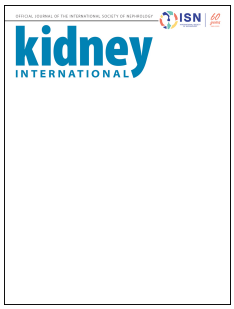
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.



SARS-CoV-2 vaccination improves HBV seroconversion rate through heterological immunity

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SARS-CoV-2 vaccination improves HBV seroconversion rate through heterological immunity

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Letter to the editor

Epidemiological studies in humans and experimental animal data have clearly demonstrated that exposure or infection with one pathogen can induce and/or modify the immune response against another unrelated pathogen[1,2]. The mechanism of this phenomenon, known as heterologous immunity, has not been elucidated in humans in details. Hemodialysis patients (HD) are known to be immunocompromised and a high degree of vaccination non-responders is observed in this population[3]. The aim of this study was to assess the effect of heterologous immunity in context of HBV and COVID-19 vaccination in HD.

We analyzed the adaptive immunity against SARS-CoV-2 and HBsAg in 16 hemodialysis patients following consecutive HBV and SARS-CoV-2 vaccination boosts applied four weeks apart each other. All patients were HBV vaccination non-responders (following 4 doses of Engerix), and non- or low-responder following prime-boost vaccination with BNT162b2 (Fig. 1A, Supplementary Table S1). Titers of binding antibodies as well as neutralizing antibodies against HBV, SARS-CoV-2 Wildtype, Delta and Omicron were estimated in follow up by ELISA and SARS-CoV-2 spike-protein (S-protein) pseudovirus assays, respectively. T cell immunity reactive against SARS-CoV-2 and HBV was analyzed by multiparameter flow cytometry (Supplementary Fig. S1). T cell receptor (TCR) repertoires of HBsAg- and S-protein-reactive T cells were analyzed by next generation sequencing.

Three weeks after third SARS-CoV-2 vaccination, all 16 HD were able to develop a protective humoral immunity against SARS-CoV-2 Wildtype (Median [IQR]-ND50 = 545.25 [297.55-1720.75]), Delta VOC (Median [IQR]-ND50 = 210.75 [65.81-705.5]) and Omicron VOC (Median [IQR]-ND50 = 189.25 [88.04-530.65]) (Fig.1B). Interestingly, while no HBsAg seroconversion could be observed 4 weeks following an HBV vaccination boost, 6 out of 16 initial HBV vaccination non-responders demonstrated seroconversion with median Ab titers of 123.5 IU/mL [53.5-562.5] (Fig.1C) three weeks after the SARS-CoV-2 boost. HBsAg- and SARS-CoV-2 specific T cells were detectable in all vaccinated patients (Fig.1D, E). In line with the results of the humoral immune response, we detected significantly more HBsAg-reactive CD4 T cells in HD patients 4 weeks after SARS-CoV-2 vaccination than before the boost (Fig.1E). However, we found no overlapping TCR repertoire in HBsAg- and S-protein-reactive T cells (Fig.1F).

Six out of 16 HBV vaccination non-responders on HD therapy were able to generate HBV antibodies and HBV reactive CD4 T cells after COVID-19 vaccination. In contrast, additional data from dialysis patients immunized with HBV vaccine only, which have been monitored for 8 weeks show, the HBV antibody response occurred within 14 days. The rest of the patients remained negative for the whole follow up (Supplementary Fig. S2). These data underpins, that the effect was due to the SARS-CoV-2 mRNA vaccination and not a delayed immune

response. Since no TCR overlap could be detected between S-protein- and HBsAg-reactive T cells and these two viruses do not share excessively many epitopes[2], unspecific activation following COVID-19 immunization rather than cross-reactivity appears to contribute to the development heterologous HBV immunity. The exact mechanisms behind these observations remain unclear but it can be hypothesised, that monocyte-dependent trained immunity[4] or an activation of few HBV-specific memory cells due a strong cytokine activation after the SARS-CoV-2 vaccine reaction are responsible for this effect of heterological immunity. Our data might have important implication for the vaccination regime for immuncompromized patients such as hemodialysis and transplant patients. However, further analyses are required to validate our observations.

