Correspondence (letter to the editor)

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Dear Editor

The study by Vahasarja et al. concluded that "the current Swedish recommendation not to administer antibiotic prophylaxis (AP) for the prevention of infective endocarditis (IE) in dentistry has not led to an increased incidence of VGS-IE among high-risk individuals." and "AP in dentistry for the prevention of IE may be discontinued".[1] However, we do not believe their data support these conclusions. Although they provide data showing no IE-incidence increase following the October 2012 Swedish recommendation to stop AP, their AP-prescribing data are lacking. They refer to the Swedres-Svarm reports, which show amoxicillin prescribing fell 37% from 3.01 to 1.90 prescriptions/1000 inhabitants/year between 2012-2017. However, the Swedres-Svarm reports make no distinction between therapeutic- and AP-related amoxicillin prescribing, and dentists more frequently prescribe amoxicillin to treat dentoalveolar and other orofacial infections than for AP purposes. Moreover, the Swedres-Svarm data show that dental prescribing of all antibiotics fell in this time period (Figure 1), particularly penicillin-V, probably due to antimicrobial stewardship efforts.[2] Furthermore, even if all amoxicillin prescriptions were for AP, because data were not linked to individual patients and procedures, it is impossible to know if residual amoxicillin prescribing was targeted at high-IE risk individuals for AP purposes. If this were the case, then the lack of IE-incidence increase could indicate AP effectiveness rather than ineffectiveness.

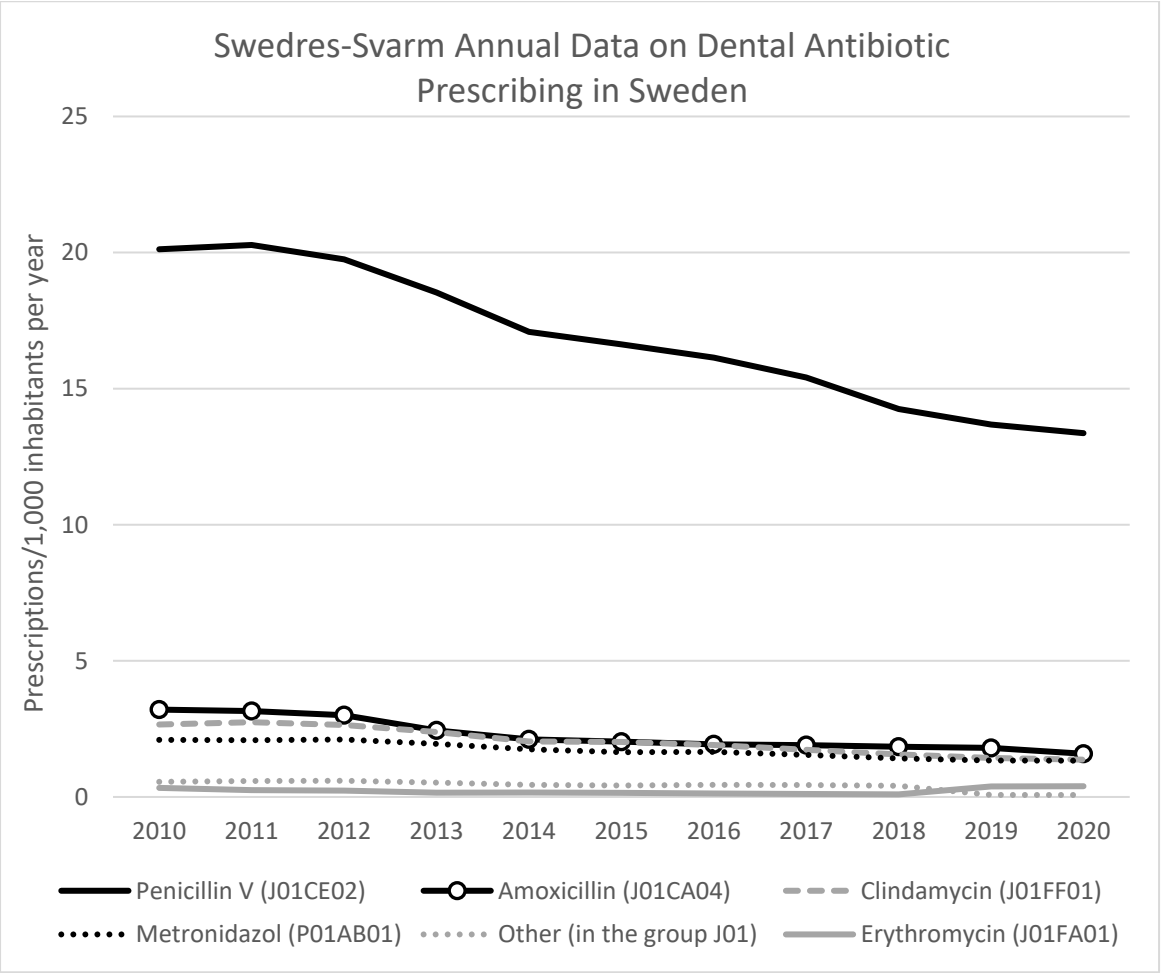
Even if the prescribing data accurately reflected AP use, the lack of effect of AP reduction on IE-incidence could easily be explained by a lack of power to detect an effect. A similar UK study following the 2008 NICE cessation of AP recommendation[3] included a 56 million population with a 78.6% fall in AP-prescribing with no effect on IE incidence.[4] The study

