Author’s response to reviews

Title: Vaccinating children against influenza: overall cost-effective with potential for undesirable outcomes

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Dear editor,

Thank you for assessing the responses. The comments of the Editorial Board member helped to strengthen our conclusions further. We have added the requested simulation results and rewrote part of the discussion to address the duration of vaccine-induced protection. We believe this would suffice, according to the Editorial Board Member, to remove “a nagging (though relatively small) concern”.

We have taken the opportunity to clarify the text with respect to two issues.

• First, we clarify explicitly that the duration of protection after infection or vaccination is always measured and defined as immunity against the dominant circulating strains (Methods, page 7, line 161-163). This allows for a direct comparison between simulation results and observations, as almost all trials and observational studies measure immunity against circulating strains. This is crucial, as it allows the model to be fitted to observations. To stress this, we have now omitted the term “generic strain” to describe the modelling approach (Discussion, page 17, line 389-391 and page 20, line 473-474).

• Second, we explain why the results arise (Discussion, page 17, line 389-404, page 18, line 422-423 and Additional file 3). This also explains why the requested simulations that explicitly include structure of types and subtypes yield similar results (Additional file 3). We present the requested simulation results with a type/subtype model, where we focus on influenza A/H3N2, in a separate appendix to avoid unnecessary confusion with the simulations we use in the main text.
Furthermore, we would like to respond to some of the comments of the Editorial Board Member for clarification.

• The Editorial Board Member states that “Evidence, such as it is, suggests that you are probably immune to a strain that you have been infected by for a very long time (possibly lifelong)” and “vaccine induced immunity to a single strain is quite long-lived as the live-attenuated vaccine mimics a natural infection”. We wonder which evidence the Editorial Board Member refers to. There is experimental evidence for a relatively short duration of protection to a strain that you have been infected by: a volunteer challenge study (Memoli et al. [1]) demonstrates that sequential infections occurred with identical influenza A virus strains approximately 1 year apart in a majority of the study participants. If vaccine-induced protection by the live-attenuated vaccine mimics a natural infection, as conjectured by the Editorial Board Member, it must have a similar short duration of protection as observed in these volunteer challenges.

• The comments mention that “these sort of claims can be very damaging to a vaccination programme”. We would like to reassure the editors, the members of the editorial board, and the potential readers of this manuscript that we are well aware of the wider implications of our findings. We work at a Public Health Institute with the specific objective of informing policy making in the Netherlands, and it is our job to evaluate vaccination programmes and advice public health policy makers. We report the intended positive effects of vaccination programmes. We also report potential unintended effects of vaccination programmes.

• The Editorial Board Member interprets the “generic strain” modelling approach as if it assumes that there is only one single strain, and that this single strain doesn’t evolve. This is incorrect. The model used in this manuscript does allow for evolution and alternation of circulating strains. The model implicitly accounts for differences in influenza strains (in type, such as influenza A versus influenza B; or in subtype influenza AH1N1 versus AH3N2; in lineage B/Yam and B/Vic, or in strains such as A/Texas/50/2012).

• The comments suggest that the model structure is “a somewhat strange model of flu (or novel model perhaps)” and not “really adequately structured and parameterized to enable these claims to be made”. The model we use in this manuscript has been described in two publications that appeared in a peer reviewed journal that is focused on infectious disease dynamics. This modelling approach is common for models of seasonal influenza that are fitted to the observed dynamics over multiple seasons (see for instance [2-5]). Perhaps there was confusion with the different structure of influenza transmission models without any immunity propagation that have been developed for different purposes, such as exploring the impact of vaccination during an influenza pandemic (Baguelin et al. [6]), or models that focus exclusively on influenza dynamics in one single season (Baguelin et al [7, 8]). Such a model structure without any immunity propagation allows for simulating the impact over one season, but it is not capable of simulating the costs and effects of a childhood influenza vaccination programme over several years (as required, per WHO guidelines, see Newall et al. [9]).

• The comments suggest that by fitting the model outcomes to final size data (that is, to the total number of patients with ILI during a season) there are no dynamics in the model. This is
incorrect. We use a dynamic transmission model for within season dynamics, exactly the same as has been used in for example Baguelin et al. BMC med 2015 [8].

Summarizing, in the paper we argue two things: first, the effect of childhood vaccination is a reduction in influenza transmission in the general population, and the direct consequence is that there are more people left susceptible. Second, the influenza vaccine is highly variable from year to year. These two arguments, taken together, imply that childhood vaccination does decrease the influenza attack rate on average (which is good news) and increase the variation in influenza attack rates (which is bad news). These arguments do not depend on the duration of vaccine-induced immunity. The conclusions are robustly supported by the simulation results of influenza transmission and immunity.

References