References:

1) Gyssens IC, Netea MG. Heterologous effects of vaccination and trained immunity. *Clin Microbiol Infect*. 2019;25(12):1457-1458. doi:10.1016/j.cmi.2019.05.024
2) Stervbo U, Rahmann S, Roch T, Westhoff TH, Babel N. Epitope similarity cannot explain the pre-formed T cell immunity towards structural SARS-CoV-2 proteins. Sci Rep. 2020;10(1):18995. Published 2020 Nov 4. doi:10.1038/s41598-020-75972-z
3) Cinkilic O, Anft M, Blazquez-Navarro A, et al. Inferior humoral and sustained cellular immunity against wild-type and omicron variant of concern in hemodialysis patients immunized with 3 SARS-CoV-2 vaccine doses compared with 4 doses. *Kidney Int*. 2022;101(6):1287-1289. doi:10.1016/j.kint.2022.03.005
4) Agrawal B. Heterologous Immunity: Role in Natural and Vaccine-Induced Resistance to Infections. Front Immunol. 2019;10:2631. Published 2019 Nov 8. doi:10.3389/fimmu.2019.02631

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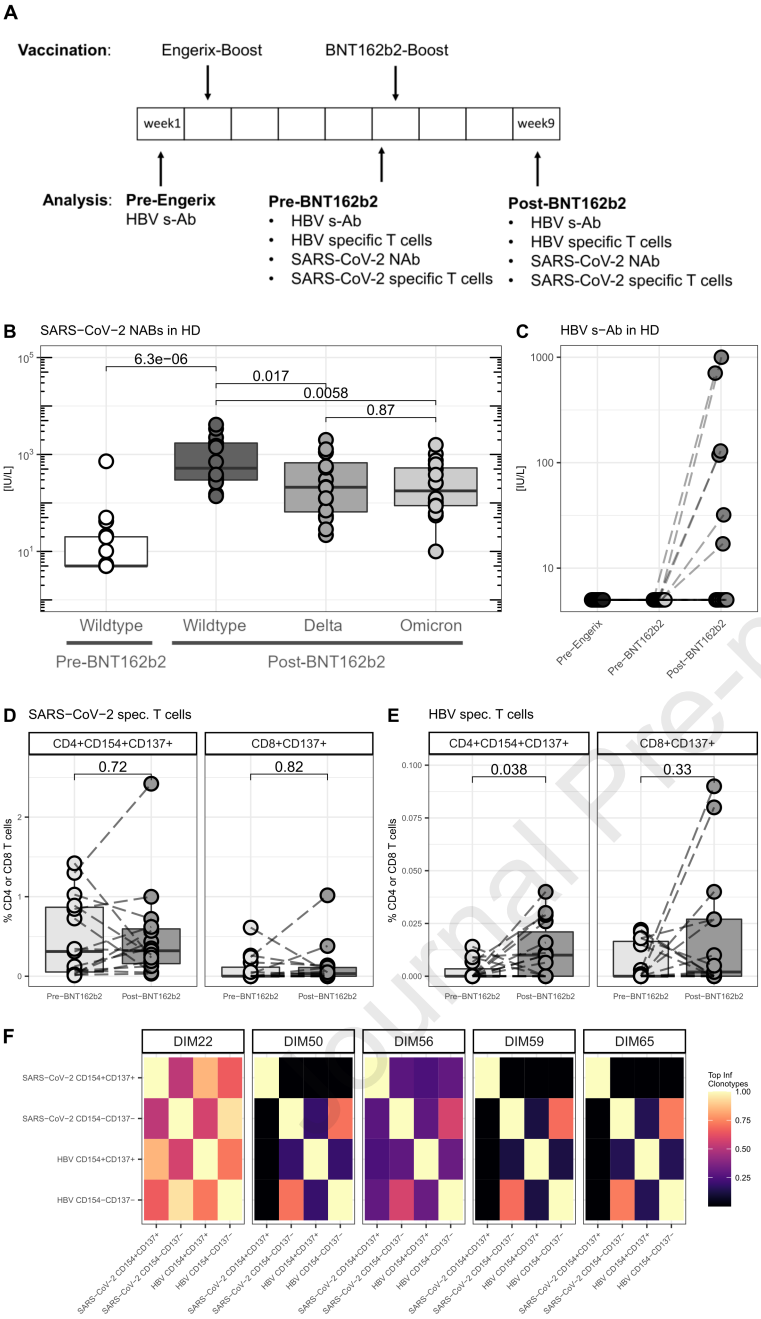
Data availability statement: The data will be available upon request.

