Redirected vaccine imprinting by co-administration of COVID-19 and influenza vaccines

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Over the past two years it has become evident that the winter months can bring devastating triple-peaks of COVID-19, influenza and RSV, with potential to add to excess mortality and stretch healthcare provision. A number of studies, straddling different countries, age-groups, and combinations of different influenza vaccines and COVID-19 boosters have now reported on findings with respect to co-administering the two vaccines compared to giving one or the other first.[1–5] The endpoints have comprised adverse event profiles and immunogenicity, although with no data as yet on efficacy. A new addition to this important dataset comes with publication of the TACTIC study – over-60s given Pfizer mRNA booster first and quadrivalent influenza vaccine 3-weeks later, quadrivalent influenza vaccine with Pfizer booster 3-weeks later, both simultaneously or Pfizer mRNA booster alone.[6] Collectively, previous studies had reassured that co-administration was generally non-inferior to individual vaccines, but as the new TACTIC study from Dulfer and colleagues shows the devil is in the detail.

TACTIC enrolled 154 individuals over 60 years of age into a single-blind, placebo-controlled randomized clinical trial comparing previously fully COVID-19 vaccinated individuals in COVID-19/influenza booster regimens as follows: quadrivalent influenza (Vaxigrip Tetra) followed by Pfizer (BNT162b2) booster 3-weeks later, Pfizer booster followed 3-weeks later by influenza vaccination, co-administration of the two vaccines or COVID-19 booster only (reference group). The authors report antibody binding data for ancestral spike and neutralizing antibody data against spike D614G, Delta and BA.1 Omicron variants of concern. Importantly, this study found that co-administration compared to booster vaccination alone did not meet the predefined criteria for non-inferiority for the primary outcome of IgG binding against spike protein of SARS-CoV-2 and showed less potent neutralization against Delta and Omicron BA.1 variants.[6] That is, when using an immunological assay of greater current, functional relevance to protection than simple antibody-binding assays to the original spike protein, the study finds a significantly reduced response.

The published datasets addressing this issue have most commonly considered adverse event (AE) profiles, spike antibody binding assays and, in some cases such as this study, functional assays of virus neutralization. The breadth of studies now encompass: flu vaccination in the form of trivalent or tetravalent as well as adjuvanted MF59C, and COVID-19 vaccines, either at 2nd or 3rd dose, of Pfizer, Moderna, AstraZeneca or Novavax.[1–5] The trend across these studies is that influenza antibody responses tend to be unaltered by simultaneous administration, while the IgG response to SARS-CoV-2 spike is generally unaltered or non-significantly reduced – that is, geometric mean ratios between concomitant and separate administration was always greater than 0.67, the cut-off used by WHO in defining vaccine non-inferiority. The TACTIC study, however, finds less potent cross-neutralizing antibody responses against variants of concern and failed to show non-inferiority for antibody binding against ancestral spike.[6]

The authors cite immune interference as a possible mechanism for this. The concept of 'vaccine interference' derives from studies in the late 1990s on paediatric co-administration of live-attenuated vaccines, notably the live-attenuated oral polio vaccine given together with live rotavirus vaccine, though even in this specific setting, response perturbation was only variably seen.[7] Furthermore, in paediatric co-administration of LIAIV and MMR Priorix, a significantly reduced response to the Rubella component was seen.[8] These unpredictable viral interactions of live vaccines have not been well-characterised at an immunological level, and certainly, there is little rationale for extrapolating such effects beyond the interactions of live vaccines into the current sphere of mRNA, protein and adenoviral vectored vaccines.[9]

Against this backdrop, what should we infer from what is perhaps the most striking and novel observation in the new, TACTIC study? That is the finding from assays of antibody neutralization titre against live SARS-CoV-2 virus, either D614G, Delta, or Omicron, that for

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cross-reactive neutralization of the variants, giving influenza vaccine and COVID-19 booster simultaneously quite significantly blunts the response.[6] So, this is a case where the choice to co-administer vaccines yields a response to current variants that for some, may drop below the protective cut-off. The reason for this likely goes to the heart of the differential immune priming with these different vaccine regimens. The specific antibody sequences capable of cross-neutralization of Delta and Omicron epitopes are a subset of all those picked up in the binding assay. The assumption must therefore be that co-administration of the two vaccines has nudged the immune imprinting of the antibody repertoire – the way in which selection from a complex repertoire of diverse B cell clones is tweaked by sequential exposures to related sequences[10,11] – away from Delta and Omicron-neutralising epitope specificities.

While a number of studies show marginally diminished immunity to spike in COVID-19/influenza co-administration protocols, the diminished Delta and Omicron neutralization data shown here is the most noteworthy. Whether the public health advantage of the convenience of co-administration (and thus potentially greater compliance) outweighs any loss in COVID-19 vaccine immunogenicity against current or future variants of concern will need to be further evaluated. The interesting question is how to explain the demonstrable interplay between concurrent vaccines, presumably targeted by non-overlapping repertoires of B cells. The old observation of 'vaccine interference' between live attenuated viruses is poorly resolved at a mechanistic level. The observations reported in the TACTIC study following concurrent influenza and COVID-19 booster vaccination seem to be a distinct phenomenon. While this is further investigated, and in order to distinguish from the somewhat confusing term of 'vaccine interference' we propose a working term of 'redirected vaccine imprinting'.

Contributors

RJB and DMA reviewed the related literature and wrote the manuscript.

Declaration of interests

DMA has received honoraria for consultancies with AstraZeneca, Pfizer and Novavax.

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