection but more answers regarding the impact of revaccination on long-term immune response persistence, a strategy that has been used for decades empirically. In the context of vaccine-dose shortages and yellow fever outbreaks in endemic area, let's base our decisions on good-quality data. Prospective studies assessing the impact of revaccination in primary vaccinees, children, adults, and immunocompromised adults are thus required.

Note

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Reply to Martin and Dauby

To the Editor—We thank Martin and Dauby for their interest in and careful evaluation of our work [1]. We completely agree with their assessment that there is a lack of data on the efficacy of yellow fever (YF) booster vaccination. More data on secondary vaccine failures are needed, including studies that compare the risk of YF infection and clinical outcome with or without a YF booster dose. There are published data on the enhancement of the YF-specific memory immune response after revaccination [2], but also on the negative effect of pre-existing antibodies on the humoral immune response following booster vaccinations [3]. Thus, further studies would certainly provide a better basis for the recommendation of booster vaccinations.

A number of factors affect the quality and the duration of the immune response after primary YF vaccination, including age at initial vaccination, ethnicity, nutritional status, season, or the exposure to other flaviviruses [4]. With regard to the interpretation of the available data, antibody levels are certainly a correlate of protection, but the contribution of vaccine-induced cellular immunity still requires further investigation.

Our meta-analysis provides evidence that a single dose of YF vaccine does not guarantee long-term protection against YF. Especially in children, waning of antibodies is already very

pronounced during the first 5 years of life. It is already known from other vaccinations that infants require a higher number of vaccine doses compared with adults, which may be due to their not yet fully developed ability to raise cellular immune responses [5]. Moreover, for certain subpopulations such as pregnant women or persons with immunocompromising conditions, 1 dose of YF vaccine may also not provide lifelong protection. For patients infected with human immunodeficiency virus (HIV) this has already been discussed in the review by Martin et al [6].

In addition, we do not have reliable data on the surveillance of breakthrough infections for large parts of the world (eg, for Africa, with 90% of the disease burden). In Latin America, some outbreak investigations found that previously vaccinated people also contracted the disease, and in some reports the mortality rates among vaccinated persons were similar to the rates in unvaccinated persons [7, 8].

Given the limitations mentioned above, the German Standing Committee on Vaccination (STIKO) has decided to recommend a booster dose for travelers [9]. Due to the high case fatality rate, this is a precautionary measure until more evidence or another vaccine is available. We think that as long as the data still show the weaknesses mentioned above, it is reasonable to consider a booster vaccination before travelling to an endemic area. Similar to Germany, several other countries have already decided in favor of a single YF booster vaccination.

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