Figure Legends:

Fig.1: Comparison of the humoral and cellular immune response in SARS-CoV-2 and HBV vaccine non-responder prior and after the HBV (Engerix) and SARS-CoV-2 (BNT162b2) boosts. (A) Schematic illustration of the course of vaccination. The indicated analyses were performed one week prior Engerix-Boost (Pre-Engerix), 4 weeks after Engerix-Boost, prior the BNT162b2 -Boost (Pre- BNT162b2) and 3 weeks after BNT162b2 -Boost (Post- BNT162b2). (B) Isolated serum from hemodialysis patients (n=16) was analyzed for neutralizing antibodies against SARS-CoV-2 Wildtype glycoprotein S prior the SARS-CoV-2 boost and Wildtype, Delta and Omicron glycoprotein S three weeks after the SARS-CoV-2 boost [ND50]. (C) Isolated serum from hemodialysis patients (n=16) was analyzed for Titers [IU/mL] of binding antibodies against HBV prior and three weeks after SARS-CoV-2 boost. Isolated PBMCs from hemodialysis patients (n=15), were stimulated for 16 h with 1 µg/ml SARS-CoV2 Wildtype overlapping peptide pools (OPPs) (D) or HBV OPPs (E). SARS-CoV-2 and HBV reactive T helper cells were identified as Life/Dead-Marker-$CD3^+CD4^+CD137^+CD154^+$ and SARS-CoV-2 reactive cytotoxic T cells were identified as Life/Dead-Marker-$CD3^+CD8^+CD137^+$. (F) TCR Repertoire of 5 initial HBV non-responder with HBV humoral immune response after SARS-CoV-2 boost. Yue-Clayton similarity of all clonotypes between populations for each donor, 1 indicate identity (yellow), 0 indicate complete dissimilarity (black).

Supplementary materials:

- Supplementary Methods
- Supplementary Table S1: Study population
- Supplementary Figure S1: Gating strategy to identify SARS-CoV-2 and HBV reactive T cells among CD4+ T and CD8+ T cells
- Supplementary Figure S2: HBV s-Ab kinetic in HBV Responder and Non-Responder.


A
Vaccination:
Engerix-Boost
BNT162b2-Boost
week1
week9
Analysis:
Pre-Engerix
HBV s-Ab
Pre-BNT162b2
HBV s-Ab
HBV specific T cells
SARS-CoV-2 NAb
SARS-CoV-2 specific T cells
Post-BNT162b2
HBV s-Ab
HBV specific T cells
SARS-CoV-2 NAb
SARS-CoV-2 specific T cells
B
SARS−CoV−2 NABs in HD
6.3e−06
0.017
0.0058
0.87
[IU/L]
Wildtype
Wildtype
Delta
Omicron
Pre-BNT162b2
Post-BNT162b2
C
HBV s−Ab in HD
[IU/L]
Pre−Engerix
Pre−BNT162b2
Post−BNT162b2
D
SARS−CoV−2 spec. T cells
CD4+CD154+CD137+
CD8+CD137+
0.72
0.82
% CD4 or CD8 T cells
Pre−BNT162b2
Post−BNT162b2
E
HBV spec. T cells
CD4+CD154+CD137+
CD8+CD137+
0.038
0.33
% CD4 or CD8 T cells
F
DIM22
DIM50
DIM56
DIM59
DIM65
SARS−CoV−2 CD154+CD137+
SARS−CoV−2 CD154−CD137−
HBV CD154+CD137+
HBV CD154−CD137−
Top Inf Clonotypes
1.00
0.75
0.50
0.25