Reviewer’s report

Title: A Clinical Prediction Rule for Diagnosing Human Infections with Avian Influenza A(H7N9) in a Hospital Emergency Department Setting

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Reviewer: Stefano Merler

Reviewer’s report:

In this paper authors describe a method to timely discriminate between A/H7N9 cases and ARI based on clinical variables readily available soon after hospital admission. They claim that the proposed method could help physicians to optimize resources, especially in case of a new epidemic wave.

The paper is interesting (in particular I like the idea of simplifying results by transforming model coefficient into scores, easy to use by physicians), the performed statistical analysis sounds correct to me, but there are a few points that should be further discussed/clarified.

Major Compulsory Revisions:

The major problem I have with this paper is that authors do not demonstrate that performances (sensitivity of 0.93, a specificity of 0.80, or 0.96-0.75 as resulting from bootstrapping) are somehow optimal and may be really helpful to optimize resources during an epidemic. Which is the overall cost of misdiagnosing 7% of A/H7N9 cases? Which is the cost of misclassifying 20% of non A/H7N9 ARI cases? In general the answer to the last question strongly depends on the overall incidence of ARI cases. In fact, which is the gain if the number of ARI is so large that 20% of them make the proposed prediction rule of unpractical use? In principle, one might be happier with sensitivity of 1 at the price, of course, of specificity lower than 0.8, or specificity 1, with sensitivity lower than 0.93.

Related to the previous point, I think that showing the entire sensitivity-specificity curve, and discussing different regions of the curve, could be more informative. Afterwards, you could still claim that the model with 0.93-0.8 sen-spe is the optimal one. Moreover, there do exist techniques, based on weighting (basically you may give more importance to A/H7N9 cases or to ARI cases), that allow us to get higher specificity or sensitivity.

Minor Essential Revisions:

Authors claim that the proposed method could be helpful in the case of the re-emergence of the epidemic. I think they should clarify that they are still thinking of a virus with little or no human-to-human transmission potential. Should A/H7N9 evolve into a (readily) human-to-human transmissible virus, the proposed prediction rule is of little value (the most important variable is “history of poultry exposure”).
It is not clear to me why authors excluded a priori from the study individuals aged less than 14 years. They say that only few cases have been observed in this age class (and of course this is true). I think that a possible explanation is that elderly have a higher probability to be exposed to infected live poultry (e.g. in the markets). The point, however, is that variable age could be discarded by the variable selection procedure, even if the 0-14 age group is considered, because “history of poultry exposure” already explains the observed profile of infections by age. This is stronger that excluding a priori the 0-14 age group from the study.

I think that a brief appendix reporting a more technical description of methods, e.g. multiple imputation, optimism-corrected estimates, etc. would be helpful.

Discretionary Revisions:

As for the predictive ability of the proposed method, perhaps authors could be able to estimate performances on new A/H7N9 cases (Jan.-Feb. 2014).

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests