Author’s response to reviews

Title: The introduction of "No jab, No school" policy and the refinement of measles immunisation strategies in high-income countries

Authors:

Filippo Trentini (ftrentini@fbk.eu)
Piero Poletti (poletti@fbk.eu)
Alessia Melegaro (alessia.melegaro@unibocconi.it)
Stefano Merler (merler@fbk.eu)

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Author’s response to reviews:

Dear Editor,

Please find enclosed the revised version of the manuscript “The introduction of "No jab, No school" policy and the refinement of measles immunisation strategies in different demographic settings.” (BMED-D-18-01492).

We thank you and the editorial board for the useful feedback on the manuscript and the opportunity to resubmit our work to BMC Medicine. We are grateful to the Reviewers for their generally positive comments on the manuscript and their detailed reports that helped us to make clearer both the assumptions and the results of the proposed analysis. We have done our best to thoroughly address all comments raised by both the Reviewers and the Editor.

We enclose in a separate file our point-by-point response to all comments of the Reviewers, explaining the corresponding changes made in the text. Main changes in the manuscript can be summarised as follows:

- following the suggestion of Prof. Felicity Cutts (reviewer #2), we decided to remove both Kenya and Ethiopia from our study. In fact, we agree that some modelling assumptions made in our analysis may be considered less appropriate for sub-Saharan African countries and that results would be more comparable and informative if we focus only on high-income countries,
characterised by similar vaccination programs and high school enrolment rates. As a consequence of this change, we propose to slightly change the title of the manuscript into:

The introduction of "No jab, No school" policy and the refinement of measles immunisation strategies in high-income countries

- following the suggestion of Prof. Don Klinkenberg, we performed a sensitivity analysis to test the robustness of obtained results under different assumptions on maternal antibodies protection. The obtained results are presented in the supplementary material and discussed in the main text.

- following the suggestion of Prof. Don Klinkenberg, we modified the main text in order to better clarify how obtained estimates should be interpreted, as we do not consider measles transmission between 2018 and 2050.

Please note that the new version of the manuscript now adheres to the stylistic guidelines of the journal and that all minor points raised by the reviewers and the editorial comments have been addressed as well.

We believe that the clarity of the manuscript has now considerably improved, and we dare to hope that it is now suitable for publication in BMC Medicine.

Sincerely yours,

Filippo Trentini

on behalf of all the authors (Piero Poletti, Alessia Melegaro and Stefano Merler)

Detailed reply to Reviewers

We are extremely grateful to the reviewers for their thorough assessment of the manuscript and their general appreciation of our work. We think that their remarks and comments truly helped us in considerably improving our manuscript.
Response to Reviewer #2: Felicity Cutts

This is a potentially very interesting paper that builds on previous work conducted by this group. At present, however, the conclusions are not relevant to Ethiopia and Kenya because current vaccination programs are not adequately captured in the models and the assumptions about how additional strategies would be implemented are not necessarily appropriate. Either the authors need to conduct extensive re-analyses incorporating the effect of past and planned campaigns (SIAs) in Kenya and Ethiopia as well as removing the restriction that the 2nd routine dose only reaches those already vaccinated in those countries, or else they should drop these two countries from their analyses. If they focus on the other countries that rarely do SIAs and have almost universal school enrolment then their assumptions may be more appropriate and the paper would be clearer.

We thank Prof. Cutts for her general appreciation of our work and the useful suggestions provided. We have done our best to address all comments she raised as detailed below. In particular, following her suggestion, we have decided to remove from the proposed analysis the two Sub-Saharan African countries – namely, Ethiopia and Kenya. Indeed, although our initial hope was to extend our previous work to consider vaccination scenarios for countries with different socio-economic and demographic conditions, we acknowledge the fact that the assumptions we have to make for SSA countries on how additional strategies would be implemented might be considered inappropriate.

After removal of these two countries, the paper now investigates the potential impact of introducing mandatory vaccination at school entry focusing on countries characterised by similar public health programs and high school attendance rates. We believe that the assumptions made in the proposed study would now result more appropriate and the discussion of public health implications would sound more incisive.

