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BelCoVac SYMPOSIUM 2023

Belgian SARS-CoV-2 Vaccination studies (BelCoVac) report (2020-2023)

Infectious diseases in humans
September 2023, Brussels, Belgium
Deposit number: D/2023.14.440/68

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How to refer to this document?
Maria E. Goossens, Alexia Charles, Stéphanie Depickère. Belgian SARS-CoV-2 Vaccination studies (BelCoVac) report. Brussel: Sciensano. Depositnumber D/2023.14.440/68.
This document is available on the Sciensano website.

Acknowledgment
The authors would like to thank all investigators and lab researchers who participated in the BelCoVAc consortium.

In the spring of 2021 the BelCoVac consortium was established, uniting the **expertise of Belgian immunological experts and clinicians** across different universities and research laboratories, the Belgian Pandemic Preparedness (BelPaPrep) Labs. The consortium allows for the generation of data which is uniform and comparable throughout the different studies it encompasses.

Each research lab was responsible for specific immune tests.

- Binding Antibodies and B-cell elispot - Isabelle Desombere (Sciensano)
- Neutralizing antibodies – Kevin Ariën (Institute Tropical Medicine)
- Avidity and T-cell flow cytometry – Arnaud Marchant (Université Libre de Bruxelles) and Eva Lion (University of Antwerp)

All studies focused on **monitoring the immune response** in a number of (vulnerable) population groups after vaccination with different COVID-19 vaccines. Funding came from the government through Sciensano and KCE.

Influence of prior infection with SARS-CoV-2 on occurrence of influenza-like illness or acute respiratory infection (PICOV) – Maria Goossens (Sciensano):

- Due to the strict non-pharmaceutical interventions enforced during the past winter seasons, a historically low number of flu-like illnesses has been recorded in nursing homes.
- As a consequence, the required sample size was not reached to determine the influence of a previous SARS-CoV-2 infection on the incidence of flu-like illnesses.

Immune response to mRNA vaccine doses in SARS-CoV-2 infection naïve nursing home residents and staff (PICOV-VAC) – Maria Goossens (Sciensano):

- After vaccination with two doses of the Pfizer/BioNTech COVID-19 mRNA vaccine, nursing home residents developed delayed and diminished immune responses when compared to nursing home staff. This was only the case for people who had not experienced a SARS-CoV-2 infection prior to vaccination.
- After booster vaccination (third dose, eight months after the first dose), this difference in immune response between residents and staff had almost completely disappeared.

Safety and immunogenicity of demi-dose of two Covid-19 mRNA vaccines in healthy population (REDU-VAC) – Maria Goossens (Sciensano):

- Vaccination of healthy people below the age of 55 years with a reduced dose (twice 20µg) of the Pfizer/BioNTech COVID-19 mRNA vaccine, results in a slightly lower immune response when compared to vaccination with the regular, full dose (twice 30µg).
- Nevertheless, this lower immune response is still multifold higher than what is induced by vaccination with e.g. Astra-Zeneca's Vaxzevria or J&J's JCOVDEN vaccines. In other words, a reduced dose of a superior mRNA vaccine could therefore potentially still be a better or equivalent alternative to a full dose of a less efficient adenoviral vectored vaccine with the aim of speeding up a vaccination campaign in times of vaccine shortages.
- Study of a third reduced dose (10µg), compared to full dose (30µg) of the Pfizer/BioNTech COVID-19 mRNA vaccine:
  - The slight difference in the immune response observed after two 20 µg doses disappeared after the administration of a full third dose (30µg).
  - People vaccinated with a third reduced dose (10µg) after two full doses (30µg) had the lowest immune response; while people vaccinated with 3 reduced doses (two times 20µg followed by 10µg) had the highest response. Due to the small sample size these results should be interpreted with caution. Further investigation is warranted.

SARS-CoV-2 vaccination in kidney transplant recipients and in hemodialysis patients: a phase IV study of the immunogenicity and its determinants (Nephro-Vac) – Alain Lemoine (Erasme):

- Kidney transplant recipients and hemodialysis patients, both severely immunocompromised, respond poorly to COVID-19 mRNA vaccination. Nevertheless, additional boosters doses are able to elicit increasingly higher responses.
- Interestingly, the above is only true for SARS-CoV-2 infection naïve patients, as previously infected patients respond as well to vaccination as healthy people. This "hybrid immunity", induced by both infection and vaccination, is remarkable. The underlying mechanism of which remains to be elucidated.
- In addition, in this cohort of nephrology patients, low antibody and specific cellular responses to vaccination were associated with incidence of vaccine breakthrough infection in the months following a third vaccine dose.
- T-cell responses may help compensate for the suboptimal antibody response to booster vaccination in kidney transplant recipients. This study shows that humoral and cellular immune responses induced by booster vaccination correlate with protection against SARS-CoV-2 breakthrough infections (BTI) in kidney transplant recipients. These data emphasize the importance of reaching and maintaining a high level of immunity through vaccination in this vulnerable population and suggest that vaccines that induce potent cellular immune responses, such as mRNA vaccines, may be particularly useful in populations with suboptimal humoral immune responses to vaccination.

Vaccination against Covid-19 in cancer patients under active treatment (Onco-Vac) – Marc Peeters (UZA):

- Cancer patients under active treatment have a delayed and reduced immune response to COVID-19 mRNA vaccination, especially those patients receiving chemotherapy (independently of the timing of administration) or rituximab. Nevertheless, most hematopoietic stem cell transplantation patients or patients with solid tumors, including those under active anti-cancer treatment, benefit from additional booster doses. Patients receiving rituximab, however, do not.
- While it had already been shown by others that immune responses to AstraZeneca's Vaxzevria are inferior to those following mRNA COVID-19 vaccination in healthy people, it was shown here that this is also the case in cancer patients. This was observed after primo-vaccination as well as after heterologous boosting with an mRNA vaccine. In patients with cancer who received double-dose ChAdOx1, a third heterologous dose of BNT162b2 was able to close the gap in antibody response.

Impact of the immune system on response to Covid-19 vaccine in allogeneic stem cell recipients (Cov-Allo) – Frédéric Baron (CHU Liège):

- Allogeneic hematopoietic stem cell transplantation recipients generally have a lower immune response to COVID-19 mRNA vaccination, as well after primo-vaccination as after booster doses. However, particularly patients experiencing chronic graft versus host disease and those receiving rituximab that present with lower antibody responses than healthy people.
- A majority of allogeneic hematopoietic stem cell transplant patients without active moderate/severe chronic graft versus-host disease are able to produce neutralizing antibodies (Ab) against Delta and Omicron variants in response to a third dose of the BNT162b2 vaccine.

Vaccination against Covid-19 in pregnant and lactating women in Belgium (PREGCOVAC) – Kirsten Maertens (University of Antwerp):

- In pregnant women, primary vaccination with two doses of mRNA vaccines (Pfizer or Moderna) elicits a quantitatively and qualitatively higher and also faster immune response compared to vaccination with two doses of AVV vaccines (Astra Zeneca). Nevertheless, after administering a mRNA booster dose, there is a catch-up of the SARS-CoV-2 RBD IgG antibody titer in the AVV group and titers are comparable with the mRNA group after boosting with a mRNA vaccine.
- In women vaccinated during pregnancy, there is transplacental transport of SARS-CoV-2 RBD IgG. Also, IgG and IgA antibodies are found in their breastmilk postpartum. This may contribute to protection of the neonate against severe infection due to COVID-19.

COVID-19 vaccination in breastfeeding mothers (COVALAC) – Eline Tommelein (Vrije Universiteit Brussel):

- COVID-19 vaccination in breastfeeding mothers resulted in the presence of both IgA and IgG antibodies in breast milk.
- Two mRNA vaccines consistently elicited higher antibody titers in breast milk compared to adenovector vaccines.
- A booster shot with an mRNA vaccine led to a remarkable and significant resurgence of both IgA and IgG antibodies in breast milk and yielded even higher titers than observed after the initial vaccination.

COVID 19 and lung transplantation: study of clinical characteristics and humoral and cellular response to SARS-CoV-2 infection and anti-SARS-CoV-2 vaccination in lung transplant patients (LUNG-VAC) – Isabelle Etienne (Erasme):

- Lung transplant patients are known to be profoundly immunocompromised. Pre-vaccination SARS-CoV-2 naive patients have a poorer response to the vaccine compared to the control population. However, boosters can increase the level of antibodies, including neutralizing antibodies. The cellular immune response to the vaccine remains low.
- Pre-infected lung transplant patients have a humoral response similar to the control population.
- After a complete vaccination schedule with 3 doses, occurrence of breakthrough infections has nevertheless been observed. Surprisingly, the infected patients have higher levels of antibodies, especially neutralizing ones, than the others (period between day 28 post dose 3 and before dose 4). This can be explained by their younger age. However, the most determining factor to get infected seems to be the lifestyle and the associated risk of exposure (work, school children).
- Presence of antibodies does not seem to be the factor that determines the risk for infection, although it protects from a severe disease.

Immunogenicity after COVID-19 vaccines in Adapted Schedules in healthy adults (IMCOVAS) – Katie Steenackers/Nikita Hanning (University of Antwerp) (funded by KCE):

- Prolonging interval between the two primary doses of an mRNA vaccine elicit a non-inferior humoral immune response compared to the standard interval.
- Lowering the vaccine dose of an mRNA led to non-inferiority for the development of neutralizing antibodies and to a robust development of avidity.
- Heterologous vaccination with 2 mRNA vaccines led to comparable humoral immune responses as homologue mRNA vaccination.
- Heterologous vaccination with mRNA and adenovector based vaccines led to inferior humoral immune responses compared to homologue mRNA vaccination.
- Intradermal administration with 20% of an mRNA vaccine is not supported by the data from this trial.
- The third dose or first booster dose showed non-inferiority for all adapted schedules compared to the reference regimen, and was independent from the brand/dose used for the third dose.

Longitudinal follow-up of SARS-CoV-2 immunity in immunocompromised populations in Belgium (COVICO) – Maria Goossens (Sciensano):

- The different groups of COVICO (PICOV-VAC, REDU-VAC, transplanted and hemodialyzed NEPHRO-VAC) had similar anti-RBD binding Ab titers at visit 1 (Jan-Feb 2023) (GMTs around 2320-2844 BAU/ml) compared to those observed 28 days after 3th dose (Sep-Oct 2021) except in LUNG-VAC for which titers were lower (GMT of 299, and still some no-responders).
  - At visit 2 (June 2023), anti-RBD binding Ab titers remained stable with a GMT between 1950-2885 BAU/ml (PICOV-VAC, REDU-VAC, transplanted and hemodialyzed NEPHROVAC) except for lung transplant patients (GMT of 173).
  - 81/246 (33%) re-infections were identiefied between visit 1 (Jan-Feb 2023) and 2 (June 2023): 3/30=10% in LUNG-VAC, 26 in NEPHRO-VAC (4/26=15% in hemodialyzed and 22/46=48% in transplanted patients), 39 in PICOV-VAC (15/38=39% in residents, 24/69=35% in staff), and 13/37=35% in REDU-VAC.

