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Should we be clinically assessing antibody responses to covid vaccines in immunocompromised people?

Serological testing to assess for a vaccine response would be a step towards providing more tailored care for immunocompromised people

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The UK government has decreed that we must all now "live with covid." All mandated isolation measures have ceased in England, free lateral flow testing for all has come to an end, and plans are in motion to scale back the surveillance programmes that have been instrumental in predicting covid waves, new variants, and vaccine efficacy. Notably absent from this bold strategy is practical guidance for the protection and mitigation of ongoing risk for people who were previously deemed to be clinically extremely vulnerable. This has left the 500 000 immunocompromised people in the UK, who have not been afforded the same level of protection from vaccination as the general population, feeling dispensable. In response to this abandonment, UK health charities have called on the government to give more support to those at highest risk from covid-19 so that they can live more normal lives.[1]

Immunocompromised people have attenuated immune responses to covid-19 vaccines, which is clinically consistent with the higher rates of breakthrough infections and lower vaccine effectiveness seen in this population.[2] This provided the rationale for the UK offering this group three primary vaccine doses plus a booster dose and, as was recently announced, a second spring booster dose (equating to a fifth dose for this population). Yet, to our knowledge, the UK has no immunogenicity data available from clinically vulnerable groups who've had four vaccine doses, which we could use to estimate the likely proportion of immunocompromised people who may not have protection against infection currently. Data from other countries suggests this may be a significant number, and if an individual has not had an immune response to four vaccine doses, in the absence of a change in immunosuppressed state, why would we expect that they will always mount a sufficient response to five?[3]

People whose immune systems haven't responded to vaccines, and who remain unidentified outside of clinical trials, are expected to "live with covid" without mandated support from their employers or free access to testing for friends and family. Conversely, for those immunocompromised people who have had an immune response to four vaccine doses, reassurance that they will truly receive a "boost" in response to the fifth vaccine dose, will be a useful incentive for repeat inoculations.[4]

Immunocompromised people represent a diverse group of people who have a variety of underlying comorbidities and immunosuppressive treatments, which are likely to affect their response to covid vaccines and outcomes from infection differently. Stratifying people by risk would help to inform tailored preventative strategies, responding to the concerns of patients and the charities representing them.[1] The best way to understand immunocompromised people's risk is, we'd argue, to measure their spike protein antibodies after vaccination. This would enable an individualised assessment of immune status and provide a predictor of the presence of neutralising antibodies. Neutralising antibodies are considered the best "correlate of protection" against covid-19 infection,[5] but such assays are not widely available. Commercial serological tests assessing for binding antibodies against the spike protein (infection or vaccination) and the nucleocapsid protein (infection), on the other hand, can be used on a mass scale and are relatively cheap with a fast turnaround time. Although the detection of spike protein antibodies will not identify the presence of neutralising antibodies, we know that individuals with no detectable anti-spike antibodies will not have neutralising antibodies.[5]

While seronegativity is uncommon in immunocompetent people after a primary vaccine course, it is a common finding in immunocompromised people, even after three doses of vaccine.[4] Identifying immunocompromised people who haven't responded to the vaccine or who are at "high risk" from covid-19 could facilitate bespoke preventative strategies, such as the use of long acting monoclonal antibody therapy for pre-exposure prophylaxis. For example, Evusheld, a combination of two monoclonal antibodies, was recently approved by the UK's Medicines and Healthcare Products Regulatory Agency to prevent covid-19 and has evidence to show it protects against symptomatic infection in this population.[6,7] Antibody testing could help us to determine which patients should have this treatment as a priority. Screening will also identify "intermediate risk" immunocompromised patients, i.e. those with antibody responses of undetermined significance, where there is more equipoise, who should be promptly managed in a reactive way with therapeutics should they become infected.

Many immunocompromised people undergo regular surveillance by hospital specialists, so the introduction of serological testing should not pose logistical concerns, although the appropriate timing of testing given waning antibodies would need to be considered, as would careful communication with immunocompromised people. One way of overcoming such challenges, if they were considered insurmountable, would be to introduce home testing

via point of care kits or capillary sampling. In addition to logistical difficulties, it should also be acknowledged that serological testing will not capture the full immune risk profile of individuals—most notably, cellular responses, which play an important role in preventing disease and may have a more influential role in immunocompromised patients on selected therapies.[8] However, serological testing to assess for a vaccine response would be a pragmatic first screening tool, and would be a step towards providing more tailored care.

As with all pandemic related guidance, adaptations of this proposed strategy would be required as new evidence emerges. Additionally, regardless of specific interventions, or lack thereof in immunocompromised people, it is imperative that the government and other funding bodies commit to ongoing research and surveillance in this population. In the meantime, let us equip immunocompromised people with the information they need to help them live safely with covid-19. Time and time again, they have been left behind by this government's approach to covid-19; they should no longer be denied the freedom to move forward with their lives.

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