Reviewer's report

Title: Interpreting changes in measles genotype: the contribution of chance, migration and vaccine coverage

Version: 1 Date: 27 August 2007

Reviewer: Katia Koelle

Reviewer's report:

General
In this manuscript, Nojiri and coauthors use a mathematical model, simulated stochastically, to explore how immigration and vaccine coverage affect genotype replacement in measles.

In general, I found the manuscript easy to understand and clearly organized. The two main results are intuitive. The first result is that at higher vaccination rates, more rapid replacement of the 'indigenous' genotype occurs (in the cases when at least one genotype persists in the population). The second result is that more rapid replacement of the 'indigenous' genotype also occurs at higher immigration rates (p) of the imported genotype. Despite these results being intuitive, it's nice to have a model illustrate these patterns quantitatively.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. It was unclear to me why the authors used a two-city model (I couldn’t find a motivation for this model design in the text). Having two cities complicates the model to some extent, by adding another variable (e) that determines the degree of mixing between cities. It is unclear to me whether having two cities is actually necessary—it seems that changing e in effect changes the host population size. Why not simply have one city, with different population sizes (N = 500,000 to N = 1,000,000), and then make sure to set the immigration rate in per capita terms (e.g. p = 1 case per million per year, instead of cases/city/year).

2. The model, presented in the appendix, is discrete-time, with a 14-day time period between time t and time t + 1. Although the results with this model appear to be correct (i.e., I don’t see any apparent bugs in the program), there seems to me to be a much more elegant ways to write and simulate the model. Specifically, if the differential equations for the system were first written, then the model would be in continuous-time, instead of discrete-time. This has the advantage of being more appropriate for measles transmission, of course. This set of differential equations could then be simulated stochastically using the Gillespie algorithm.

3. (Related to above comment) I think the patterns that the authors find at
different parameter values could be substantiated by a quick differential equation analysis. Once the system is written in terms of differential equations, and expressions for the fixed points are computed, then it can be easily seen that at higher immigration rates \( p \), there is a higher equilibrium proportion of infected individuals that carry the imported genotype. (A similar analysis can be done to determine the effect of vaccine coverage.) This analysis would not replace the stochastic simulations (because neither replacement nor extinction would occur in the deterministic system), but add another short analysis that would introduce some degree of mathematical rigor to their results.

4. Many previous models have looked at measles dynamics. Instead of presenting an entirely new model, why not build on model formulations that already exist in the literature, and have therefore already been peer-reviewed? For the discrete-time formulation, I point the authors to the work by Ottar Bjornstad, Barbel Finkenstadt, and Bryan Grenfell (e.g. Ecological Monographs, Vol. 72, No. 2, 169-184. May, 2002). For the continuous-time formulations, I point the authors to the work by Earn, Rohani, Bolker, and Grenfell (e.g. Science, Vol. 287, No. 5453, 667-670. Jan., 2000). These models differ slightly from the current model, and they include term-time forcing (i.e., seasonality) in measles transmission, something that the authors may want to consider incorporating into their model as well.

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Minor comments:
- I suggest incorporating more of the model in the main text than just hiding it in the supplemental material.
- p.5: ‘The method was used to determine the level of vaccine coverage…’. Clarify to something like: ‘The level of vaccine coverage was specified in the model’. (The level of vaccine coverage was not determined, but specified as an input.)
- p.6: ‘and an importation rate of cases of 0.5, 1, and 1.5 per city per year’. An importation rate of 1 per city per year was never analyzed. Also, change to importation rate per population size per year instead of per city?
- p.7: ‘…no single genotype was predicted to persist in the population’ These results should be put in terms of previous results on the critical community size (CCS) of measles.

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Discretionary Revisions (which the author can choose to ignore)

What next?: Accept after minor essential revisions
**Level of interest:** An article of limited interest

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**
I declare that I have no competing interests