The first paragraph talks about some components of measles elimination strategies but ignores one of the main strategies used in low income countries including Kenya and Ethiopia - Supplementary Immunization Activities (SIAs) or campaigns. As the authors know from their previous paper (Trentini et al 2017), there have been multiple national and subnational campaigns in both these countries covering varying age ranges (see spreadsheet of SIAs on http://www.who.int/immunization/monitoring_surveillance/data/en/). For example, SIAs were conducted among varying age groups in Ethiopia in 2013, 2015, 2016 and 2017; while Kenya conducted a catch-up measles-rubella campaign up to age 15 years in 2016 with high coverage (see Subaiya et al 2018) and then introduced rubella vaccine into the routine schedule. Ethiopia
has not yet introduced rubella vaccine but when it does in the next few years, a wide age range campaign up to age 15 years will be done (see WHO rubella vaccine position paper).

The conduct of wide age range SIAs will have a big effect on any potential benefit of school-entry vaccination hence needs to be taken into account in this paper. Conduct of SIAs should be part of the base-case vaccination scenario in Kenya and Ethiopia. For example, in addition to taking account of recent SIAs done in both countries, the authors should be aware of existing plans for follow-up SIAs in both countries in 2019 (see summary of SIAs on http://www.who.int/immunization/monitoring_surveillance/data/en/).

p.5: The authors make several assumptions that can be challenged when considering low income countries. First, they assume that only individuals who have been previously vaccinated with a first dose are considered eligible for the second dose routine program. This is not necessarily the case, indeed one major factor that made WHO change their recommendation about introduction of a routine 2nd dose was the hope that continuing to offer routine vaccination in the second year of life would increase coverage of both the first and the second doses by extending the period of eligibility for the 1st dose from 9-11 months to 9-23 months. This allows more time for mothers who have difficulty reaching health centres to attend and offers more opportunities for health center contacts to be used to administer measles vaccine. Hence, many children who would have been unvaccinated under the one-dose schedule are expected to receive at least one dose under a two-dose schedule. The extent to which this happens in practice is so far unknown but should be considered in this paper at least under a sensitivity analysis. Second, school entry vaccination in low income countries is unlikely to target only children who have not yet received two doses because of the difficulty in obtaining documented evidence of previous vaccination. If the authors look at DHS data they will see that even in the 2nd year of life, a large proportion of children lack a home-based record even if the mother says that they have been vaccinated. Hence a school-entry program that offers at least one dose of vaccine to all children should be assessed at least as part of a sensitivity analysis, as this may be the only feasible option at present.

Interpretation of results: the authors estimate population immunity in different age groups under different scenarios but all this in the context of low measles transmission which is not currently the case in Ethiopia. The length of time that a child remains susceptible to measles and at risk of infection should be considered when comparing different strategies for offering a 2nd dose. Furthermore, the assumptions from the authors that in effect, school entry vaccination will reach children who missed the routine first dose whereas vaccination in the 2nd year of life can only reach children who already received the routine first dose in the first year of life, automatically gives school entry vaccination an advantage. It is not clear that in reality this advantage would
hold, especially given low school enrolment rates in some areas and population groups and the difficulty in enforcing any school vaccination laws.

We acknowledge that these are all relevant issues for appropriately investigating the impact of alternative vaccination strategies in sub-Saharan African countries. Considerable differences in how vaccination strategies and immunisation activities are usually implemented or may be implemented in the future do definitely exist between high- and low-income countries. In particular, by considering only high-income countries only, we can fairly assume that 1) the introduction of a school-entry vaccination would reach almost all children (due to enrolment rates close to 100%) and 2) the second dose vaccine administration targets children who were not effectively immunised with the first dose. On the opposite, these assumptions may result – at least partially - inappropriate for countries like Ethiopia and Kenya. Furthermore, sub-Saharan African countries have relied in the past and would probably rely in the future, on repeated erratic vaccination catch-up and follow-up campaigns (the so-called Supplementary Immunization Activities - SIAs) that, as a matter of fact, currently represent a key component of routine immunisation plans. Although we have considered all SIAs performed in the past as contributing to shape the initial conditions on the immunity levels for these two countries, we agree that an assessment of alternative vaccination policies in these countries should include a comparison with the potential effect of future SIAs. However, the inclusion of future SIAs in a reliable way (especially in terms of coverage levels, frequency and efficacy) would represent a very difficult (nearly impossible) task and is beyond the scope of the proposed analysis. As the paper mainly focuses on the potential benefits of introducing mandatory vaccination at school entry, we deem that the clarity of the manuscript and the robustness of the proposed analysis will benefit from the exclusion of both Ethiopia and Kenya.