Initial results of these studies have been presented at the Superior Health Council, Task force vaccination, Task force therapeutics and Crisis Cell Public Health.

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- Report from IMCOVAS (IMCOVAS csr – final version 1.0 dd 08June2023)

Posters

Safety and immunogenicity of a reduced dose of the BNT162b2 mRNA COVID-19 vaccine (REDU-VAC): A single blind, randomized, non-inferiority trial

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Poor Antibody Response to BioNTech/Pfizer Coronavirus Disease 2019 Vaccination in Severe Acute Respiratory Syndrome Coronavirus 2–Naive Residents of Nursing Homes

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Third dose of COVID-19 mRNA vaccine closes the gap in immune response between naïve nursing home residents and healthy adults

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Different COVID-19 vaccine platforms in pregnancy: A multidimensional approach to humoral immunity

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COvid VACcination during LACtation: the COVALAC study

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Do lung transplant recipients respond to Covid-19 vaccine despite immunosuppressive treatment? LUNG-VAC cohort

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Humoral and cellular immune correlates of protection against COVID-19 in kidney transplant recipients

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Hybrid immunity overcomes defective immune response to COVID-19 vaccination in kidney transplant recipients

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Immune responses to BNT162b2 mRNA COVID-19 vaccine in allo-HCT recipients: preliminary findings from a systems vaccinology study

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Reduced humoral immune response after BNT162b2 COVID-19 mRNA vaccination in cancer patients under anti-neoplastic treatment

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Humoral and cellular immune responses against SARS-CoV-2 after 3rd dose BNT162b2 following dual-dose vaccination with BNT162b2 vs ChAdOx1 in cancer patients

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Humoral immune response after ChAdOx1 COVID-19 vaccination in cancer patients under anti-neoplastic treatment

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Long-term dynamics of anti-SARS-CoV-2 IgG antibodies post-COVID-19 primo and dual booster vaccination in a Belgian oncological population

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Predictive model for BNT162b2 vaccine response in cancer patients treated with antineoplastic drugs based on blood cytokines and growth factors

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Safety and immunogenicity of a reduced dose of the BNT162b2 mRNA COVID-19 vaccine (REDU-VAC): A single blind, randomized, non-inferiority trial

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CONCLUSION: Binding and neutralizing antibody response of reduced doses of the BNT162b2 mRNA vaccine were inferior to the full dose, but still markedly higher than responses induced by other approved COVID-19 vaccines with proven efficacy. They may offer additional benefit as compared to the vaccines currently in use in most low and middle-income countries, warranting larger immunogenicity and effectiveness trials.

Fractional dosing of COVID-19 vaccines could accelerate vaccination rates in low-income countries. Dose-finding studies of the mRNA vaccine BNT162b2 (Pfizer-BioNTech) suggest that a fractional dose induces comparable antibody responses to the full dose in people <55 years. Here, we report the safety and immunogenicity of a fractional dose regimen of the BNT162b2 vaccine.

Methods

- REDU-VAC is a participant-blinded, randomised, phase 4, non-inferiority study investigating safety, reactogenicity and immunogenicity
- Adults 18–55 years old, either COVID-19 previously infected or infection naïve, were randomly assigned to receive 20µg/20µg (fractional dose) or 30µg/30µg (full dose) of BNT162b2, with an interval of 21 days
- Blood samplings done before the 2 doses administration (days 0 and 21), on day 28 after dose 2 (day 49), and at month 6 after dose 1
- SARS-CoV-2 anti-receptor binding domain (RBD) specific IgG concentrations, neutralizing antibody titres against SARS-CoV-2 Wild type (WT) and against Delta and BA.1 omicron variants. Cellular responses measured on a subsample of 45 randomly selected participants.
- Primary outcome: geometric mean ratio (GMR) of SARS-CoV-2 anti-RBD IgG titres at day 28 post dose 2 between the reduced and full dose regimens
- The reduced dose was considered non-inferior to the full dose if the lower limit of the two-sided 95% CI of the GMR was >0.67.
- Primary analysis was done on the per-protocol population, including infection naïve participants only: 60 vs. 64 people in the 20µg and 30µg cohorts respectively

Table 1. Demographics, characteristics by study groups

		Per-protocol		Intention-to-treat	
Characteristic		20 µg (n=60)	30 µg (n=64)	20 µg (n=70)	30 µg (n=71)
Age (years, mean ± SD)		40.4 ± 7.5	41.0 ± 8.2	39.8 ± 7.9	41.0 ± 8.0
Sex	Female	43 (72%)	43 (67%)	49 (70%)	49 (69%)
Ethnicity	White	56 (93%)	63 (98%)	65 (93%)	69 (97%)
BMI (mean ± SD)		23.8 ± 3.3	24.8 ± 4.3	24.3 ± 3.9	24.8 ± 4.2
Comorbidities (under control)	Cardiovascular	1 (1.7%)	2 (3.1%)	2 (2.9%)	2 (2.8%)
	Oncological	0	1 (1.6%)	0	1 (1.4%)
	Respiratory	0	1 (1.6%)	0	1 (1.4%)

Per-protocol	20 µg	30 µg	GMR
SARS-CoV-2-anti-RBD IgG			
n	60	64	-
GMT in BAU/ml	1705	2387	0.714
(95% CI)	(1315-2211)	(1899-3001)	(0.540-0.944)
Neutralizing antibodies (Wuhan)			
n	60	64	-
NT_{50}	160	216	0.740
(95% CI)	(124-206)	(172-270)	(0.562-0.974)
Neutralizing antibodies (Delta)			
n	56	63	-
NT_{50}	39	40	0.962
(95% CI)	(31-48)	(33-49)	(0.760-1.217)

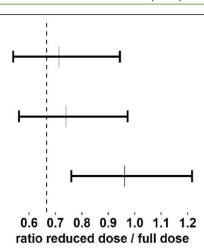

Fig 1. Immune responses by study arm at day 49 and non-inferiority analysis in the per-protocol cohort. GMTs (95% CI) at day 49. GMRs (95% CI) adjusted with a linear mixed-effect model including gender, age and SARS-CoV-2 anti-RBD IgG titre at baseline as fixed variables and location as random variable. Dashed line: WHO recommended non-inferiority margin of 0.67.

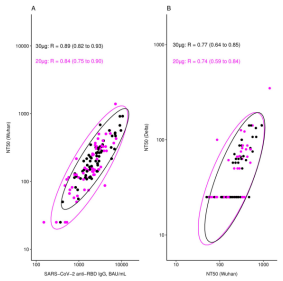

Fig 2. Correlations between immune responses per study arm (purple = 20µg, black = 30µg, day 49). Pearson correlation coefficients (95% CI) are given. Ellipses represent the 95% CI for the two study arms (purple = 20µg, black = 30µg), assuming multivariate normal distributions.

Results

- **anti-RBD binding IgG levels**
  - Day 49 (primary outcome): non-inferiority not demonstrated (Fig. 1)
  - All participants had seroconverted at day 28 post dose 2 (Fig. 3A)
  - At month 6, IgG waned but all participants remained seropositive (Fig. 3)
- **Neutralizing Abs**
  - Strong correlations between anti-RBD IgG and neutralizing Ab against WT, in both arms (Fig. 2)
  - Non-inferiority not demonstrated at day 49 (Fig. 1)
  - Neutralizing capacity against VOCs much lower compared to WT. Only 40% of participants with nAb for Delta, and 0% for BA.1 (Fig. 3B, C, D)
  - Strong correlation between nAb against WT and Delta (Fig. 2)
  - Non-inferiority demonstrated for Delta nAb (Fig. 1)
- **Cellular response**
  - S1- and S2-IFN-γ ELISpot: No statistical difference between 20µg and 30µg in the frequencies of T cells.
  - Flow cytometry: no statistical difference between 20µg and 30µg in the proportion of S1 or S2 specific CD4+ and CD8+ T cells expressing CD154 (CD4+ T cells only), IFN-γ, IL-2, and TNF-α
- **Breakthrough infections**
  - 18 reported, happening 5-8 months after dose 1, coinciding with the major wave due to Delta VOC
  - Only in naïve people, in both 20µg and 30µg arms (p=0.8)
  - No difference in the GMTs of bAb and nAb at day 49 or month 6 (p>0.14)
- **Adverse events (AE)**
  - No serious AE reported
  - No difference in frequency and severity (except in the reported severity of nausea after dose 2 (moderate in 20µg arm and mild in 30µg arm)

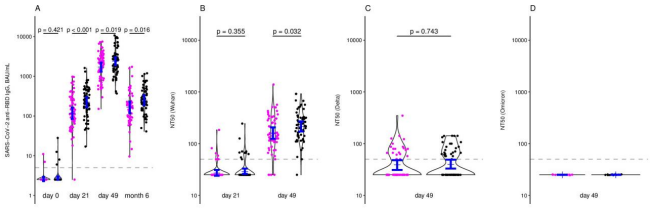

Fig 3. Kinetics of immune responses per study arm (purple = 20µg, black = 30µg) of the per-protocol cohort. Blue bars: geometric mean titres with 95% CI.

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ACKNOWLEDGEMENTS

We thank all the laboratory personnel, the nurses, and the study participants for their availability, flexibility and dedication.

This research was funded by the Belgian Federal Government through Sciensano.

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Poor Antibody Response to BioNTech/Pfizer Coronavirus Disease 2019 Vaccination in Severe Acute Respiratory Syndrome Coronavirus 2–Naive Residents of Nursing Homes

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CONCLUSION: The poor Ab responses to mRNA vaccination observed in infection-naive NH residents and in some naive staff members suggest suboptimal protection against breakthrough infection, especially with variants of concern. These data support the administration of a third dose of mRNA vaccine to further improve protection of NH residents against COVID-19.

In 2020, residents of nursing homes (NHs) were at high risk of coronavirus disease 2019 (COVID-19)–related disease and death and may respond poorly to vaccination because of old age and frequent comorbid conditions. A longitudinal cohort of residents of NHs and staff (control) was followed to assess the magnitude and quality of antibody responses to SARS-CoV-2 Wuhan (wild-type [WT]) strain and B.1.351 Beta variant, VOC first identified in South Africa.

Methods

- 78 residents and 106 staff members, naive to infection or previously infected with severe acute respiratory syndrome coronavirus (SARS-CoV-2), were recruited in NHs in Belgium before immunization with 2 doses of 30µg BNT162b2 messenger RNA (mRNA) vaccine at days 0 and 21.
- Binding antibodies (Abs) to SARS-CoV-2 receptor-binding domain (RBD), spike domains S1 and S2, RBD Ab avidity, and neutralizing Abs (nAbs) against SARS-CoV-2 wild type and B.1.351 (Beta) were assessed at days 0, 21, 28, and 49.

