Failure to respond to COVID-19 vaccination identifies individuals with previously undiagnosed severe antibody deficiency: preliminary data from the COVID-19 ENLIST study

1. STUDY QUESTION

Can failure to respond to COVID-19 vaccination identify individuals with undiagnosed antibody deficiency?

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2. METHODS

PRELIMINARY ANALYSIS OF MULTI-CENTRE PROSPECTIVE OBSERVATIONAL STUDY COHORT

Samples: Serum was obtained from solid-organ transplant recipients enrolled in the COVID-19 ENLIST vaccination sub-study (REC reference: 20/YH/0309).

Laboratory analysis: Anti-SARS-CoV-2 spike S1 IgG serological responses were first determined using a commercial assay (EUROIMMUN) after ≥ 2 doses, as reported **(1,2)**. Total IgG, IgA, and IgM levels were analysed using the Optilite® turbidimeter in consecutive stored sera with anti-SARS-CoV-2 spike IgG levels above ("responders", n=15) and below ("non-responders", n=18) the assay's cut-off for a positive anti-spike IgG response.

Outcomes: Presence of abnormally low immunoglobulin result (below 5th percentile UK healthy adult range) in COVID-19 vaccine "responders" vs "non-responders" OR Presence of severely low immunoglobulin IgG < 4g/L **(3)**

3. KEY RESULTS

Cohort:	Healthy adults	Solid organ transplant recipients	
Immunoglobulin class and lower limit of normal	UK reference range (expected %)	Vaccine responders (n=15)	Vaccine non-responders (n=18)
IgG < 6 g/L	5.0%	6.8 %	22.2 %
IgG < 4g/L *	0.4%	0.0 %	5.5 %
IgA < 0.8 g/L	5.0%	0.0 %	11.1 %
IgM < 0.5 g/L	5.0 %	40.0 %	44.4 %

* Severe IgG hypogammaglobulinaemia, **(3)**

4. FINDINGS VISUALISED

Serum IgG distribution

Serum IgA distribution

Serum IgM distribution
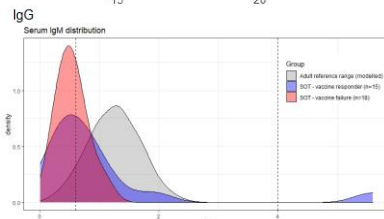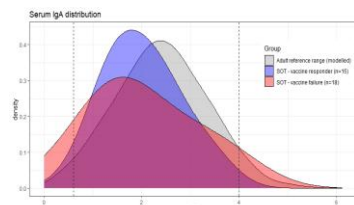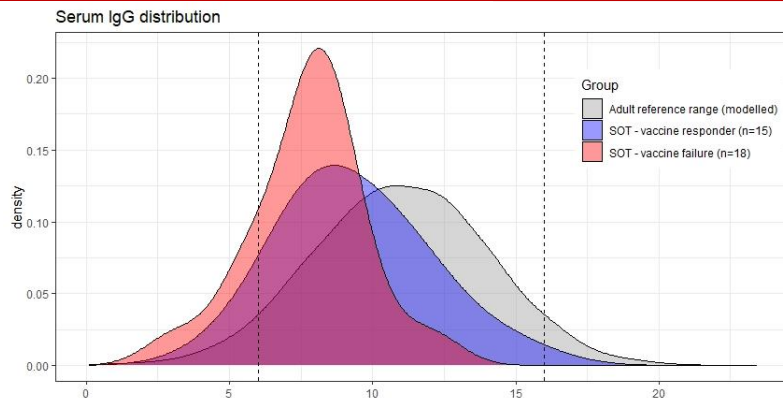
5. STUDY SIGNIFICANCE

- Antibody deficiency is a treatable cause of infection susceptibility, however, recognition is reliant on laboratory and clinical diagnosis **(4)**.
- Solid organ transplant recipients are at increased risk of hypogammaglobulinaemia due to factors including the use of anti-rejection medications, but severe deficiency remains uncommon **(5)**.
- Remarkably, this pilot study identified an individual with an IgG level of 3.1g/L, consistent with severe IgG deficiency, directing clinical assessment with potential consideration of immunoglobulin replacement therapy.
- This preliminary data support the hypothesis that failure to produce a detectable IgG response to the SARS-CoV-2 spike following at least 2 COVID-19 vaccine doses maybe associated with a reduction in the serum levels of IgG and suggests expansion of this pilot study.

6. KEY CONTRIBUTORS

7. CORE REFERENCES

1: Ponsford MJ et al, Journal of Clinical Immunology, 2022. **2**: Asderakis A et al, Transplantation, 2022 **3**: Florescu DF, American Journal of Transplantation, 2013; **4**: Ponsford MJ et al, British Medical Journal, 2019. **5**: Sarmiento E et al, Transplantation Infectious Disease, 2021.