Letter to the editor

Regarding Ong SWX, Zhabokritsky A, Daneman N, Tong SYC, Wijeysundera HC, Evaluating the use of 18F-FDG PET/CT in the workup of Staphylococcus aureus bacteraemia: a cost utility analysis, Clinical Microbiology and Infection, https://doi.org/10.1016/j.cmi.2023.06.022.

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To the editor

We were delighted to read O*ng et al.* in Clinical Microbiology and Infection continuing to extend information on the utility of 18F-FDG PET/CT in *S. aureas* bacteraemia (SAB) beyond nuclear medicine specialists into the infectious diseases community (1). In our recent systematic review of the use of 18F-FDG PET/CT in bacteraemia we found 9 of 10 articles had a first author from an infectious diseases background whilst only 3 of 10 were published in an infectious diseases journal (2). From a similar contemporaneous analysis Buis et al. found that all the articles included in their meta-analysis on SAB specifically were written by infection specialists but 60% (3 of 5) were in nuclear medicine journals (3).

We welcome this cost-effectiveness evaluation study, which is much needed to reflect on how the identification of cases for treatment is improved, in light of the trade-offs between the risks of untreated sepsis and concerns with antibiotic resistance. However, we'd like to highlight that the

findings of this study may differ somewhat across other settings, countries and health systems, beyond the resource use and costs specific to Canada.

In the UK we collect data on SAB via a mandatory surveillance system (4). These data characterise the population of individuals diagnosed with SAB in the UK. The comparison with the population modelled by Ong et al reveals meaningful differences. The reference case in their modelling is a 50-year-old man. However, in England data reveals SAB to be most frequent in men over 85 years of age, with most reported cases in absolute numbers in the 75-84 year old age range (4). We note that the authors have provided supplementary figures referring to patients in the age range 40-80 and report that the cost-effectiveness of the intervention persists at a mean age of 65 which is reassuring, though associated with a lower cost effectiveness at advanced age, as might be expected due to the reduced subsequent life expectancy. Additionally, the 50% rates of MRSA in bacteraemia modelled by Ong et al is fortunately not the case in the UK where the mandatory reports of SAB in 2021/2022 found a significantly lower rate of only 5% (4). This is likely to have a significant impact over the cost-effectiveness of 18F-FDG PET/CT.

Additionally, and as highlighted by the authors, the evidence on the accuracy of 18F-FDG PET/CT in SAB (i.e. its sensitivity and specificity) is unclear. Accuracy is challenging to quantify due to the lack of a reference gold standard. Specificity in cancer studies may suggest that a biopsy sample showed evidence of the malignancy; however, biopsy is not routine for lesions revealed on 18F-FDG PET/CT in SAB. Clinical experience has shown that it is rare that a biopsy reveals *S. aureus* and when it does one wonders if it should have been avoided and was clinically unnecessary as the risk of the procedure might have been outweighed by the risk of prolonged antibiotic therapy and monitoring (5). The cost-effectiveness model, despite grounded on diagnostic accuracy evidence, does not consider the limitations of this evidence, and its conclusions can therefore only be tentative.

A frequent finding in whole body imaging, including 18F-FDG PET/CT, is incidental nodules or lesions requiring further investigation. Adding this cost to the model could contribute to the accurate portrayal of the cost of investigations. For sensitivity this is complex. A 'hot spot' on a 18F-FDG PET/CT scan may be from infection or non-infective inflammation. Differentiating between infectious foci and non-infective inflammation can be complex and verification can be lacking, for example when the 18F-FDG PET/CT signal occurs post-surgery. Cost effectiveness may be compared to other potential investigations such as MRI, with the baseline rate of such investigations included in the analysis. Costs of confirmatory tests such as an MRI for equivocal 18F-FDG PET/CT results should be included in the economic modelling.

In conclusion, the cost effectiveness of 18F-FDG PET/CT in SAB is complex. First, clear specification of the patient population of relevance is required, which is likely to vary across countries and healthcare systems. The population represented here significantly differs from those eligible UK. Additionally, whilst the current evaluation has considered how 18F-FDG PET/CT may alter the diagnostic pathway (either savings potentially made on alternative imaging modalities or higher due to additional procedures), it did not consider tests, clinic appointments and even treatment needed following incidental findings on 18F-FDG PET/CT. Additionally, the limitations of the diagnostic accuracy evidence, over which the cost-effectiveness model is grounded, should be explicitly recognised.

Nevertheless, we congratulate the authors on their study. We feel that the primary use of this evaluation should have focussed on setting relevant research priorities for an important clinical question. We agree further investigation on this topic is essential, as highlighted by *Song et al*.

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