Reviewer's report on "Spatio-temporal modeling of co-dynamics of smallpox, measles and pertussis in pre-healthcare Finland"

In this study, the authors develop a Bayesian spatiotemporal regression model to quantify measles, pertussis, and smallpox co-dynamics based on historical mortality data from 1820 to 1850 in Finland. One key result is the estimation of positive correlations in the dynamics of the three pathogens, which the authors interpret as the potential consequences of general immunosuppressive effects at the population level.

Overall, the paper is well-written and interesting. This dataset is unique and will be highly valuable to this research field. The proposed model is generally sound, using advanced inference techniques (Hamiltonian Monte Carlo) and including several—but not all, see my comments below—complexities of infectious disease dynamics, such as seasonality, spatial interactions, and pathogen interactions. However, some kind of validation of the model is missing at this stage, for example, based on a simulation study. In addition, some assumptions about the model formulation appear arbitrary, and extensive sensitivity analyses are needed to assess the results' robustness. Overall, despite the overall quality of the study, much more work would be required to support the authors' claim (stated in the abstract) that the positive correlations may indicate biological mechanisms such as immunosuppressive effects. More specific comments are listed below.

Major comments

1. Even though the proposed approach is interesting, it must be validated via a simulation study. For example, the authors could develop a SIR-based transmission model of measles, pertussis, and smallpox co-dynamics with explicit interaction mechanisms (see, for instance, Refs.[1–3] for the form of such a model), then test their statistical model based on synthetic data simulated from this transmission model. Such pre-validation would significantly strengthen this study and help the authors calibrate their statistical model for optimal performance. My relatively extensive experience with interaction models[3–7] suggests that purely statistical approaches may be inadequate to infer interactions, but I'd be happy to be convinced otherwise. If needed, I can help the authors design this simulation study.
2. The initial data consists of daily deaths from different Finnish regions. Before analysis, however, the authors aggregate these data monthly and binarize them into presence/absence data, which are then modeled using logistic regression models. Data aggregation generally makes me nervous, as it typically destroys information. Here, these two data pre-transformations seem arbitrary and overkill. Why not use a count regression model (maybe with a zero-inflation component to consider the data sparseness), which would seem more natural for these data? If the data must be aggregated, then at the very least, the authors should justify the temporal unit and test alternative values. In particular, the generation time of measles[8] and smallpox[9] is shorter than one month, so I expect weekly or biweekly aggregation to be more reasonable. To my first comment, a simulation study would help arbitrate these different options.
3. Although the model includes several components relevant to infectious disease dynamics, a major omission is population (or herd) immunity or, equivalently, population susceptibility—yet a major driver of epidemic dynamics. According to earlier research[10], adding covariates for the cumulative number of past cases may capture this population immunity. Again (see my first comment), a simulation study would help examine this aspect and calibrate the model accordingly.

4. Also, regarding the model structure, the other diseases are only considered at a lag of 1 month. This choice must be justified, especially considering the authors' claim of general immunosuppressive effects that may last much longer. Indeed, measles-induced immunosuppression may last several years[11]. Again, the way to address this potential concern would be through extensive sensitivity analyses with different assumptions about the lag structure.
5. Do the data contain any information about the age of cases? If so, it would be interesting to compare the mean age for the different diseases. Significant differences, if any, would make an interaction less likely.
6. Looking at Table 1, what would be the biological mechanisms by which pertussis and smallpox facilitate measles? The authors talk about immunosuppressive effects, but such effects have only been demonstrated for measles. In contrast to measles infection, pertussis infection is not systemic, so such effects seem unlikely.

Minor comments

- Introduction, lines 33–34: "Coinfections of parasites (Graham, 2008) and viruses and respiratory bacterial infections are 33 well known (e.g., Bakaletz, 2017), […]". Regarding viruses and bacteria, there is also extensive evidence for the pneumococcus–influenza system[4,12–14]. Our lab, and others, also conducted research on flu–SARS-CoV-2[3,5,7] and flu–RSV[6] interactions.
- Results, lines 180–181: "[…] the R statistics are always 180 below 1.004, and the effective sample sizes are approximately between 800 and 40,000." An effective sample size of 800 seems particularly low, suggesting convergence issues for some parameters.
- Figure 4: the relatively consistent seasonality across the three diseases is interesting. Can specific hypotheses (*e.g.*, social events, climate) explain this finding?
- Discussion, line 269: "This is in concordance with the earlier findings of Rohani et al. (2003) […]". Please note that, unlike the authors' findings of a positive interaction, this study found evidence of a *negative* interaction between measles and pertussis through ecological interference.

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