On the reporting of efficacy results for CIN3+ irrespective of HPV type, we clearly state in the discussion that although CIN2+ is the main endpoint used in licensure studies in young women, VIVIANE was not powered to assess vaccine efficacy against CIN2+ because of its infrequent occurrence in adult women. We did not show efficacy for CIN2+ irrespective of HPV type, thus analysis of CIN3+, a subset of the CIN2+ cases, would not have been meaningful. However, CIN3+ case numbers by group were reported even though the numbers in both groups were similar. A formal statistical analysis of efficacy would have added nothing.

Finally, the complete clinical study reports for the study's interim and final analyses, as well as the anonymised patient-level dataset, are available to interested researchers.[2,3] We therefore believe that we are comprehensive and transparent in disclosing the results of this trial.

CMW's institution received from the GSK group of companies a contract for the clinical trial site and reimbursements for travel related to publication activities and for HPV vaccine studies. CMW's institution has also received equipment and reagents for HPV genotyping studies from Roche Molecular Systems. FS is an employee of the GSK group of companies and holds shares in the GSK group of companies. CMW and FS prepared the response on behalf of the VIVIANE study group. GlaxoSmithKline Biologicals SA covered development and publication costs associated with this response.

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Pneumococcal conjugate vaccines in different settings

We generally assume that a vaccine should have similar effects in comparable epidemiological settings. For this reason, the apparent geographical differences between high-income countries in the extent of replacement invasive pneumococcal disease (IPD) following pneumococcal conjugate vaccine (PCV) introduction, particularly in people aged 65 years and older, are puzzling,[1] and worthy of Joseph Lewnard and William Hanage's excellent reflections.[2] However, I believe the authors overlooked one marker of potentially significant differences in patient populations between the different settings.

Previous studies had noted that the much higher paediatric IPD incidence in the USA than in most other high-income countries was probably attributable to a much greater frequency of blood culturing of febrile children in US ambulatory settings. It was suggested that the singular inclusion of many mild IPD cases in the US setting might help in the interpretation of some hitherto puzzling geographical differences in reported serotype distribution.[3]

In the present analysis, the authors dismissed the possibility that the population of adults aged 65 years and older with IPD in the USA includes a relatively higher proportion of milder disease than in the UK, noting that only 6% of US patients with IPD in that age group were outpatients. Furthermore, the authors pointed out that since 2015, UK IPD incidence in adults aged 65 years and older has been actually higher than in the USA.

Unfortunately, clear interpretation of incidence from 2015 and beyond is obscured by 10–15 years of prior PCV use. A different story might emerge with the use of data from the dawn of the PCV era (figure). Pre-PCV IPD incidence in those aged 65 years and older in the USA (and Norway and Denmark) were substantially higher than in several other countries. These differences appear to correlate with the magnitude of the decrease in overall IPD incidence (figure).

It is not clear how differences in patients treated in hospital—if that is what these data reflect—might translate into differences in replacement disease. We know that in children the PCV-induced nasopharyngeal replacement of vaccine types with non-vaccine types is largely a replacement of highly invasive with much less invasive serotypes—often 1000 times less invasive. As a consequence, one would expect and sees much less IPD in the post-PCV era. In older adults, however, differences in the relative invasiveness of non-vaccine and vaccine types

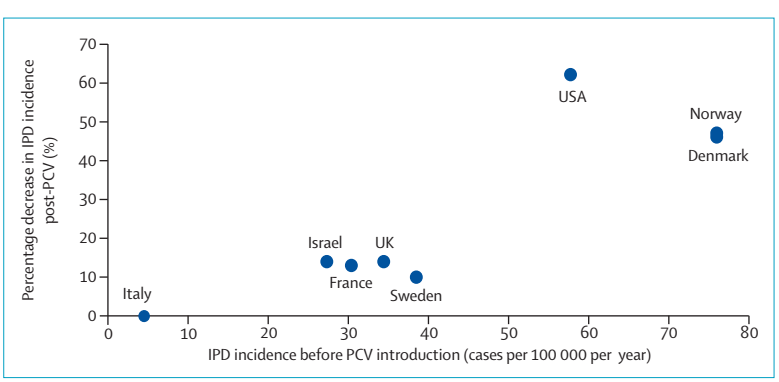

Figure: **Association of pre-PCV IPD incidence with post-PCV percentage decrease in IPD in adults aged 65 years and older**
Data extracted from country-specific graphs in reference 2. PCV=pneumococcal conjugate vaccine. IPD=invasive pneumococcal disease.