Table 1. Demographics, characteristics by study groups

Characteristic		Naive staff (n=40)	Naive residents (n=53)	Pre-infected staff (n=66)	Pre-infected residents (n=25)	Total (N=184)	P-value
Age (years, mean ± SD)		46.8 ± 10.2	86.1 ± 9.0	46.6 ± 10.5	85.0 ± 8.0	63.2 ± 21.6	<0.001
Sex	Female	29 (72%)	37 (70%)	56 (85%)	16 (64%)	138 (75%)	0.12
Ethnicity	White	38 (95%)	53 (100%)	59 (89%)	25 (100%)	175 (95%)	0.03
BMI (mean ± SD)		27.0 ± 5.5	23.3 ± 5.1	27.1 ± 4.7	22.6 ± 4.3	25.4 ± 5.3	< 0.001
Self-reported smoking status	Former smoker	2 (5%)	4 (8%)	5 (8%)	5 (20%)	16 (9%)	0.03
	Nonsmoker	29 (73%)	47 (89%)	50 (76%)	19 (76%)	145 (79%)	
	Current smoker	9 (23%)	2 (4%)	11 (17%)	1 (4%)	23 (13%)	
Daily exercise	< 30min	6 (15%)	27 (51%)	7 (11%)	12 (48)	52 (28%)	< 0.001
	30-60min	8 (20%)	24 (45%)	19 (29%)	7 (28%)	58 (32%)	
	≥60min	24 (60%)	2 (4%)	38 (58%)	5 (20%)	69 (38%)	
	None	2 (5%)	0 (0%)	2 (3%)	1 (4%)	5 (3%)	
Health status	Very good	14 (35%)	4 (8%)	20 (30%)	3 (12%)	41 (22%)	< 0.001
	Good	22 (55%)	33 (62%)	39 (59%)	10 (40%)	104 (57%)	
	Reasonable	4 (10%)	16 (30%)	6 (9%)	11 (44%)	37 (20%)	
	Bad	0 (0%)	0 (0%)	1 (2%)	1 (4%)	2 (1%)	
Quality of life index (mean±SD)		0.9 ± 0.1	0.7 ± 0.2	0.9 ± 0.1	0.8 ± 0.2	0.9 ± 0.2	< 0.001

Results

- **Ab levels**
  - Naïve resident showed lower levels of Abs to RBD and S1 than naïve staff after 1st vaccination (~ 7-fold) and 2nd vaccination (2-fold).
  - Delayed peak Ab response in naive residents (Fig. 1a).
  - Higher in previously infected than in naïve in both groups (Fig. 1b).
- **Avidity**
  - Slower IgG avidity maturation observed in naïve residents (Fig. 2b)
  - Rapid and high avidity in previously infected participants (Fig. 2a)
- **Neutralizing Abs**
  - Lower levels of nAbs in naïve resident than naïve staff (Fig. 2d)
  - Previously infected participants had higher levels of nAbs (Fig. 2d)
  - Levels of nAbs against Beta lower than against WT (5-10-folds)
- **Interindividual variability (Fig. 3)**
  - 5 clusters with distinct Ab levels, avidity and neutralizing activity at day 49 (Fig 3a-d), not correlated with age (Fig. 3e)
  - Cluster 5, highest Ab responses, only with infected staff and residents
  - Cluster 1, lowest Ab responses, mix of naïve residents / staff members ➔ poor Ab responders

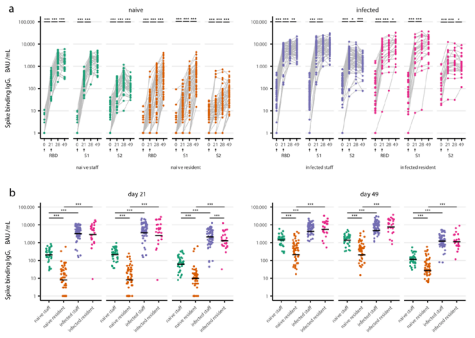

Fig. 1. SARS-CoV-2 spike-specific binding antibody (Ab) responses to BNT162b2 vaccination in residents and staff. Arrows: vaccine on days 0 and 21. Black bars indicate geometric mean titers.

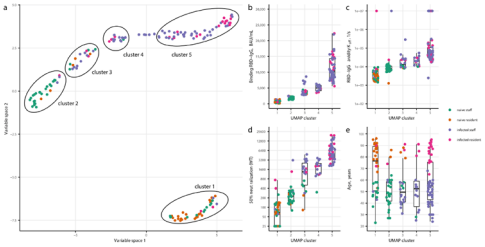

Fig. 3. Low vaccine responders in naive residents and staff. a, Cluster (Uniform Manifold Approximation and Projection [UMAP]) analysis of all study participants with available receptor-binding domain (RBD)/spike 1 (S1)/spike 2 (S2) binding IgG antibody (Ab) concentrations, RBD-IgG avidity, and SARS-CoV-2 wild-type (WT) neutralization at day 49. DBSCAN (density-based spatial clustering of applications with noise) was used to identify clusters. b-d, Clusters 1 to 5 plotted against RBD binding IgG, RBD IgG avidity, and WT neutralizing titers, respectively. e, Ages of participants included in clusters of Ab responses. Black bars: geometric mean titers.

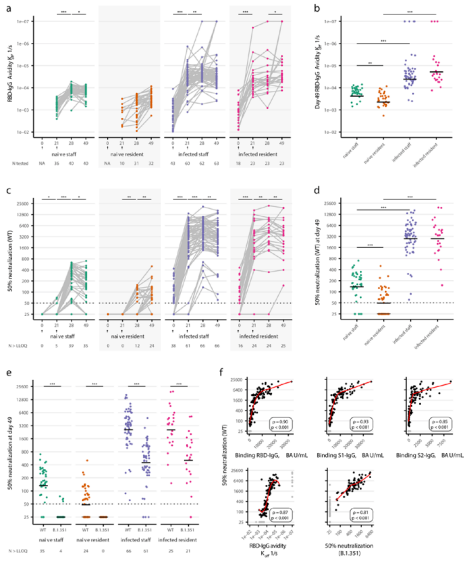

Fig. 2. Avidity (a-b) and neutralizing Ab levels (c-e). "N tested": number of participants with sufficiently high Ab concentrations for avidity testing. "N > LLOQ": number of participants with quantifiable nAbs. Black bars: geometric mean titers.

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ACKNOWLEDGEMENTS

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This research was funded by the Belgian Federal Government through Sciensano.

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Third dose of COVID-19 mRNA vaccine closes the gap in immune response between naïve nursing home residents and healthy adults

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CONCLUSION: A third dose of mRNA COVID-19 vaccine closes the gap in humoral and cellular immune response observed after primary vaccination between nursing home residents and staff members but suggest that further boosting might be needed to achieve optimal protection against variants of concern in this vulnerable population.

Nursing home residents, a frail and old population group, respond poorly to primary mRNA COVID-19 vaccination. A third dose has been shown to boost protection against severe disease and death in this immunosenescent population, but limited data is available on the immune responses it induces.

Methods

- 85 nursing home residents and 88 staff members, dually vaccinated and naïve to SARS-CoV-2 infection, received a 3rd dose of mRNA COVID-19 vaccine.
- SARS-CoV-2 specific humoral and cellular immune responses were evaluated at day 0, day 28, and month 6 post third dose administration.
- Breakthrough infections were monitored in the six months following third dose administration.
- Analyses were performed on two cohorts: the complete cohort (n=173), and the immunogenicity cohort (n=84) for which complete data were available for day 28 post dose 3 as well as post dose 2.

Table 1. Demographics, characteristics by study groups

		Complete cohort (n = 173)		Immunogenicity cohort (n = 84)	
Characteristic		Staff (n=88)	Residents (n=85)	Staff (n=42)	Residents (n=42)
Age (years, mean ± SD)		48 ± 11	83 ± 11	47 ± 10	82 ± 12
Sex	Female	74 (84%)	46 (54%)	33 (79%)	23 (55%)
Ethnicity	White	85 (97%)	83 (98%)	40 (95%)	40 (95%)
BMI (mean ± SD)		27.1 ± 5.9	25.1 ± 5.1	26.3 ± 5.7	24.6 ± 5.1
Self-reported smoking status	Former smoker	5 (5%)	6 (7%)	3 (7%)	2 (5%)
	Nonsmoker	70 (80%)	69 (81%)	32 (76%)	33 (78%)
	Current smoker	13 (15%)	10 (12%)	7 (17%)	7 (17%)
Comorbidity (at least one self-reported)	Yes	5 (6%)	55 (65%)	3 (7%)	30 (71%)
Time lapse between dose 1 and 3 (days) (mean ± SD)		253 ± 18	247 ± 36	238 ± 11	249 ± 15

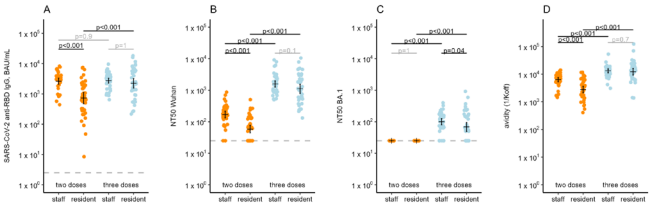

Fig. 1. Humoral immune responses after two (orange) and three (blue) vaccine doses in staff and residents (immunogenicity cohort). Black bars indicate GMT with 95% CI.

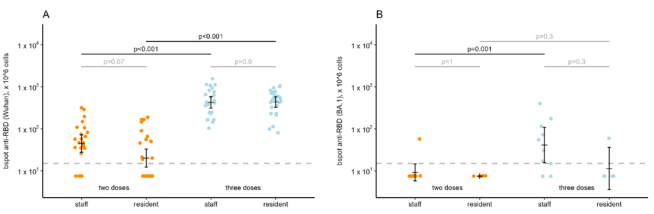

Fig. 2. Frequency of memory B cells (MBC) after two (orange) and three (blue) vaccine doses in staff members and residents of nursing homes, measured by B cell ELISpot and expressed as Spot Forming Cells (SFC) per million input cells, for Wuhan and Omicron BA.1. Black bars indicate GMT with 95% CI.

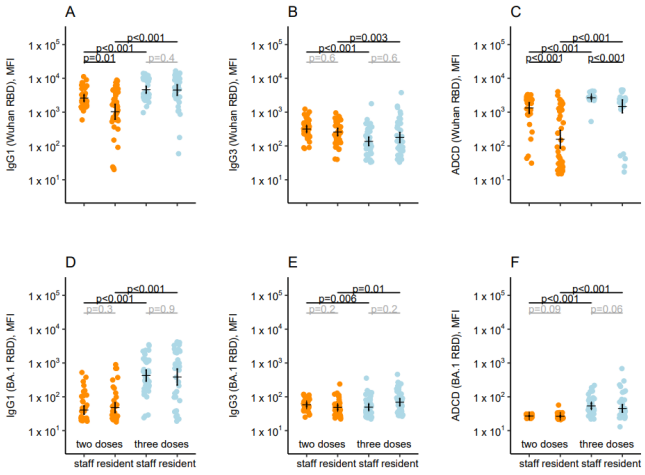

Fig. 3. IgG subclasses and antibody dependent complement deposition (ADCD) measured for RBD Wuahn and Omicron BA.1. Black bars indicate GMT with 95% CI..

