Author’s response to reviews

Title: Hospital-Acquired Influenza in an Australian Tertiary Centre 2017: A Surveillance Based Study

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Version: 1 Date: 05 Mar 2019

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Version: 1 Date: 28 February 2019
Author’s response to reviews:

Dear reviewers,

We would like to thank you for your valuable comments and suggestions in improving the manuscript. We present a point-to-point response below, and have indicated changes by quoting the line numbers from the updated manuscript as well as including track-changes in the manuscript document.

Response to Thomas Benet (Reviewer 1):

C1: The inclusion of influenza cases with diagnosis <=6 days after onset in the CAH group might lead to misclassification bias of the disease (some of them can be HAI). I would recommend either to exclude cases with sample collection between 48h-6 days who have unknown date of onset, or to test if patients with sample collection in the 1-2d period differ from those with sample collection in the 3-6d period with unknown date of onset (and report in if they are different or not, in order to conclude if the definition is relevant or not).

R1: Thank you for your comment. We agree that cases with an unknown date of symptom onset had the potential to be misclassified as community-acquired. There were four patients who had unknown symptom onset and had sample collection between 48h-6days. We have relooked at their patient files and confirmed that they did not acquire influenza in the study hospital. The reasons for this included: a presentation to hospital with ILI symptoms however exact date of onset unknown, transfers from regional hospitals with existing influenza diagnoses and symptoms, and acquiring influenza from a family member at home. Thus, these patients did not meet the criteria for HAI and were classified as CAI. We have acknowledged this in the study design section lines: 106-107.

C2: The results of the multivariate regression are not convincing. Basically, logistic regression aims to assess factors associated with HAI (potentially risk factors for HAI) compared with CAI. Here, complications are tested to explain the outcome (CAI vs. HAI). In addition, the 30 days outcome might be replace by a single variable (i.e. 0: hospitalized, 1: discharged, 2: readmitted, 3: deceased), readmission might be excluded from the analysis as OR cannot be calculated. I would recommend either to correct with multivariate analysis or to suppress it from the Methods and Results as the main study objective is descriptive.

C3: There is not linear regression (which outcome?) in the result section while it is stated that a linear regression was implemented. It should be corrected. In addition, given the high number of tests, there is an increased risk for falsely significant result, I would recommend either to add a correction method for multiple testing or to limit the number of tests as some results can be only descriptive but not comparative.
C4: L112, Methods: The reference of the logistic regression is not stated. According to the result I suppose that it is HAI, replace it by CAI as a reference would be more interesting. Tested variable might be noted.

C5: L116, Methods: what are the thresholds for multivariate analysis?

R2-5: Thank you for your above comments. Upon review of the statistical methodology used, the classification of HAI and CAI as the ‘exposure’ and multiple outcome measures being tested (in the form of complications), we agree that the most appropriate way to present the data for this study is via crude odds ratios. The multivariate analysis has been suppressed. We have rewritten the statistical methods section in lines: 118-129.

We have also revised the way our data is presented in table form. Table 1 now presents the demographic/exposure factors (independent variable) to demonstrate any differences between groups (CAI/HAI: dependent variable), and table 2 presents the crude odds ratios for outcomes (dependent variable) related to acquisition (CAI/HAI: independent variable).

C6: The inclusion of confirmed cases only is a positive point. However, virological diagnosis tests that were used must be detailed in the Methods section. Was there any change compared with previous year?

R6: We have included details regarding the virological testing. There was no change in testing compared with the previous years. Changes detailed in lines: 94-96.

C7: Incidence rates of HAI are not reported. It would be interesting to report information on the overall incidence or attack rate in the hospital, and if possible by unit (instead of reporting the number of cases (cf. Figure 3). Ideally, a comparison of incidence with previous year would give additional information on the potential increased of HAI cases compared with previous year.

R7: Thank you for your suggestion. We have included the overall incidence rates in the hospital during the study period in comparison to the previous year. Lines: 139-141. Unfortunately we did not have access to unit specific data so were only able to give overall incidence rates.

C8: Figure 4. The incubation period of influenza is not the same than the infectious period (approximately from -1d to +5d after onset), information on the infectiousness compared with the incubation might be added in the manuscript. The synoptic chart is interesting, but it would be useful to add potential transmissions between patients or the infectious period.

R8: Thank you for your suggestion. We have added a sentence in the manuscript detailing the incubation vs infectious period, as in lines: 233-235. We have indicated putative transmission pathways (within ward) in the text lines: 238-241.
As viral shedding may be prolonged in immunocompromised hosts, as well as those with severe influenza and comorbidities, we have not included the post symptom onset infectious period in the synoptic chart as the quoted range may not be applicable to the HAI cases.

C9: L82, Background: The hypothesis and objective is not clearly stated. Please detail this point in this section.

R9: We have stated the objective more clearly in lines: 77-82. As we were not aiming to test a specific hypothesis, we have not included one in the manuscript.

C10: L85, Methods: this is a surveillance based study

R10: We agree with the assessment and have adjusted accordingly in the title and lines: 29 & 86.

C11: L125-6, Results: Was the definition of HAI the same in the previous year?

R11: The definition was the same for the previous years. We have added clarification to this in line: 138.

C12: L150-2, Results: This definition can be moved to the Methods section.

R12: We have moved the definition to the methods section, lines: 101-104.

C13: L184, Results: Were patients moved into double rooms with ILI or influenza case?

R13: We have included the number of patients who were not moved into double rooms with other HAI cases, as in lines: 203-206. Due to internal renovations of the wards since the study period, it was not feasible to determine if the other patients were CAI cases from the hospital records.

C14: Results: It should be useful to have some descriptive data on the hospital: number of admissions /y, type of departments, type of buildings, etc.

R14: We have added some descriptive data in the methods section, in lines: 90-91.

C15: Results: I understand than the surveillance concern only patients, however healthcare workers (HCWs) are important triggers of nosocomial influenza. During your investigations, did you find evidence of HAI among HCWs. Were some symptomatic HCWs tested for influenza. In addition, information on the mean vaccination coverage of HCWs should be interesting.
R15: Thank you for your comment. We agree that HCWs likely play an important role in transmission of HAI. It was difficult to ascertain their involvement as we did not have concrete data regarding evidence of influenza among HCWs. Certainly there was anecdotal data of high rates of medical staff absence on at least one of the affected wards, though given it is anecdotal this was not included. Accessing staff health records was not within the purview of the ethics approval for this study. We do have HCW vaccination rates and have included this in lines: 160-161.

C16: L299, Discussion: epidemiological analysis revealed good concordance with contact studies (RFID) and typing. Please add a corresponding reference.

R16: We have added reference to RFID studies in a suggestion for future research, as in lines: 325-328.

Response to Reviewer 2:

C1: A comment on similar/dissimilar observations from other hospitals in Australia during the same Influenza season.

R1: Thank you for your suggestion. Unfortunately we were not able to comment on similar observations from other hospitals as we did not have access to this data.

C1: Additionally, the acknowledgement that this type of study in order to provide unequivocal interpretations would need to include a wider sampling strategy as well a genomic component as a means of validating observed clustering (e.g. see similar work from Europe: Houlihan CF et al, 2018 J Inf Dis, 218(9)).

R2: Thank you for your comment and the provided reference. We have acknowledged this as a suggestion for future studies in lines: 325-328.

Changes to meet journal requirements:

As requested, we have revised the declarations section to meet the journal requirements. This included adding consent to participate (lines: 347-349), consent for publication (lines: 350-351), and elaborating on the funding section (lines: 359-361).