Long-term Follow-up of mRNA COVID-19 Vaccinations Reveals Persistent Gap between Naive and Infected Individuals Dependent on Breakthrough Infections

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Conclusions

- **Individuals with breakthrough infections (BI) had significantly higher RBD-IgG levels compared with those without any infection since the first dose of mRNA COVID-19 vaccination.**
- **Higher RBD-IgG were seen in those with hybrid immunity compared with those with only vaccine-induced immunity up until 10 months past the 2nd vaccine dose. When including BI, the difference in IgG persisted beyond the 4th dose.**

Background

Differences in vaccine-induced immunity and hybrid immunity against SARS-CoV-2 in terms of IgG and T-cell responses appear to diminish already after two vaccine doses. However, data on breakthrough infections (BI) is often lacking, and long-term data beyond four vaccine doses is still limited.

Methods

Health care workers (HCWs) at the Department of Infection Diseases, Sahlgrenska University Hospital in Gothenburg, Sweden, were recruited at the start of mRNA Pfizer-BioNTech BNT162b2 COVID-19 vaccinations. Samples were collected from Jan 2021 until Dec 2022, before (PreDX) and 1 month after (PDX) each dose (Fig 1).

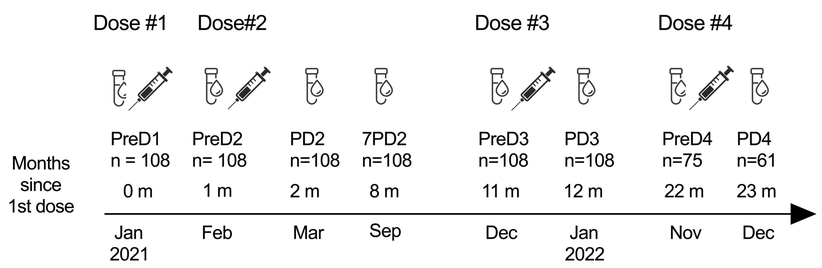

Fig 1: Time line of the Study Design. Blood samples has been collected at every vaccine dose and one month after each dose. Number of months since the first dose are marked on top of the timeline and the dominating SARS-CoV-2 strains in Sweden are marked underneath.

We analyzed IgG against the RBD- and the N-antigens along with T-cell responses using an in-house cytokine-based assay (IFN-γ, IL-2, TNF-α) of supernatant after S-antigen peptide stimulation. BI were identified by a positive PCR/antigen test or by N-IgG seroconversion.

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Results

In total, 32% of the 108 HCWs were infected prior to the first vaccine dose. BI were rare until the third dose in Dec 2021, but increased rapidly thereafter, following the introduction of Omicron in the region.

After the third dose and the emergence of Omicron, HCWs with BI had significantly higher RBD levels compared with those without any BI (PD3-PreD4).

Infected HCWs with hybrid immunity consistently had significantly higher RBD-IgG levels compared with uninfected HCWs, except at PD3, when including BI (Fig 2a and 2b).

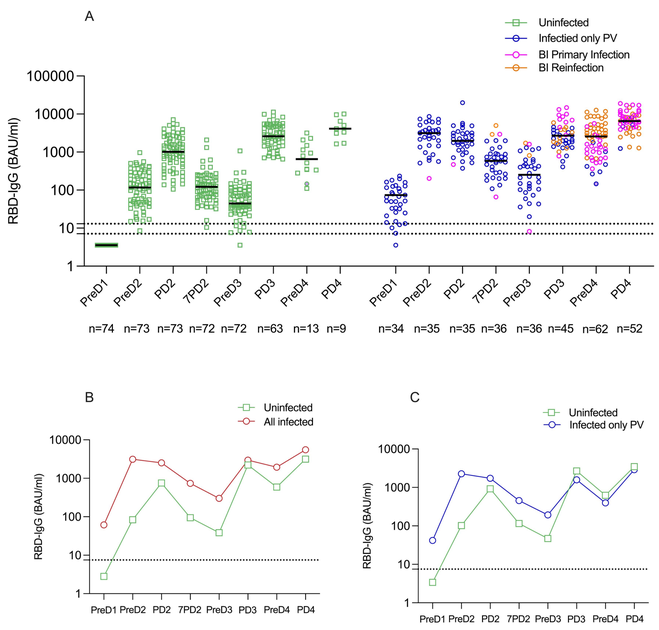

Fig 2. Concentrations of RBD-IgG antibodies after mRNA COVID-19 vaccinations, since pre dose 1 (PreD1) and at each time point until one month post dose 4 (PD4).
BI = Breakttrough infection. PV = Prio to vaccination

When excluding those with BI, RBD-IgG levels were still significantly higher in the group with hybrid immunity than those with vaccine-induced immunity only until PD3, but this difference tended to be reversed thereafter (Fig 2c).

IFN-γ correlated the best to RBD-IgG. Infected HCWs had significantly higher levels of IFN-γ at all time points except two, following the trend of RBD-IgG (Fig 3). Levels of IL-2 varied less, and significant differences between groups were only evident in the first month. Levels of TNF-α varied the most both within and between individuals across timepoints.

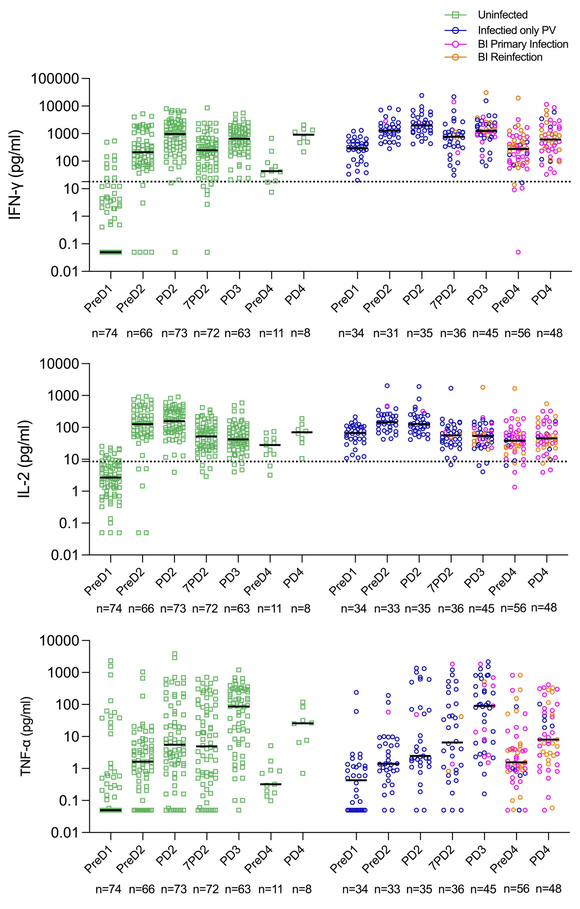

Fig 3. Concentrations of T-cell specific cytokines after mRNA COVID-19 vaccinations, since Dose 1 (PreD1) until one month post dose 4 (PD4).
BI = Breakttrough infection. PV = Prior to vaccination