Reviewer's report

Title: Incidence and characteristics of invasive Staphylococcus aureus infections: a population-based study in 3 regions of Korea, 2009-2011.

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Reviewer: Kevin Laupland

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In this report, Song and colleagues aim to report a population-based study of invasive Staphylococcus aureus infections. This is a significant undertaking. Data is collected from a multiple sites within a large population in Korea during a two-year period. While a number of population-based studies of invasive/bacteremic S. aureus infections have been reported from centers in North America, Europe, Australia/New Zealand, there is a lack of data in this regard from the Asian region.

Population based surveillance studies are ideal to define the epidemiology of an infectious disease. This is because in these designs usually all incident cases of disease occurring in residents of a well-defined (geographically and demographically) population are included and non-residents are excluded. As a result, sampling bias is minimized. Incidence rates can be calculated because the number of cases and population at risk are known.

My main comments regarding this study relate to the population-based design. Many of these have been recognized and discussed by the authors and include:

1. Residency status was not known but estimated for group 2 and 3 patients (ie non-ASC). This is a significant major bias.
2. Only 10/44 hospitals acute care labs participated in the study. These were not randomly selected from the overall cohort and hence represent a major potential (“volunteer”) bias. The number of estimated missed cases (3170) exceeds that of included cases (2806).
3. I am not clear whether there may be any other labs (community based, small hospital, nursing home, minor commercial labs, etc) that process invasive specimens; if so failure to include them imparts a bias. Most previous population-based studies on invasive/bacteremic S. aureus infections have estimated coverage of 90-100% of all labs in a region.
4. Surveillance regions were not captive. As many as one half of patients in one of the regions (Goyang) seek care elsewhere.
5. The detailed clinical data is obtained from the ASC academic cohort. These patients have been demonstrated in multiple studies to be markedly different from patients in populations at large. Inclusion of all patients, with minimization of selection bias is a major key aspect of population-based studies for which this study does not fulfill.
6. It is not clear if the same criterion to define a resident (is this a postal code, census tract, community name etc) is matched to the denominator data.

7. Audit was performed at ASC but not in the same degree at the other labs. It is known that audit frequently identifies different incident cases as compared to passive report.

8. The results report an estimated rate for all of Korea. Sampling of surveillance regions within Korea was not random. Intra-regional variability occurs within countries. While such an estimate is reasonable to propose, in my opinion this should not be part of the study results but suggested in the discussion.

9. It is not clear as to how the issue of duplicates were handled. For example, if a patient had a MSSA infection with positive cultures of blood (days 1, 3, 5) and pleural fluid (day 4), negative on both on day 7 positive blood again on day 18 following completion of antibiotics, then recurrence 3 months later with septic arthritis due to MSSA and 3 months later MRSA bacteremia, was this considered 1, 2, 3, or 4 incident infections within that year?

This study represents a significant effort for which the authors are commended. However, the majority of the results of the paper are based on the non-population based ASC cohort, with only a small proportion of the study focused on the overall population-based cohort (one sentence of the results in the abstract; first two paragraphs of the main results and Table 1). Given this, and the multiple limitations in design as detailed above, in my opinion, this is questionably a population-based study. Rather, I would consider this a multi-centered cohort study with an attempt to estimate population-based incidence rates.

To this end it is my recommendation that the title of the paper be changed to remove reference to population based design. Furthermore, the text should also be reorganized to indicate that the incidence data were based on a significant number of estimates and assumptions/presumptions. The estimating criteria should be explicitly stated in the methods. Alternatively, the paper could be presented as a multi-centred cohort study with incidence estimate data reserved for presentation in the discussion.