Results

- 28 days post third dose, levels of **binding** and **neutralizing** antibodies, and antibody **avidity**, normalized between staff and residents (fig.1).
- All residents had detectable wild type specific neutralizing antibodies post dose 3, compared to just 57% post dose 2.
- **Omicron**-specific neutralizing antibodies remained slightly lower in residents compared to staff.
- A similar normalization was observed in levels of **IgG subtypes** 1 and 3, and in levels of **antibody dependent complement deposition**.
- **Memory B cells** specific for wild type virus were detectable in all participants after third dose. BA.1 specific responses were much lower and only detectable in staff.
- **Breakthrough infections,** in the following six months post third dose were detected in 47% of residents and 49% of staff but were all pauci-symptomatic.
- Incidence of breakthrough infection was **correlated** with levels of SARS-CoV-2 specific IgGs, neutralizing antibodies, antibody avidity and ADCD responses.

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ACKNOWLEDGEMENTS

We thank all laboratory personnel, study nurses, and study participants for their availability, flexibility and dedication.

This research was funded by the Belgian Federal Government through Sciensano.

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Different COVID-19 vaccine platforms in pregnancy: a multidimensional approach to humoral immunity

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CONCLUSION - The use of mRNAVs in pregnancy could be preferred over AVVs as after mRNA vaccination higher antibody titers with a better neutralizing capacity and stronger avidity are reached more quickly. These maternal antibodies are transported across the placenta to the infant, possibly providing protection in the first months of life. The observation that the use of mRNAVs is superior to AVVs in pregnancy is important for the development of future vaccines that can be used during pregnancy.

INTRODUCTION - Pregnant women are a priority group for COVID-19 vaccination because of the increased risk for severe maternal and fetal/neonatal disease associated with COVID-19[1-3]. Our study compared humoral immune responses in pregnant women across different COVID-19 vaccine platforms and investigated the transfer of vaccine-induced immunity from mother to infant during pregnancy.

Methods

- A prospective observational cohort study on COVID-19 vaccination during pregnancy with study design described in Figure 1.
- An ELISA assay, neutralization test and Biolayer Interferometry (BLI) method were used to test respectively titers, neutralization (NA) and avidity of the anti-Receptor-Binding Domain (RBD) Immunoglobulin (IgG) antibodies in serum samples.

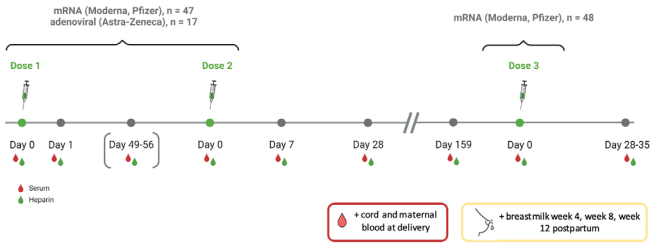

FIGURE 1: Study design

Results

1. Humoral immune responses maternal serum

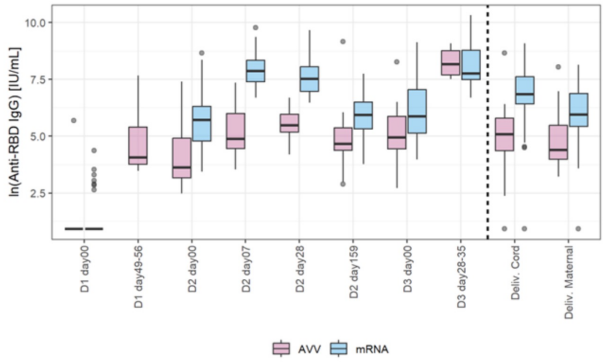

FIGURE 2: Anti-RBD IgG at different timepoints before and after COVID-19 vaccine dose 1 / dose 2 / dose 3 and at delivery

An increase in anti-RBD IgG and NA titers is observed in maternal serum after both messenger-RNA (mRNA) and adenoviral vector (AV) vaccination. mRNA vaccine (mRNAV) recipients show significantly higher titers, NA levels and avidity of the anti-RBD IgG antibodies after the first and second vaccine dose compared to AV vaccine (AVV) recipients at all timepoints for which a measurement is available (Figure 2, 3, 4). A more rapid peak antibody response is observed in women vaccinated with mRNAVs as they reached the highest anti-RBD IgG antibody titer at day 7 after the second dose whereas for women receiving AVVs, the highest titer was observed at day 28 after the second vaccine dose (Figure 2). After postpartum mRNA booster vaccination, no significant differences are observed between both study groups (Figure 2, 3).

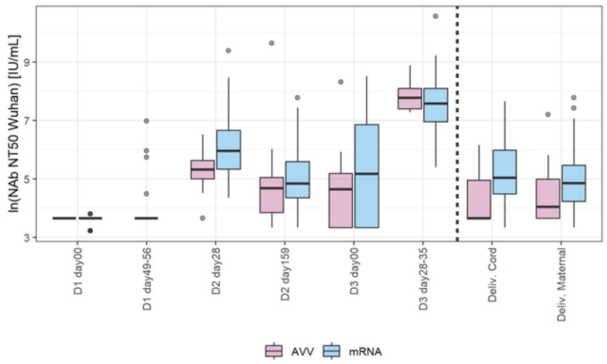

FIGURE 3: NA NT50 Wuhan at different timepoints before and after COVID-19 vaccine dose 1 / dose 2 / dose 3 and at delivery

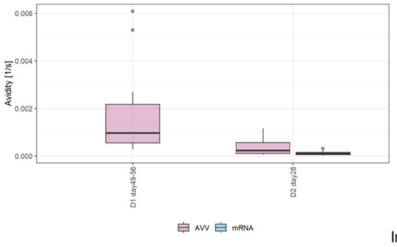

FIGURE 4: Avidity of anti-RBD igG at day 49-56 after dose 1 in the AVV group and at day 28 after dose 2 in the AVV and mRNA group

2. Transplacental transfer

Higher titers of anti-RBD IgG and NA are observed in cord blood after mRNA compared to AV vaccination. A positive correlation between maternal and cord blood anti-RBD IgG levels was seen, both after mRNA and AV vaccination (Figure 5).

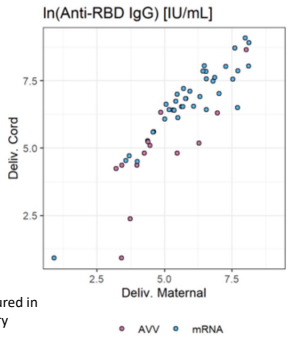

FIGURE 5: Correlation between anti-RBD IgG measured in maternal serum versus in cord blood at delivery

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ACKNOWLEDGEMENTS

We thank all the laboratory personnel, the nurses, and the study participants for their availability, flexibility and dedication.

This research was funded by the Belgian Federal Government through Sciensano.

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COvid VACcination during LACtation: the COVALAC-study

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INTRODUCTION

Similar to other populations, breastfeeding women encounter SARS-CoV-2 and might contract COVID-19. The availability of new vaccines against COVID-19, urged for guidance about vaccination during lactation.

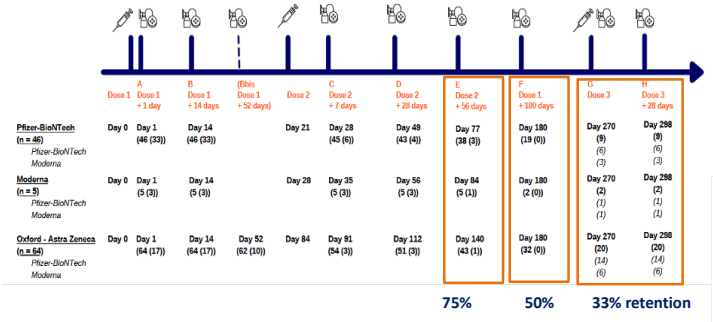
AIM

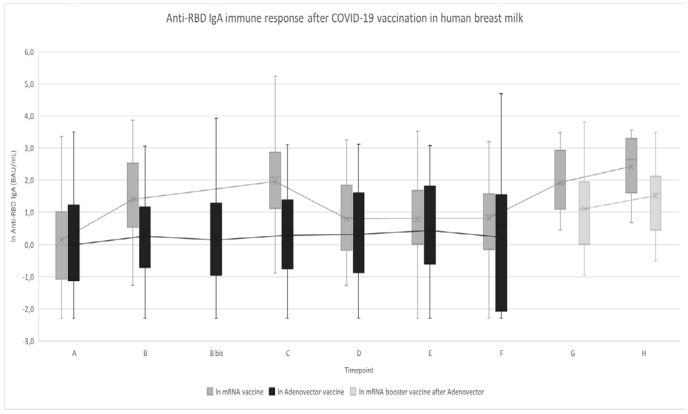
Get an insight in the excretion of antibodies into breastmilk after vaccination with different types of COVID-19 vaccines, namely mRNA-based vaccines and adenoviral vector based vaccines (AVV).

METHODS

o Design: Prospective cohort study, part of PREGCOVAC.BE
o Setting: Belgium
o Participants: Women, older then 18 years and breastfeeding for at least 14 days, vaccinated with a COVID-vaccine, either mRNA or AVV, during the lactation period.
o Variables: COVID-19-specific sIgA and IgG antibodies against the spike protein and its receptor binding domain (RBD) were measured on all available breast milk samples with a Luminex Multiplex® assay

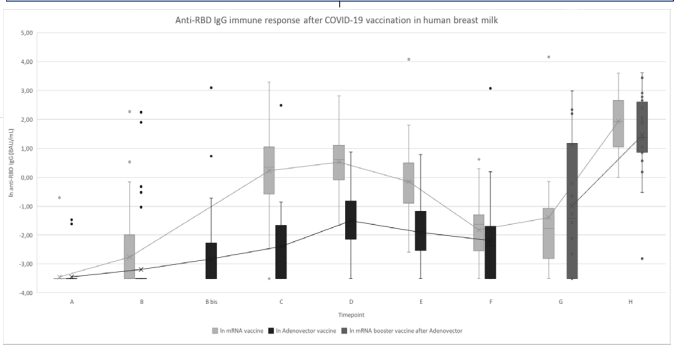
WORK PLAN, SAMPLE COLLECTION & CURRENT PROGRESS





