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Matters arising

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Reply to: Methodological Issues in Taquet et al.'s analysis preclude any conclusions regarding AS01 adjuvant's specific role in dementia prevention

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In our study[1], we compared the risk of dementia between matched cohorts of patients who received AS01-adjuvanted vaccines (against shingles and/or RSV) with those who received non-adjuvanted vaccines. Taken together with our natural experiment comparing the recombinant (AS01-adjuvanted; Shingrix, GSK) and live (Zostavax, Merck) shingles vaccines[2], and with other published studies, these findings "provide support for the hypothesis that [AS01] vaccines could well protect against dementia via the action of the AS01 components". We suggest that this conclusion is appropriately cautious and nuanced given the nature of the data.

Our reasoning to suggest a potential role for AS01 in this protection proceeds as follows:

1. In our natural experiment, we found causal evidence that the AS01-adjuvanted shingles vaccine leads to a lower risk of dementia than the live shingles vaccine. This could be explained by more effective prevention of shingles and/or by the presence of AS01, the key distinguishing component.
2. If AS01 contributes to the protection against dementia, then the AS01-adjuvanted RSV vaccine should also reduce dementia risk. We observed this when comparing it with the influenza vaccine (another commonly used vaccine in the elderly) in the present study.
3. If the AS01 effect is genuine, then a biological mechanism ought to underpin it. Evidence from animal studies support this; notably, systemic injection of an AS01 component reduced cerebral amyloid β in an Alzheimer's disease mouse model and improved their cognition[3]. This mechanistic explanation remains speculative as results from animal models do not always translate to humans.

The cornerstone of this reasoning is the first point (i.e., the natural experiment evidence showing a greater reduction in dementia risk with Shingrix compared to Zostavax). By omitting it from their summary table and focusing only on the *observational* comparisons between shingles vaccination and dementia, which we agree are at risk of confounding, Williams et al. gave an incomplete representation of the available evidence. Natural experiments cannot completely rule out the risk of unmeasured confounding, but strongly decrease that risk compared to more conventional cohort studies. In our natural experiment, we compared people vaccinated after October 2017 with those vaccinated just before that date, regardless of vaccine type (Shingrix or Zostavax). There is no obvious reason for systematic differences across this time cutoff, so vaccination timing functions as a quasi-random assignment, minimizing confounding. This design is less prone to bias than a conventional cohort that directly compares recipients of different shingles vaccines. In addition, by comparing two vaccinated cohorts, our studies avoid the healthy vaccinee bias, i.e., the confounding that arises when people who seek vaccination (typically healthier at baseline) are compared with people who do not.

We agree that a direct comparison between the AS01-adjuvanted RSV vaccine (Arexvy, GSK) and the RSVpreF vaccine (Abrysvo, Pfizer) would have been stronger evidence for the second step of the reasoning. Unfortunately, as brand names were not consistently available in patient records, we lacked the statistical power for this analysis.

It is entirely possible that several vaccines reduce dementia risk. This possibility is not at odds with the possibility that AS01 contributes to and enhances the effect. Indeed, in terms of shingles vaccination, there is causal evidence from natural experiments[2,4,5] that *both* the live and recombinant shingles vaccines protect against dementia (albeit with the latter providing stronger protection[2]).

Other points made by Williams et al., while clearly important, were already made in our original manuscript. For instance, we already discussed the possibility of a saturation effect explaining the lack of a dose-response relationship.

In summary, there is growing evidence that several vaccines protect against dementia. As we noted, the mechanisms underpinning this protection remain to be determined. Our study provides some support for the possibility that AS01 may play a role in this protection. We agree that further mechanistic studies and, ideally, randomized clinical trials are needed in order to answer this question clearly.

Data availability

No datasets were generated or analysed during the current study.

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Author contributions

M.T. drafted the first version of the response with input from P.J.H. and J.A.T. All authors critically revised the manuscript for important intellectual content.

Competing interests

J.A.T. is a consultant for GSK and co-director of the Oxford-GSK Institute for Molecular and Computational Medicine. GSK had no involvement of any kind in this study. The other authors declare no competing interests.

Additional information

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