Finally, please also note that, we rephrased a couple of paragraphs both in the Method and in the Discussion sections to clarify the assumption of no measles transmission between 2018 and 2050s, making clear that we are actually estimating the fraction of individuals at risk of measles infection after 2018. In the new version of the manuscript we clearly state that the proportion of susceptible individuals in a given year y estimated by the model represents the fraction of individuals that would either be susceptible in year y or would have been infected between 2018 and y.

Line 14: Reported measles cases worldwide were about 140,000: please correct to 173330 (http://www.who.int/immunization/monitoring_surveillance/data/en/).
Note that this is less than 2% of estimated cases occurring worldwide. For example in 2016 there were an estimated 6 976 800 (95% CI: 4 190 500-28 657 300) cases globally while only 132137 cases were reported to WHO (see Dabbagh et al 2017).

Lines 16-17: European cases accounted for one sixth of total cases - again, this is reported cases, it is clearly not reality. I would rephrase this and say that reported incidence was among the highest in Italy and Romania although reporting rates are likely to be much higher in European countries than in low income countries where access to care is much lower.

Addressed by adding this paragraph in the Introduction:

" In 2017, measles cases reported to the World Health Organization (WHO) amounted to 173330 worldwide and measles incidence rates were among the highest in Italy and Romania. Although measles cases reported to WHO may represent 2% of measles cases worldwide [1] and reporting rates are likely to be much higher in countries with a better access to care [5], the European region has experienced a four-fold increase of reported cases compared to the previous year [6] and 35 deaths."

p.4 Line 41: I think the authors mean following the indications of the World Health Organization, not the World Health Assembly. They should reference the WHO Measles Position Paper (2017).

Thanks for pointing this out. However, please note that, by removing Kenya and Ethiopia from our analysis, also this sentence has been removed.

Reference 6: this weblink does not work.

Addressed. We modified the reference with the link below.

Page 6 line 54: please clarify whether coverage for both doses in the routine programs in these countries needs to be at least 95%.

In order to clarify the point, we changed the sentence as follows:

"We found that, in all countries with the exception of Italy, coverage levels above or equal to 95% for both first and second routine doses would allow to reach the 7.5% threshold for herd immunity (see Fig. 2)."

Page 7: the results for Kenya and Ethiopia need to take account of SIAs. SIAs have, since 2000, provided a second opportunity and for many children, a 2nd dose of measles vaccine. In Ethiopia, so many SIAs have been conducted that many children will have received more than 2 lifetime doses.

Please note that, by removing Kenya and Ethiopia from our analysis, also this sentence has been removed.

Page 7 line 35: a catch-up campaign targeting ages 1-15 years is not only targeting school-age children.

Thanks for pointing this out. We have rewritten the sentence as follows:

"We therefore investigate i) a baseline scenario where routine programs and coverage levels remain unchanged as before the introduction of compulsory vaccination at school entry in Italy and Australia; ii) a scenario where coverage levels associated with the baseline vaccination activities are assumed to vary between 60% and 100%; iii) a scenario where baseline vaccination activities are complemented with vaccination at school entry, implemented on the basis of country-specific compulsory school programs (appendix pp 5-6), with coverage levels between 20% and 100%; iv) a scenario where baseline vaccination activities are complemented with
vaccination at school entry and a catch up campaign among 1-15 years old in 2018 with coverage levels of both strategies assumed to vary between 20% and 100%.

Page 7 lines 56-60 and page 8: please clarify under what assumption of coverage of the first routine dose and of the dose at school entry the cited susceptibility levels are estimated to be achieved in Kenya and Ethiopia.

Please note that, by removing Kenya and Ethiopia from our analysis, this assumption does not need to be clarified any more.

Reviewer #3: Don Klinkenberg

General remarks

It is a well written paper with clear results and an important message.

We thank Dr. Klinkenberg for his general appreciation of our work and the useful suggestions provided. We have done our best to address all his comments as follows.