was criticised for being underpowered, having insufficient follow-up and the possibility that residual AP-prescribing was targeted at those at highest IE-risk, hiding any effect of AP reduction. The study was repeated with a further three years data (by which time AP-prescribing had fallen 88%). This transformed a study underpowered to detect a significant change into one that detected a significant increase in IE incidence (0.11 cases per 10 million people/month above the previous trend, 95% CI 0.05-0.16, $p<0.001$), amounting to an extra 35 IE-cases per month.[5] If a study of 56 million with a 78.6% fall in AP-prescribing was underpowered, one wonders if a study of 10 million with an uncertain 37% fall in AP-prescribing would have sufficient power to detect a clinically significant effect. We believe studies concluding no effect should be accompanied by a power calculation to demonstrate they can detect a clinically significant effect, should it exist.

Of note, a recent case-crossover and cohort study demonstrated a significant association between invasive dental procedures and IE in those at high IE-risk and AP effectiveness in reducing IE-incidence following such procedures.[6]

In conclusion, the lack of data specifically quantifying AP use and the potential lack of sufficient power, makes it impossible for the authors to draw the conclusions that they did. The conclusions could therefore be misleading to patients, clinicians, and guidelines committees.

Figure 1.


Swedres-Svarm Annual Data on Dental Antibiotic Prescribing in Sweden
Prescriptions/1,000 inhabitants per year
25
20
15
10
5
0
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
2020
Penicillin V (J01CE02)
Amoxicillin (J01CA04)
Clindamycin (J01FF01)
Metronidazol (P01AB01)
Other (in the group J01)
Erythromycin (J01FA01)

References

1. Vahasarja N, Lund B, Ternhag A, et al. Infective endocarditis among high-risk individuals - before and after the cessation of antibiotic prophylaxis in dentistry: a national cohort study. Clinical infectious diseases **2022**. Feb 4;ciac095. doi: 10.1093/cid/ciac095. Online ahead of print.
2. Public Health Agency of Sweden, National Veterinary Institute. Swedres-Svarm Reports - Annual reports on Swedish antibiotic sales and resistance in human medicine (Swedres) and Swedish veterinary antibiotic resistance monitoring (Svarm). Available at: https://www.sva.se/en/our-topics/antibiotics/svarm-resistance-monitoring/swedres-svarm-reports/. Accessed Sept 18, 2022.
3. National Institute for Health and Care Excellence (NICE). Prophylaxis against infective endocarditis. Clinical Guideline [CG64]. Available at: http://www.nice.org.uk/guidance/cg64. Accessed March 2008.
4. Thornhill MH, Dayer MJ, Forde JM, et al. Impact of the NICE guideline recommending cessation of antibiotic prophylaxis for prevention of infective endocarditis: before and after study. Bmj **2011**; 342: d2392.
5. Dayer MJ, Jones S, Prendergast B, Baddour LM, Lockhart PB, Thornhill MH. Incidence of infective endocarditis in England, 2000-13: a secular trend, interrupted time-series analysis. Lancet **2015**; 385(9974): 1219-28.
6. Thornhill MH, Gibson TB, Yoon F, et al. Antibiotic Prophylaxis Against Infective Endocarditis Before Invasive Dental Procedures. J Am Coll Cardiol **2022**; 80(11): 1029-41.

Footnotes:

1. **Funding Sources.** There are no funding sources for this correspondence.

2. **Conflicts of interest.** Prof. Thornhill is in receipt of grant funding support from Delta Dental Research and Data Institute of Michigan and the National Institutes for Health (USA) unconnected with the submitted work. Dr Dayer reports support from Biotronik in the last three years, which was unconnected to the submitted work. Dr Prendergast reports unrestricted research and educational grants from Edwards LifeSciences, lecture fees from Abbott, Anteris and Edwards Lifesciences, and has received consultancy fees whilst serving on the Scientific Advisory Board for Anteris and Microport (all unconnected to the submitted work). Dr Lockhart is in receipt of grant funding from the National Institutes for Health unconnected with the submitted work. Dr Baddour has received royalty payments (authorship duties) from UpToDate, Inc., and consulting fees from Boston Scientific and Roivant Sciences (all unconnected to the submitted work). None of the other authors reports a financial relationship in the previous three years with companies that might have an interest in the submitted work.

Prof. Thornhill has no nonfinancial interests relevant to the submitted work. Drs Baddour and Lockhart were members of the American Heart Association Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease and were involved in drafting the 2007 and 2021 American Heart Association guidelines on the prevention of infective endocarditis. Dr Dayer was a consultant to the review committee that produced the 2015 update to NICE clinical guideline 64 on prophylaxis against infective endocarditis. Dr Prendergast was a member of the Task Force on the Prevention, Diagnosis and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC) that produced the 2009 ESC guidelines and acted as an

external advisor to the committee that produced the NICE clinical guideline 64 on Prophylaxis Against Infective Endocarditis in March 2008.