seem much less stark.[4] This might be predicted to lead to proportionately more replacement disease after PCV in that age group, the extent of which might further vary by patient population characteristics. At least worthy of further investigation.

I declare no competing interests.

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Authors' reply

We are grateful to William P Hausdorff for his interesting letter[1] regarding our Personal View[2] on the perplexing variation in the extent of pneumococcal serotype replacement, especially among adults aged 65 years and older, suggesting a role for systematic differences in surveillance and the severity of the underlying invasive pneumococcal disease (IPD). It is true that differences in blood culturing practices can influence estimates of IPD incidence, and the serotype distribution associated with IPD. A systematic difference in the reduction in IPD incidence following pneumococcal conjugate vaccine (PCV) implementation might be explained by differences in the nature of the disease measured in each place, coupled with differences in the way PCVs affected the serotypes associated with those disease manifestations.

The correlation plotted by Hausdorff would suggest that surveillance systems capturing a broader spectrum of clinical illness (such as that in the USA) might report larger reductions in cases because of the prevention of milder illness, with severe cases persisting. However, a pronounced drop in IPD among older adults followed PCV7 implementation in both the USA and the UK.[3,4] It is only following PCV13 that these patterns have diverged, with incidence appearing to stabilise in the USA but increasing, to the time of writing, in the UK.[2]

Puzzlingly, these observations cannot be reconciled with the logic of severity alone. If the reduction in the USA is due to the removal of less severe disease, then why was the initial effect of PCV7 similar in the UK, which according to this hypothesis underestimates the incidence of milder infections? And then if, following PCV13, there has been an increase in severe disease in the UK, why has there been no similar increase in the USA, where surveillance should be more than capable of detecting it alongside milder infections?

In short, the mystery remains. As Hausdorff argues, how pneumococcal serotypes vary in the nature and severity of disease in the older population has been hitherto neglected.[5] Why carried serotypes would cause disease among older adults in the UK, but curiously not the USA, is an issue that we agree wholeheartedly should be addressed. Studies of colonisation, transmission, and disease progression among older adults are warranted to identify epidemiological dynamics at play. The continuing discussion and ongoing observation of replacement illustrates the importance of this work to basic science and public health.

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Identification of *Streptococcus pyogenes* $M1_{UK}$ clone in Canada

Nicola Lynskey and colleagues[1] reported on the rapid emergence of a new group A streptococcus (GAS) *emm*1 lineage in the UK ($M1_{UK}$), which was characterised by increased production of the SpeA toxin. Isolates were associated with scarlet fever cases and invasive *emm*1 cases, providing a possible explanation for the increased incidence of invasive GAS disease in the UK. Despite numerous large-scale genomic studies examining the association between genetic variation and virulence, the exact reasons for the recurrent epidemics of invasive GAS disease remain unresolved.[2,3]

The $M1_{UK}$ strain was found to differ from pandemic *emm*1 ($M1_{global}$) by 27 key single-nucleotide polymorphisms (SNPs). Of all the GAS genomes available in the published global genomic databases, only single $M1_{UK}$ clones were identified, in Denmark and the USA.[1]

From 2010 to 2017, the incidence of invasive GAS cases increased in Canada by 63%, from 4·1 cases per 100 000 population to 6·7 cases per 100 000 population.[4] Laboratory-based surveillance for invasive GAS *emm* types and antimicrobial resistance has been