greater (CIN2+) and grade 3 or greater (CIN3+) and adenocarcinoma in situ. To date, the VIVIANE trial is the study with the longest duration of follow-up (up to 7 years). Despite the participants being older than 25 years, in the according-to-protocol cohort for efficacy, 56·5% of participants in the vaccinated group and 56·5% of participants in the control group were DNA-negative and seronegative for both HPV 16 and 18. In the total vaccinated cohort, 57·3% of participants included in the vaccinated group and 54·0% of participants included in the control group were DNA-negative and seronegative for both HPV 16 and 18. We are therefore surprised that the authors do not provide specific information and analyses that might be relevant to these patients.

Since the vaccine did not show any effect on the rate of all CIN2+ irrespective of HPV type (table 4 in the Article[2]), the vaccine's effect among women who were DNA-negative and seronegative for HPV 16/18 would be interesting to know. Even post-hoc and subject to certain limitations, this analysis would have had the merit of providing valuable insight into the effectiveness that might be expected from HPV routine vaccination in girls. Indeed, these results might represent the best approximation available to date of HPV routine vaccine efficacy in uninfected women because the vaccine is ineffective in women already infected and therefore not therapeutic.[3]

Similarly, the authors mention that there were 50 CIN3+ cases (including four women with adenocarcinoma in situ) in the group of vaccinated women and 45 CIN3+ (one woman with adenocarcinoma in situ) in the unvaccinated group. To our knowledge, we are the first to point out these results, which is surprising given their clinical relevance: CIN3+ and adenocarcinoma in situ are the precancerous lesions that are least likely to regress spontaneously.[4,5]

This result has not been analysed statistically, but the relative risk for CIN3+ can be calculated as 1·11 (95% CI 0·75–1·66) and for adenocarcinoma in situ as 4·00 (0·45–35·79). These data do not show any efficacy for the vaccine in preventing high-grade cervical lesions. These results have not been commented on by the authors, but their relevance is obvious.

For the sake of transparency, the authors should present, analyse, and comment on all the data. Beyond this single publication, the existence of these results raises the question of the validity of the method and conclusions of Cochrane meta-analysis,[1] where they have not been considered.

CR co-founded Re-Check, a non-profit organisation specialised in investigating and mapping health affairs. CR and J-PS are co-authors of an investigative book on the HPV vaccination ("La piqûre de trop?", Xenia, 2010) and published four investigations in Swiss mainstream media on HPV vaccine. CR and J-PS co-authored a comment on Cochrane HPV vaccine MA's methodology and a Letter to Editor on this topic in *British Medical Journal* and *EBioMedicine*. RB and CM-T declare no competing interests.

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Authors' reply

Although we agree that cervical intraepithelial neoplasia grade 2 or greater (CIN2+) and grade 3 or greater (CIN3+) are essential clinical endpoints in vaccine efficacy studies for HPV, we disagree with Rémy Boussageon and colleagues on several points.

The authors claim that we do not provide specific information and analyses that might be relevant to patients. In line with good publication practice, we focused our Article[1] on the reporting of the results of the prespecified primary and secondary endpoints of the trial, which reflect what the trial was designed for. The comment that it would have been interesting to know the vaccine's effect among women who were DNA-negative and seronegative for HPV 16/18 is puzzling and suggests little understanding of the analysis cohorts. As outlined in the methods, the appendix, and the discussion, the according-to-protocol cohort for efficacy was the primary analysis cohort for efficacy. Endpoints related to HPV 16/18 were evaluated in women who were DNA-negative and seronegative for the corresponding HPV type at month 0 and DNA-negative at month 6. We strongly disagree with the suggestion that this DNA negative and seronegative subset of women aged 26–72 years would represent the effectiveness expected from HPV routine vaccination in adolescent girls. Besides HPV DNA and serostatus, the biology and epidemiology of HPV infection are very different in adult women versus the adolescent target population. The proportion of women in our trial who had received previous treatment for HPV 16/18 at baseline is typical for this age group in the general population.

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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1 Wheeler CM, Skinner SR, Del Rosario-Raymundo MR, et al. Efficacy, safety, and immunogenicity of the human papillomavirus 16/18 AS04-adjuvanted vaccine in women older than 25 years: 7-year follow-up of the phase 3, double-blind, randomised controlled VIVIANE study. *Lancet Infect Dis* 2016; **16:** 1154–68.

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3 Clinical Study Data Request. Study ID: 104820. https://clinicalstudydatarequest.com/SearchAllPostings.aspx?searchparam=104820 (accessed Sept 2, 2019).

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

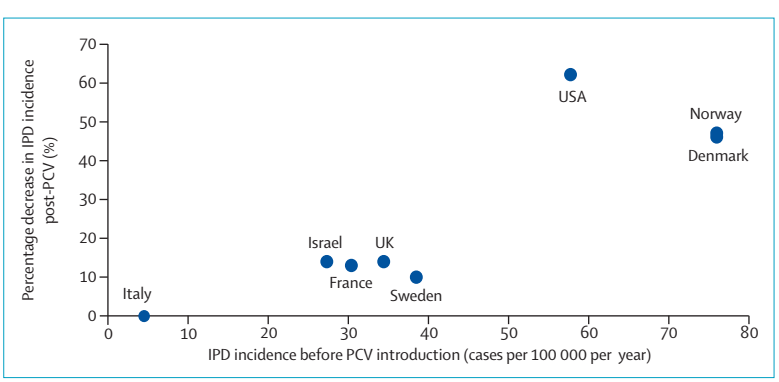

Figure: **Association of pre-PCV IPD incidence with post-PCV percentage decrease in IPD in adults aged 65 years and older**
Data extracted from country-specific graphs in reference 2. PCV=pneumococcal conjugate vaccine. IPD=invasive pneumococcal disease.