RESULTS

o ***115 vaccinated women were included***
- 46 BNT162b2 vaccine (mRNA group)
- 5 mRNA-1273 vaccine (mRNA group)
- 64 ChAdOx1-S vaccine (adenoviral vector group - AVV))



o ***SARS-CoV-2 specific anti-RDB IgA antibodies***
- Rise in SARS-CoV-2 specific anti-RBD IgA titers 14 days after dose 1 (TP B), in both mRNA (mean 1.40 ng/ml; range -1.1-3.9, SD 1.27) and AVV vaccine (mean 0.26 ng/ml, range -2.30-3.07, SD 1.50)
- Highest titres at day 56 after dose 2 in AVV group (TP E) (mean 0.43 ng/ml, range -2.30-3.08, SD 1.60)
- Highest titres at day 7 after dose 2 in mRNA group (TP C) (mean 1.96 ng/ml, range -0.9-5.2, SD 1.18)

o ***Anti-RBD IgA antibodies after booster vaccination***
- Significant increase in antibody titers after both homologous and heterologous booster vaccination (mean 1.8 ng/ml; range -0.51-3.6 ng/ml; SD 1.16)
- Possible exponentiated by natural SARS-CoV-2 infections, confirmed with anti-SARS-CoV-2 Nucleocapsid in human milk (4/115 at TP A, 5/31 at TP H)

o ***SARS-CoV-2 specific anti-RBD IgG antibodies***
- Rise in SARS-CoV-2 specific anti-RBD IgG titers 14 days after dose 1 (TP B), in both mRNA (mean -2.6 BAU/ml, range -3.51-2.27, SD 1.32) as AVV (mean -3.19, range -3.51-2.25 , SD 1.44)
- Strong rise 28 days after dose 2 (TP D) - in both mRNA group (mean 0.52 BAU/ml, range -1.66-2.22, SD 1.01) as AVV (mean -1.51, range -3.51-0.16, SD 0.97)

o ***Anti-RBD IgG antibodies after booster vaccination***
- Strong rise after booster vaccination with mRNA, irrespective of baseline vaccination with mRNA or AVV (mean 1.62 BAU/ml; range -2.81-3.61 BAU/ml; SD 1.35)
- Possible exponentiated by natural SARS-CoV-2 infections, confirmed with anti-SARS-CoV-2 Nucleocapsid in human milk (4/115 at TP A, 5/31 at TP H)

CONCLUSION

o The use of mRNA vaccines could be prefered over adenovector vaccines. mRNA vaccines lead to higher antibody toters compared to AVV. This increase in antibody titers is seen in a shorter timeframe.
o The study contributes to the knowledge on SARS-CoV-2 vaccination and the use of different vaccine-platforms during breastfeeding. As vaccination during lactation could result in clinically relevant sIgA-titers in breastmilk and possible protecting the child in early life, it is of importance that women have this information to decide whether to take the vaccine.

*No conflicts to disclose

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Do lung transplant recipients respond to Covid-19 vaccine despite immunosuppressive treatment? LUNG-VAC cohort

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Conclusions

- Pre-vaccination naive LTX recipients have poorer humoral response to the vaccine compared to healthy people
- Boosters can however increase the level of binding and neutralizing antibodies
- Cellular response remains low, even after boosters

Lung transplant recipients (LTX) are particularly susceptible to viral respiratory infections (1). The chronic immunosuppressive state is also associated with reduced immune responses to viral vaccines (2). Clinical studies are required to assess the immunogenicity and safety profiles of available vaccines, including mRNA vaccines, to define optimal immunization strategies for these vulnerable patients.

Methods

- We conducted a monocentric, prospective study in a cohort of 67 SARS-CoV-2-naive and 8 previously infected lung transplant recipients (LTx) vaccinated, sequentially, with four doses of BNT162b2 Pfizer/BioNTech mRNA SARS-CoV-2 vaccine. We analyzed the presence and evolution of humoral and cellular responses over time and compared it to those observed in a healthy control population (40 naïve and 66 pre-infected controls).
- This study was approved by the C.U.B Erasme Ethics Committee (reference P2021/182/B4062021000096).
- Demographic and clinical data were collected.
- We assessed binding (anti-RBD IgG) and neutralizing (NT50) antibody levels and cell-mediated immune responses (S1 and S2 specific cells producing INFY by ELISPOT) on the day of vaccination (D0) and 28 days after (D28), for each of the different doses.

Results

51% of naïve patients present a seroconversion (anti-RBD IgG > 5,4 BAU/ml) 28 days post second dose (D2D28). This proportion raised up to 58% and 71% respectively after dose 3 and 4. There is no impact of age, sex, time since Tx or comorbidities on response. We found no negative impact of immunosuppressive regimen mycophenolate mofetil on the humoral response (**table 1**).

LTX recipients have poor binding humoral response compared to healthy people. However, this response may improve after boosters, even if it never reaches a normal response. Anti-RBD IgG geometric means are 12,2 [1,5 – 97,5], 27 [2,2 - 328] and 62,7 [4,6 – 854,9] BAU/ml at D2D28, D3D28 and D4D28 (**figure 1**).

Only 4 of the 67 naive patients have developed NT50 after 2 doses of vaccine (6%). This proportion increases to 31% after 3 doses (18/57 patients) and stabilizes at 32% at D4D28 (9/28), in contrast to healthy controls which already reach 100% at D3D28 (**figure 2**).

Cellular responses are weak and do not increase after boosters (**figure 3**).

Table 1: Demographic and clinical characteristics of naive recipients, stratified by seropositivity to anti-RDB IgG antibodies after doses of SARS-CoV-2 mRNA Vaccine.

Data are n (%), mean ±SD, median [range]. Seropositivity was defined as > 5.4 BAU/ml. All patients are treated with calcineurin inhibitors and steroids ± antimetabolites (mycophenolate mofetil or azathioprine) as immunosuppressive therapy. GFR: glomerular renal filtration, ml: milliliter, kg: kilogram.

	All participants	21 days after dose 1 (D21) n=66			28 days after dose 2 (D49) n=65		
		Sero-positive	Sero-negative	P value	Sero-positive	Sero-negative	P value
	66	9 (14%)	57 (86%)		33 (51%)	32 (49%)	
Age, years	52 ± 14	46 ± 17	53 ± 13	0.181	51 ± 15	54 ± 12	0.5
Gender n (%)							
Female	33 (50)	6 (67)	27 (47)		17 (51.5)	15 (47)	
Male	33 (50)	3 (33)	30 (53)	0.282	16 (48.5)	17 (53)	0.708
Time since transplantation n (%)							
<2 y	9 (14)	1 (11)	8 (14)		5 (15)	3 (9)	
2-5 y	23 (35)	2 (22)	21 (37)		11 (33)	12 (38)	
6-9 y	9 (14)	2 (22)	7 (12)		5 (15)	4 (13)	
>9 y	25 (38)	4 (44)	21 (37)	0.806	12 (36)	13 (41)	0.919
Comorbidities n (%)							
Hypertension	37 (58)	5 (54)	32 (86)	0.974	17 (46)	20 (54)	0.317
Diabetes	26 (39)	5 (19)	21 (81)	0.286	13 (50)	12 (46)	0.826
Obesity	7 (11)	1 (14)	6 (86)	0.958	5 (71)	2 (29)	0.244
Chronic renal failure (GRF < 30 ml/min)	8 (12)	0 (0)	8 (100)	0.231	3 (38)	5 (63)	0.419
Immunosuppressive therapy n (%)							
No antimetabolites	26 (39)	4 (15)	22 (85)		16 (62)	10 (38)	
Included antimetabolites	40 (61)	5 (13)	35 (88)	0.739	17 (44)	22 (56)	0.156
Mycophenolate	26 (39)	2 (8)	24 (92)	0.465	10 (40)	15 (60)	0.17
mg/kg	22.5 [6.8 - 40]	32 [24.1 - 40]	21.3 [6.8 - 38.5]	0.196	21.1 [6.8 - 40]	24.4 [14.7 - 38.5]	0.835
azathioprine	14 (21)	3 (21)	11 (79)	0.382	7 (50)	7 (50)	>0.999
mg/kg	0.9 [0.4 - 2.4]	1.1 [1 - 1.8]	0.7 [0.4 - 2.4]	0.088	0.9 [0.7 - 1.8]	0.7 [0.4 - 2.4]	0.535
Methylprednisolone mg/kg	0.08 [0.04 – 0.19]	0.08 [0.04 – 0.12]	0.08 [0.05 – 0.19]	0.662	0.07 [0.04– 0.16]	0.09 [0.06 – 0.19]	0.124
IgG anti RBD title BAU/ml	4 [1-10]	29 [8-113]	3 [3-3]	<0.001	41 [7-228]	3 [3-3]	<0.001

	All participants	28 days after dose 3 (D3D28) n= 57			28 days after dose 4 (D4D28) n=28		
		Sero-positive	Sero-negative	P value	Sero-positive	Sero-negative	P value
	33 (58%)	24 (42%)			20 (71%)	8 (29%)	
Age, years	50 ± 16	55 ± 10	0.245		50 ± 15	55 ± 12	0.382
Gender n (%)							
Female	15 (45.5)	11 (44)			6 (37.5)	7 (54)	
Male	18 (54.5)	14 (56)	>0.999		10 (62.5)	6 (46)	0.535
Time since transplantation n (%)							
<2 y	4 (12)	4 (16)			3 (19)	2 (15)	
2-5 y	9 (27)	11 (44)			5 (31)	6 (46)	
6-9 y	6 (18)	3 (12)			4 (25)	1 (8)	
>9 y	14 (42)	7 (28)	0.485		4 (25)	4 (31)	0.885
Comorbidities n (%)							
Hypertension	17 (51.5)	15 (60)	0.599		10 (27)	7 (19)	0.522
Diabetes	13(39)	9 (36)	0.265		6 (23)	3 (12)	0.195
Obesity	4 (12)	2 (8)	0.69		2 (39)	0 (0)	0.173
Chronic renal failure (GRF < 30 ml/min)	3 (39)	4 (16)	0.45		1 (13)	2 (25)	0.627
Immunosuppressive therapy n (%)							
No antimetabolites	14 (58)	10 (42)			16 (62)	10 (38)	
Included antimetabolites	19 (56)	15 (44)	>0.999		17 (44)	22 (56)	0.75
Mycophenolate	13 (59)	9 (41)	>0.999		10 (40)	15 (60)	0.332
mg/kg		25 [15 - 38]	0.112			24.4 [14.7 - 38.5]	0.271
azathioprine	20 [7 - 30]	6 (50)	0.382		21.1 [6.8 - 40]	7 (50)	0.14
mg/kg	6 (50)	0.8 [0.6 - 1.8]	0.937		7 (50)	0.7 [0.4 - 2.4]	0.667
Methylprednisolone mg/kg	0.8 [0.6 - 1.8]				0.9 [0.7 - 1.8]		
IgG anti RBD title BAU/ml	145[20-1071]	3 [3-3]	<0.001		361 [57-2291]	7 [1-36]	<0.001

Figure 1: Evolution of anti-RBD IgG titers in infection-naive lung transplant recipients after doses of mRNA BNT162b2 vaccine compare to healthy controls.

