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Letter to the Editor

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Arguments for a two-dose yellow fever vaccination regimen in travellers

Andreas Neumayr, MD, DTM&H, MCTM[1,2]*, Cornelia Stähelin, MD, DTM&H[3], Esther Kuenzli, MD, DTM&H, MScCID[1,2], and Christoph Hatz, MD, DTM&H[1,2]

[1]Department of Medicine, Swiss Tropical and Public Health Institute, P.O. Box, Socinstrasse 57, CH-4002 Basel, Switzerland, [2]University of Basel, Basel, Switzerland and [3]Department of Infectious Diseases, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

*To whom correspondence should be addressed. Tel: +41 61 284-8255; Fax: +41 61 284-8183; Email: andreas.neumayr@swisstph.ch

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We read with interest the publication by Lindsey and colleagues reporting on the persistence of yellow fever (YF) virus-specific neutralizing antibodies after vaccination among US travellers.[1]

We would like to comment on an aspect which is briefly mentioned in the publication but which has been largely neglected in most discussions following the WHO recommendation to reduce YF vaccination to a single dose in a person's life.[2] In their discussion, Lindsey and colleagues state that '…some proportion of those individuals that were sero-negative >10 years post-vaccination could have been primary non-responders to vaccination'.[1] This assumption is not unjustified since no vaccine has ever proven to confer 100% protection, especially not when administered as a single dose. This fact is reflected in the recommended two-dose regimens of other live vaccines: measles/mumps/rubella (MMR) and chicken pox. The second dose in these regimens is not a 'booster dose' but a 'second chance to seroconvert' for primary non-responders. Thus, the wording of the authors' subsequent conclusion '…a *booster* dose of vaccine could be considered for certain travellers whose immunologic response to the vaccine might be suboptimal or who received their last dose of YF vaccine at least 10 years previously …'[1] is not entirely correct, since for the mentioned fraction of primary non-responders it would not be a 'booster dose' but a 'second chance to seroconvert'. Although primary vaccination failure in YF is apparently rare, it should not be ignored. During the recent YF outbreak in Brazil at least seven cases of YF were reported in previously YF vaccinated individuals.[3] Until proven otherwise, primary vaccination failure must be considered in these cases. The WHO recommendation to discontinue 10-yearly vaccinations against YF is comprehensible under public health and herd immunity considerations. However, from the individual health perspective in travel medicine, the non-refutable risk of primary vaccination failure demands critical appraisal. Why not always give a second YF vaccine dose in analogy to MMR and chicken pox to ensure the best possible protection? The sole valid argument raised against such an approach would be the potential risk of serious side effects following a second dose of YF vaccine. Not a single case of the often quoted and feared YF vaccine-associated viscerotropic disease has ever been reported following a YF post-primary dose.[4] According to published data, the risk of sustaining a serious adverse event (SAE) after receiving a post-primary dose of YF vaccine is 14 in 14′134′035 million doses (Table 1).[4] These few cases of possible YF vaccine-associated neurologic disease (Table 1; cases 1–4) were all reported as an autoimmune-mediated event rather than direct vaccine viral invasion of the central nervous system.[4] Considering that SAEs include all timely but not necessarily causally related events, the number of SAEs truely related to YF re-vaccination is even lower. Compared to the number of SAEs, the number of anticipated primary vaccination failures appears to be considerably higher if Lindsey and colleagues (who also contributed to the data compiled in Table 1) report that 6% of vaccinees sampled <10 years following primo-vaccination tested sero-negative by PRNT and speculate that '…some proportion of those individuals that were sero-negative >10 years post-vaccination could have been primary non-responders…'.[1] When reading this comment and looking on the available data it remains inconclusive to us why the discussion continues to focus on the longevity of protective antibodies and on definitions of risk groups ('…certain travellers whose immunologic response to

Table 1. Severe adverse event report after receiving a second or booster dose of YF vaccine (adapted from Ref. [4])

Study	Case	Severe adverse event report after receiving a second or a booster dose of YF vaccine
CDC 2015[a]	1	Guillain–Barré syndrome (GBS) 16 days post-vaccination
	2	GBS 7 days post-vaccination
	3	Encephalitis 4 days post-vaccination
	4	Bilateral optic neuritis 2 days post-vaccination
	5	Anaphylaxis with angioedema on the day of vaccination
	6	Fever and right lower quadrant pain 5 days post-vaccination
	7	Lower extremity cellulitis 7 days post-vaccination
	8	Acute appendicitis requiring surgery 2 days post-vaccination
	9	Fever and syncope 1 day post-vaccination
	10	Myalgia and upper extremity weakness 3 days post-vaccination
	11	Lymphadenitis 26 days post-vaccination, subsequently diagnosed as Hodgkin's lymphoma
Lindsey 2008[b]	12	Appendicitis requiring surgery at 1 day post-vaccination
Khromava 2005[c]	13	Numbness and weakness at 12 days post-vaccination
	14	Abdominal pain and yellow stools requiring hospitalization at 7 days post-vaccination

[a]Observational study; 2007–13; non-endemic population; total number of vaccine doses: 3 631 535.
[b]Observational study; 2003–06; non-endemic population; total number of vaccine doses: 902 500.
[c]Observational study; 1990–2002; non-endemic population; total number of vaccine doses: 9 600 000.

the vaccine might be suboptimal or who received their last dose of YF vaccine at least 10 years previously and will be in a higher-risk setting based on season, location, activities, and duration of their travel'[1]). We support the authors' conclusion that '…for travellers with no financial barriers or medical contraindications or precautions, YF re-vaccination is likely to be an attractive option for decreasing risk of a life-threatening infection'[1] but would opt for a more pragmatic approach and generally call for the adoption of a two-dose YF vaccination regimen in travellers. In addition, the above discussed points suggest that this second dose should be given in a timely manner and not delayed for ≥10 years as proposed by the authors.

References

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