There are two points that deserve a little extra attention:

(1) the assumption of absence of transmission. The authors state that future infections would arise from a small proportion of the susceptible population, suggesting that only a negligible fraction of susceptibles will be infected. However, this is somewhat at odds with the idea of a risk of resurgence coupled to a threshold for herd immunity. If herd immunity is relevant, major outbreaks may also occur before 2050 in countries with too many susceptibles, significantly changing the proportion of susceptibles in 2050. I think it should be made very clear that you calculate the proportion of people that were not vaccinated AND not infected before 2018: all people at risk for infection between 2018 and 2050. These people may either be susceptible in 2050, or they have experienced a measles infection between 2018 and 2050. I think that this improves interpretation without assuming absence of transmission.
We completely agree that the proportion of susceptible individuals we are estimating in a given year \( y \) actually represents the fraction of individuals that would either be susceptible in year \( y \) or have been infected between 2018 and \( y \). We also acknowledge that, in the previous version of the manuscript, the justification of the assumption of absence of measles transmission between 2018 and 2050 was completely misleading and needed to be clarified. Indeed, as the fraction of susceptible individuals increases over a certain threshold measles circulation can also increase, reducing the number of susceptible individuals in the population.

Following the reviewer suggestions, we changed a couple of paragraphs of the main text both in the Method section and in the Discussion section to clarify how we compute the proportion of individuals at risk of measles infection in the period 2018-2050 and how the obtained results should be interpreted.

The text in the method section now reads:

"In this work, we extend the model to simulate, for each country, how the susceptibility of the host population would change in the future, under current and additional vaccination programs. Changes in measles immunity profiles caused by alternative immunisation strategies and coverage scenarios are simulated for the period 2018-2050, by neglecting the potential impact of the circulation of the infection to estimate the temporal changes in the overall fraction and age distribution of individuals at risk of measles infection after 2018. The fraction of residual susceptibility estimated in a given year \( y>2018 \) therefore include individuals who may experience natural infection between 2018 and \( y \), due to possible measles resurgence between 2018 and \( y \)."

The text in the Discussion now reads:

"The focus of our work is on the potential impact of immunisation strategies in reducing the proportion of individuals at risk of infection in the future. As such, in our analysis, we did not consider measles transmission between 2018 and 2050. Although the occurrence and magnitude of future measles epidemics are largely uncertain and difficult to predict [25], it is worth stressing that sufficiently high level of susceptibility in the population can promote measles circulation before 2050, therefore reducing the fraction of susceptible individuals in the host population. Our estimates of the residual susceptibility over time should be therefore carefully interpreted as representing, for each year considered, the fraction of individuals who either is still susceptible to measles infection or has experienced a natural infection after 2018."
(2) the result that school-entry vaccination is so much better than a second regular vaccination in Kenya and Ethiopia. This is under the assumption that school-entry vaccination is independent of regular vaccination. Is that assumption correct? For instance, are there communities where children don't get vaccinated and may not even go to school, let alone get vaccinated when they do?

We acknowledge that some assumptions made in our analysis may not be adequate for sub-Saharan African settings. Following the comments and suggestions provided by both the reviewers, we have decided to remove from the proposed analysis the two African countries-Ethiopia and Kenya. As the paper investigates the potential impact of introducing mandatory vaccination at school entry, we believe that it is preferable to focus only on high-income countries characterised by similar public health programs and high school attendance rates. Indeed, in this case, the assumptions made in the proposed study would result more appropriate and the discussion of public health implications would sound more incisive.

Minor point:

In the model there is a group with maternal immunity, and all children are born into that group. That is a bit strange if seroprevalence in the age group of the mother is low. On the other hand, this M class does not seem to affect the results much. I suggest you briefly comment on this point in the supplementary material itself.

Thanks for raising this point. By following the reviewer's comment we now briefly discuss this point in the main text. Please also note that, in order to show that the robustness of our results is not affected by this assumption, we decided to perform a sensitivity analysis showing that model results do not change much when assuming that all individuals at birth have no maternal protection at all. As showed in sub-section “Sensitivity analysis on maternal antibodies protection” of the Supplementary material, obtained differences in the susceptibility level for 2050 were found around 4% for US and Australia and less than 1% for all other countries. There results are briefly mentioned in the main text as follows:

“Finally, our estimates were obtained under the assumption that, at birth, all individuals are protected by maternal antibodies, and that there is no vaccine waning immunity. Although it is likely that children born from susceptible mothers have no maternal protection against the infection, we show that the robustness of our results is not affected by this assumption (appendix p 5).”