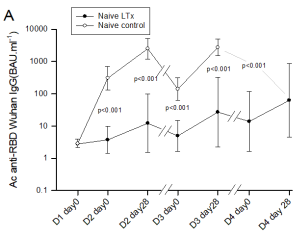


Figure 2: Evolution of neutralizing antibodies (NT50) in infection-naive lung transplant recipients after doses of mRNA BNT162b2 vaccine (A) compare to healthy controls (B)

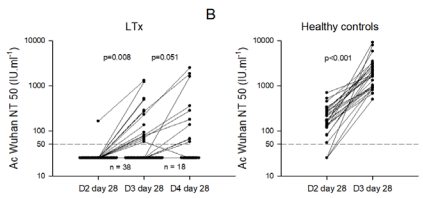
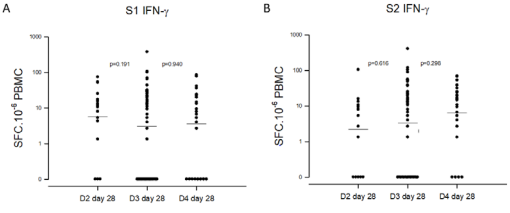


Figure 3: Cell-mediated immune response after doses of vaccine in naive lung transplant. A: S1- specific cells producing IFN-Y. B: S2-specific cells producing IFN-Y



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ACKNOWLEDGEMENTS

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Humoral and cellular immune correlates of protection against COVID-19 in kidney transplant recipients

D. Kemlin[1,2], N. Gemander[1], S. Depickère[3], V. Olislagers[1], D. Georges[1,7], A. Waegemans[1], P. Pannus[3], A. Lemy[4], M. E. Goossens[3], I. Desombere[3], J. Michiels[5], M. Vandevenne[7], L. Heyndrickx[5], K.K. Ariën[5, 6], A. Matagne[7], M.E. Ackerman[8], A. Le Moine[2], A. Marchant[1].

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The risk of symptomatic COVID-19 in naïve kidney transplant recipients was best predicted by neutralizing antibody and S2-specific IFN-γ responses, measured one month after the booster dose.

As solid organ recipients are at high risk of severe COVID-19 and respond poorly to primary SARS-CoV-2 mRNA vaccination, they have been prioritized for booster vaccination. However, even if neutralizing antibody titer is associated with protection against COVID-19 in global population, an immunological correlate of protection has not been identified in immunocompromised populations.

Methods

- Prospective monocentric cohort study in kidney transplant recipients still COVID-19 free one month after the third dose of BNT162b2 mRNA vaccine (n=54).
- Symptomatic SARS-CoV-2 breakthrough infections (BTI) were reported from September 1st 2021, to February 1st, 2022. Delta and omicron were the dominant variants.
- Exploration of associations between BTI, vaccine responses and patient characteristics.

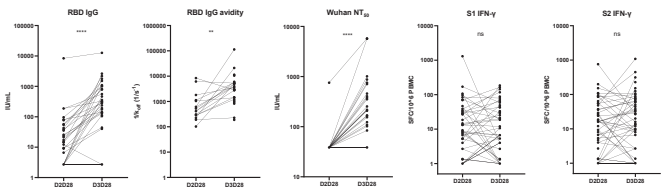
Results

1. High incidence of breakthrough infections (BTI)

- Symptomatic COVID-19 was diagnosed in 32% of kidney transplant recipients (n=17).
- Curative monoclonal antibodies were administered in 83% cases.
- All had mild COVID-19, except one who required oxygen.

2. Increasing of the levels and quality of SARS-CoV-2 spike-specific antibodies by the booster dose

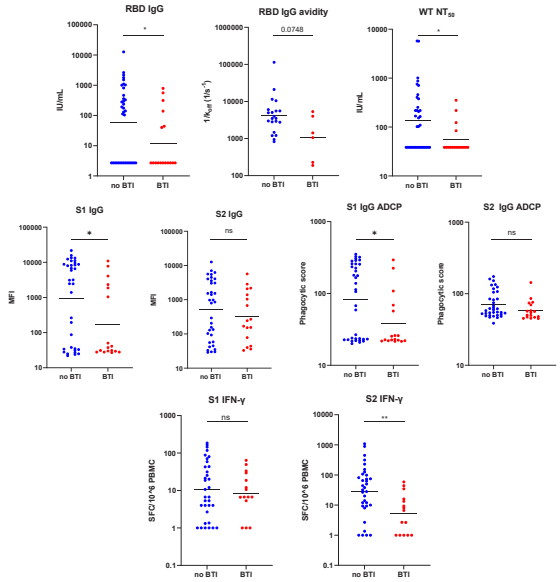
Contrary to humoral response, IFN-γ responses to SARS-21 CoV-2 S1 and S2 were not significantly different after the 2nd and 3rd dose.



Immune response to second and third COVID-19 mRNA vaccinations in kidney transplant recipients. Immune responses, including SARS-CoV-2 receptor binding domain (RBD)-specific binding IgG titer (RBD IgG) and avidity (RBD IgG avidity), SARS-CoV-2 Wuhan neutralizing antibody titer (Wuhan NT_{50}) and S1 (S1 IFN-γ) and S2 (S2 IFN-γ) domain-specific IFN-γ-producing cells, were measured one month after the 2nd dose (D2D28) and one month after the 3rd dose (D3D28). Wilcoxon signed rank test. ** p<0.01; and **** p<0.0001. ns: not significant.

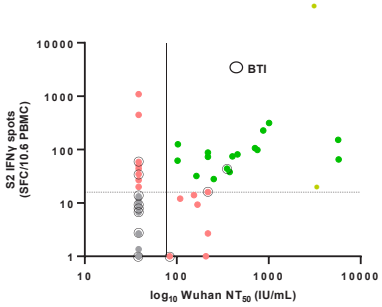
3. High neutralizing antibody titer and S2-IFNγ responses associated with a low incidence of BTI

- No demographic or clinical parameter correlated with the risk of BTI.
- Only immune parameters, both humoral and cellular, were associated with the risk of BTI. They were highly correlated.



Immune response to booster COVID-19 vaccination in kidney transplant recipients with and without symptomatic BTI. Immune responses were measured 28 days after a third dose of BNT162b2 COVID-19 vaccine in participants who developed (red symbols) or did not develop (blue symbols) BTI. S1-specific binding IgG (S1 IgG), S2-specific binding IgG (S2 IgG), S1-specific binding IgG antibody-dependant cellular phagocytosis (S1 IgG ADCP) and S2-specific binding IgG antibody-dependant cellular phagocytosis (S1 IgG ADCP). Geometric means. Wilcoxon-Mann-Whitney test. * p<0.05; ** p<0.01. ns: not significant.

- In multivariate analysis, the risk of BTI was best predicted by neutralizing antibody titer and S2-specific IFN-γ responses.
- The lowest risk of BTI was observed in high responders patients with high humoral and cellular responses. An intermediate and similar risk was observed in patients with either high humoral or high cellular responses.



Risk BTI according to neutralizing antibody against Wuhan and S2 T-cell response
Patients were categorized on the basis of median neutralizing antibody titer and S2 IFN-γ spot frequency in low responders (grey), medium responders (red) and high responders (green) Circled symbols indicate patients with BTI. Dotted line indicates the median S2 IFNγ response (16.1 SFC/10^6 PBMC). Black line indicates the median neutralizing antibody titer (77 IU/mL).

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ACKNOWLEDGEMENTS

We thank all the laboratory personnel, the nurses, and the study participants for their availability, flexibility and dedication.

This research was funded by the Belgian Federal Government through Sciensano. DK and NK received a PhD studentship from the FRS-FNRS and the Fonds Erasme, Belgium.

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Hybrid immunity overcomes defective immune response to COVID-19 vaccination in kidney transplant recipients

N. Gemander[1], D. Kemlin[1,2], S. Depickère[3], N. S. Kelkar[4], P. Pannus[1], S. Sharma[1], A. Waegemans[1], V. Olislagers[1], D. Georges[1,5], E. Dhondt[6], M. Braga[6], L. Heyndrickx[6], J.Michiels[6], A. Thiriard[1], A. Lemy[7], M. Vandevenne[5], M. E. Goossens[3], A. Matagne[5], I. Desombere[8], K. K. Ariën[6,9], M. E. Ackerman[4,10], A. Le Moine[1,2], A. Marchant[1]

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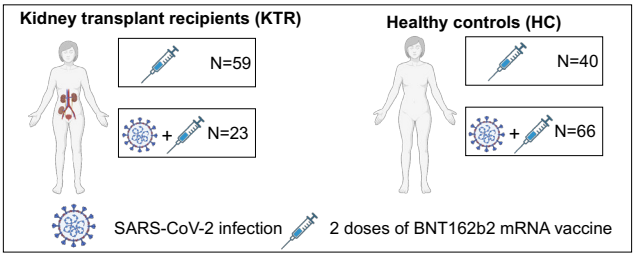
Conclusion

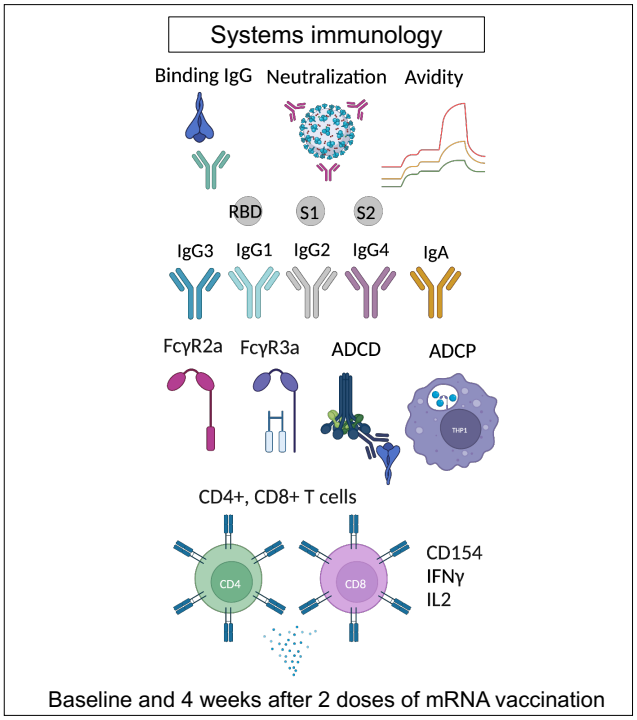
Hybrid immunity overcomes immune suppression and provides potent humoral and cellular immunity to SARS-CoV-2 in kidney transplant recipients.

Introduction

Comorbidities and immunosuppressive therapies are associated with reduced immune responses to primary COVID-19 mRNA vaccination in kidney transplant recipients (KTR). In healthy individuals, prior SARS-COV-2 infection is associated with increased vaccine responses, a phenotype called hybrid immunity. In this study, we explored the potential influence of immune suppression on hybrid immunity in kidney transplant recipients assessing neutralizing, non-neutralizing functions of antibodies and cellular immune responses before and after mRNA vaccination.

