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## Response to Letter from Prof. A. Smith et al.

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### Keywords:

Antibiotic stewardship, adverse drug reactions, allergy, infection, amoxicillin, phenoxymethylpenicillin

### Abbreviations:

Adverse reaction (AR)  
Medicines and Health Regulatory Agency (MHRA)  
National Health Service (NHS)  
United Kingdom (UK)

Dear Prof. Giannobile

Prof. Andrew Smith and colleagues,(Smith et al. 2020) focus on the adverse reaction (AR) data limitations listed by the MHRA but omit to mention the crucial second sentence of item-1: “....*This is because we have limited information about how many people have taken the medicine without experiencing a reaction.*” By combining each antibiotic’s prescribing-data with its AR-data, we accounted for this.(Thornhill et al. 2019) MHRA Point-1 was, therefore, addressed by the study methodology and the other points in the Discussions ‘Limitations’ section. We also recognise that an AR report in the Interactive Drug Analysis Profile does not necessarily mean that medication caused the reaction.

The prescribing data was for England and corrected annually for population size to match the AR-data, which was for the UK. As stated in the ‘Methods’, it did not capture private-prescribing. Private-practice, however, does not correlate with private-prescribing. The majority of antibiotic-prescribing occurs during NHS-covered emergency and essential dental-treatment rather than cosmetic and non-essential dentistry, which accounts for most private-practice. Furthermore, the AR-risk with private and NHS-prescriptions should not substantially differ.

They also focused on the higher AR-rate observed with phenoxymethylpenicillin than amoxicillin. The reasons for this difference are unclear but probably relate to the different minor antigenic-determinants of each. The role of these in penicillin allergy has been extensively studied (Adkinson et al. 2018; Blanca 1995) and is thought to explain why some individuals are allergic to phenoxymethylpenicillin but not amoxicillin (Blanca et al. 1990) and *vice versa*.(Blanca 1995) The paper’s length constraints prevented us fully addressing

this and other interesting topics, including narrow-spectrum antibiotics and antimicrobial stewardship.

Despite their limitations, studies like this provide the best estimates currently available of the AR-risk with different antibiotics.

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Author Thornhill M.H: Contributed to conception and drafted manuscript.

Author Dayer M.J: Contributed to conception and critically revised manuscript.

Author Durkin, M.J: Contributed to conception and critically revised manuscript.

Author Lockhart P.B: Contributed to conception and critically revised manuscript.

Author Baddour L.M: Contributed to conception and critically revised manuscript.

All authors gave their final approval and agree to be accountable for all aspects of the work

### **Conflicts of Interest Statement:**

The authors report no conflicts of interest.

### **References:**

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