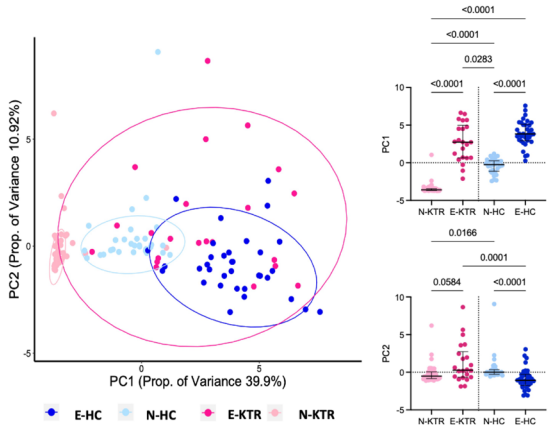
Methods





Results

Principal Component Analysis (PCA) integrating immune responses after mRNA vaccination



N-KTR and E-KTR have unique vaccine response profiles across many different immune effectors

SARS-CoV-2-naive kidney transplant recipients (N-KTR)

- Low antibody and T cell response to mRNA vaccination compared to experienced kidney transplant recipients and healthy controls (HC)
- Risk factors for low vaccine responses
  - Age
  - Recent or retransplantation
  - Arterial hypertension
  - Mycophenolate mofetil

SARS-CoV-2-experienced kidney transplant recipients (E-KTR)

- High antibody and T cell response to mRNA vaccination similar to experienced healthy controls (E-HC)
- Risk factors for low vaccine responses
  - Recent transplantation

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- Rincon-Arevalo et al, Sci Immunol. 2021 Jun 15;6(60):eabj1031.
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ACKNOWLEDGEMENTS

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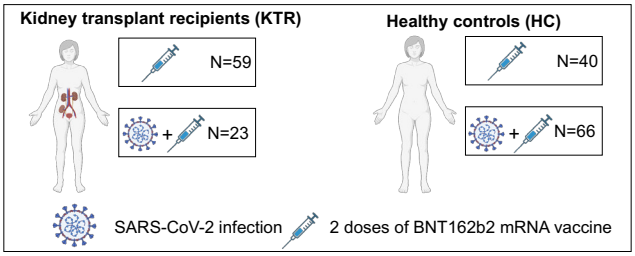

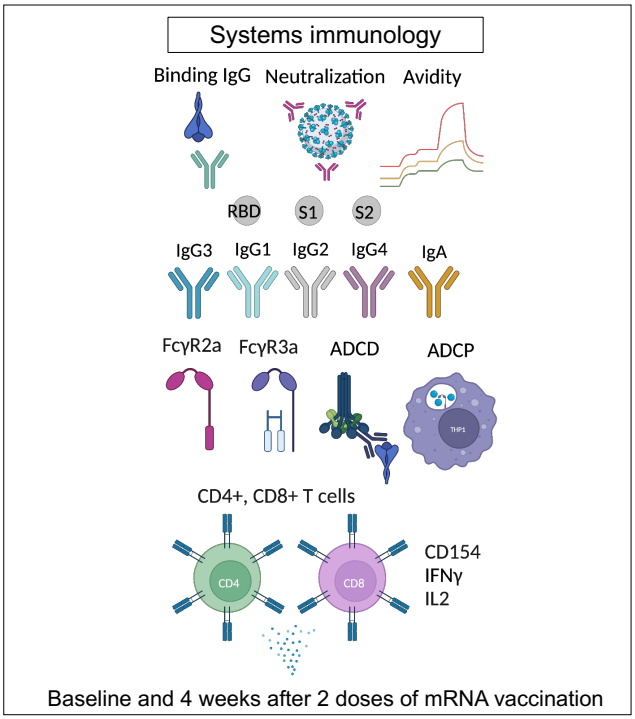

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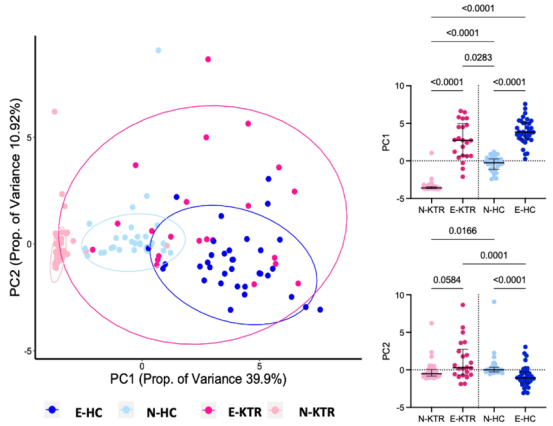

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Reduced humoral immune response after BNT162b2 COVID-19 mRNA vaccination in cancer patients under anti-neoplastic treatment

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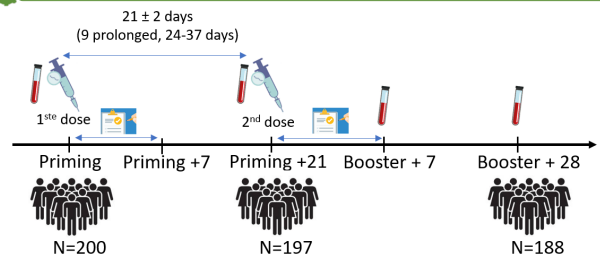
*Equally contributing

Take home messages

- The BNT162b2 vaccine is well-tolerated in cancer patients
- Two doses of BNT162b2 results in a blunted humoral immune response in cancer patients under active treatment
- The humoral immune response after BNT162b2 vaccination differs among anti-neoplastic treatments
- Two doses of BNT162b2 may be insufficient to protect patients receiving chemotherapy or rituximab

Although patients with solid tumors often develop immune response signatures similar to those of non-cancer patients, they are at increased risk of severe COVID-19[1,2]. Patients with hematological malignancies that were exposed to SARS-CoV-2 display a heterogeneous humoral immune response, an exhausted T-cell phenotype and a high prevalence of prolonged viral shedding[3,4]. Hence, it is clear that SARS-CoV-2 vaccines should safeguard this population at risk. However, ongoing anti-neoplastic treatment with cytotoxic drugs was an exclusion criterion in the pivotal phase III trial that investigated the effectiveness of the Pfizer-BioNTech BNT162b2 mRNA vaccine[5]. This study aims to investigate the safety and effectiveness of this SARS-CoV-2 vaccine in cancer patients receiving different types of anti-neoplastic treatment.

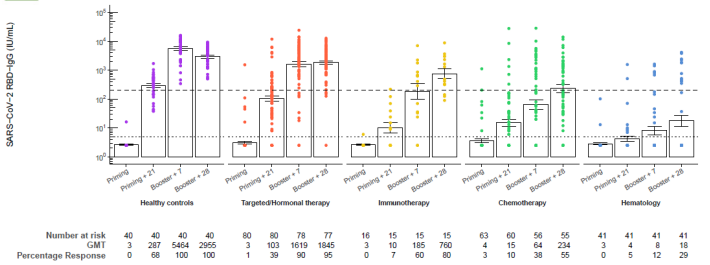
Methods



- Quantitative detection of IgG antibody levels (Wantai SARS-CoV-2 IgG ELISA)
- In vitro SARS-CoV-2 neutralization test towards the Wuhan (wild type) strain

Patient reported outcomes of local and systemic adverse events

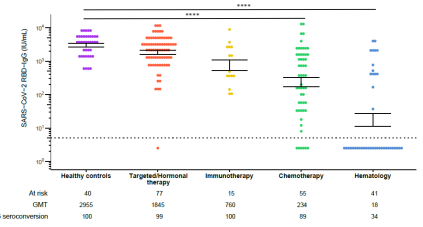
Delayed antibody response in cancer patients undergoing treatment



Number at risk	40	40	40	40	80	80	78	77	16	15	15	15	63	60	56	55	41	41	41	41
GMT	3	287	5464	2955	3	103	1619	1845	3	10	185	760	4	15	64	234	3	4	8	18
Percentage Response	0	68	100	100	1	39	90	95	0	7	60	80	3	10	38	55	0	5	12	29

Linear mixed-effects model with participants as a random intercept for log-transformed IgG over time, interaction: p<0.0001

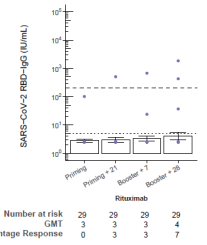
Lower antibody titers in patients with solid tumors undergoing chemotherapy and hematologic cancer patients



At risk	40	77	15	55	41
GMT	2955	1845	760	234	18
% IgG seroconversion	100	99	100	89	34

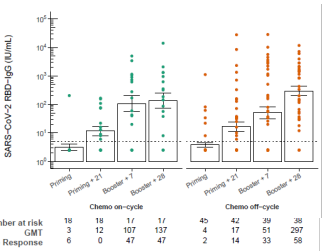
One-way ANOVA with pairwise-comparison using Tukey's honestly significant difference post hoc test

Most patients receiving B-cell depleting therapy are unable to mount a humoral response



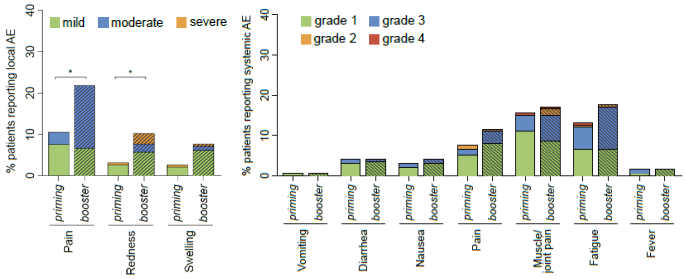
Number at risk	29	29	29	29
GMT	3	3	3	4
Percentage Response	0	3	3	7

Antibody response is independent of the timing between vaccination and chemotherapy administration



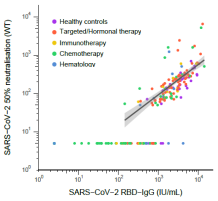
Number at risk	18	18	17	17	40	42	39	38
GMT	3	12	107	137	4	17	51	297
Percentage Response	6	0	47	47	2	14	33	58

Local pain and redness was higher after booster dose, but systemic AEs were similar after each dose

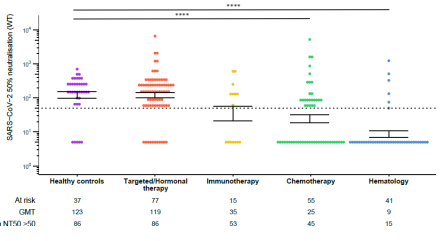


McNemar test with Bonferonni-Holm correction: *p<0.05

As SARS-CoV-2 RBD-IgG levels correlated with NT50 28 days post-booster, differences between cohorts persist when comparing NT50 values



Spearman correlation for values above the LLQ



At risk	37	77	15	55	41
GMT	123	119	35	25	9
% with NT50 >50	86	86	53	45	15

One-way ANOVA with pairwise-comparison using Tukey's honestly significant difference post hoc test

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FUNDING
This research was funded by the Belgian Federal Government through Sciensano.

ACKNOWLEDGEMENTS
We are grateful to the B-VOICE study team for patient inclusion and sample collection. We also thank all our patients for study participation.

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1666p: Humoral and cellular immune responses against SARS-CoV-2 after 3rd dose BNT162b2 following dual-dose vaccination with BNT162b2 vs ChAdOx1 in cancer patients

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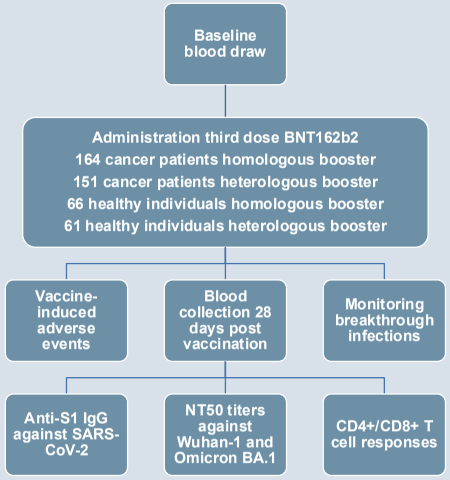
Introduction

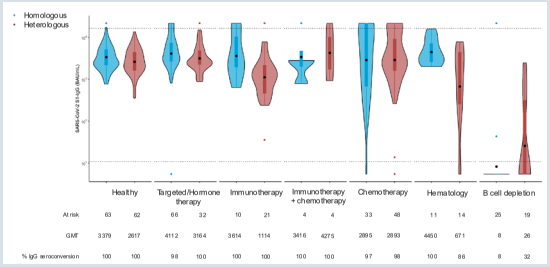
- Cancer patients display reduced humoral responses after dual-dose COVID-19 vaccination
- Third vaccination dose boosts immune responses
- Homologous (same as dual-dose vaccination) and heterologous (different as dual-dose vaccination) boosters have been administered

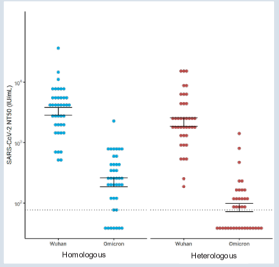
Patients and methods

- Homologous booster: BNT162b2 after dual-dose BNT162b2
- Heterologous booster: BNT162b2 after dual-dose ChAdOx1



Results



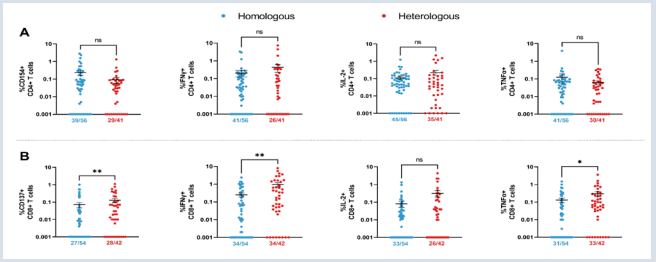


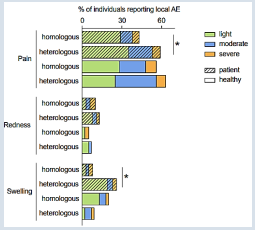
Vaccine induced antibody response

- Similar SARS-CoV-2 anti-S1 IgG antibody levels
- Hematological patients receiving B-cell depleting therapy mount lower binding antibody responses
- Similar NT50 against Wuhan-1
- Higher NT50 against Omicron BA.1 after homologous boosting
- Comparable occurrence of breakthrough infections

T cell reactivity

- Similar CD4+ T cell response between homologous and heterologous boosting
- Lower CD154 response after heterologous boosting in hematology cohort
- 30% did not mount a CD4+ T cell response
- Higher CD137, IFNγ and TNFα response after heterologous boosting
- 50% (homologous) and 33% (heterologous) did not mount CD8+ T cell response
- Majority of patients receiving B-cell depleting therapy mount CD8+ T cell response





Adverse events (AEs)

- >50% reported pain at injection site
- More local pain/swelling after heterologous boosting
- No vaccine related serious AEs
- Acceptable safety profile

Conclusion

1. Higher NT50 against Omicron BA.1 after three doses BNT162b2
2. Higher CD8+ T cell responses after dual-dose ChAdOx1 followed by BNT162b2
3. Local AEs more common after dual-dose ChAdOx1 followed by BNT162b2

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No conflicts of interest to declare

Study sponsored by Kom op tegen Kanker

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Humoral immune response after ChAdOx1 COVID-19 vaccination in cancer patients under anti-neoplastic treatment

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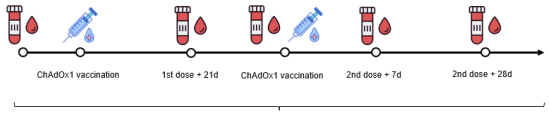
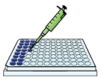
Take home messages

- ChAdOx1 COVID-19 vaccine is well-tolerated in onco-hematological patients
- No to limited antibody response after dual-dose ChAdOx1 vaccination in patients receiving B cell depleting therapy
- Dual-dose ChAdOx1 elicits lower anti-S1 antibody levels compared to BNT162b2 vaccination, especially in patients treated with targeted/hormonal and immunotherapy

Cancer patients are at higher risk of developing severe COVID-19 and low antibody responses have been reported after BNT162b2 vaccination in cancer patients[1-3]. However, efficacy of the ChAdOx1 COVID-19 vaccination in cancer patients undergoing treatment is unclear.

Methods

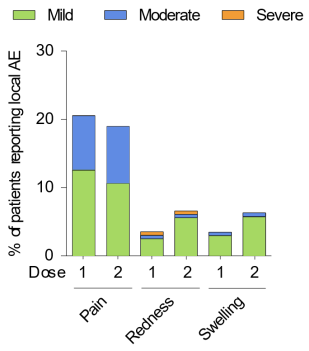




- Retrospectively request relevant serum samples from Biobank Antwerp
- Anti-S1 IgG antibody detection
- Siemens Healthineers Atellica IM SARS-CoV-2 IgG assay
- LLQ: 10.90 BAU/mL, ULQ: 16350.00 BAU/mL

Results

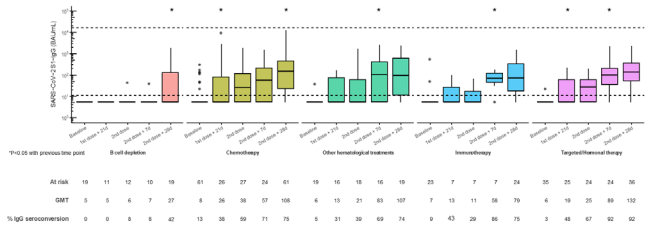
Adverse events



Fisher exact test

- 20% of the patients reported mild to moderate pain at injection site
- Similar safety profile after 1st and 2nd dose ChAdOx1

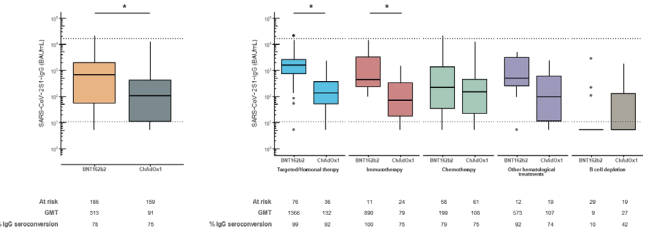
Primo-vaccination with ChAdOx1



Linear mixed-effects model with participants as a random intercept for log-transformed IgG over time, interaction: p<0.0001

- Primo-vaccination induced humoral antibody response in all patient cohorts
- Lower antibody titers after dual-dose ChAdOx1 vaccination in patients receiving B cell depleting therapy compared to chemotherapy and targeted/hormonal therapy

Dual-dose ChAdOx1 elicits lower SARS-CoV-2 anti-S1 IgG antibody titers compared to BNT162b2



T-test with pairwise comparison using Turkey's honestly significant difference post hoc test
Fisher exact test

- Especially in patients receiving immunotherapy and targeted/hormonal therapy
- Patients receiving B-cell depleting therapy vaccinated with ChAdOx1 are 6.03 times more likely to develop antibodies after primo-vaccination compared to BNT162b2 vaccination

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ACKNOWLEDGEMENTS

We are grateful to the B-VOICE and Tri-VOICE plus study teams for patient inclusion and sample collection. We also thank all our patients for study participation.

This research was funded by the Belgian Federal Government through Sciensano.

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Long-term dynamics of anti-SARS-CoV-2 IgG antibodies post COVID-19 primo and dual booster vaccination in a Belgian oncological population

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Take home messages

- **More than 90% of cancer patients mount a detectable antibody response against SARS-CoV-2 after 2nd booster (4 vaccination doses)**
- **Similar antibody dynamics over time regardless type of primo-vaccination**

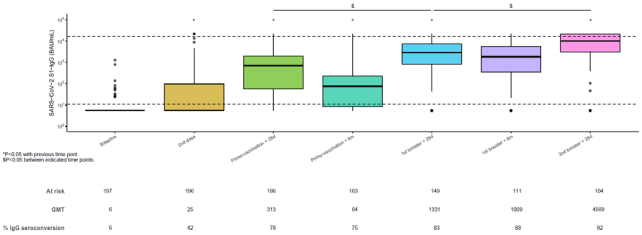
Due to their immunocompromised status, cancer patients have reduced immune responses against SARS-CoV-2 after COVID-19 primo-vaccination[1]. The administration of booster vaccines has been recommended for this population to improve the humoral immune response against SARS-CoV-2[2-4].

Methods

- B-VOICE (N=200): 2x BNT162b2 + 2x BNT162b2 booster
- Tri-VOICE plus (N=180): 2x ChAdOx1 + 2x BNT162b2 booster
- Real-V (N=379): Vaccination within national vaccination campaign
- Up to ten serum samples collected per patient over a period of one year after first dose administration
- Quantitative detection of anti-S1 IgG antibodies with the Siemens Healthineers Atellica IM SARS-CoV-2 IgG assay. LLQ: 10.90 BAU/mL, ULQ: 16350.00 BAU/mL
- Linear mixed-effects model with participants as a random intercept for log-transformed IgG over time, interaction: p<0.0001

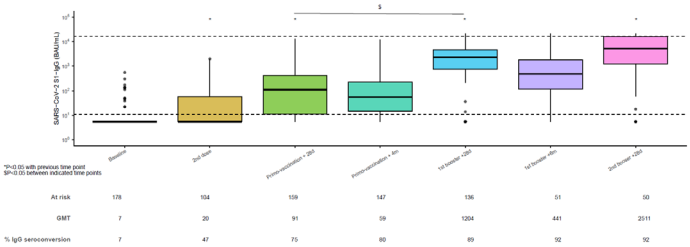
Results

B-VOICE



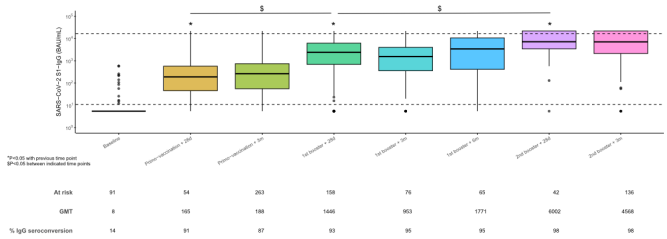
- 78% of cancer patients produces antibodies after primo-vaccination
- Antibody waning six months after primo-vaccination with BNT162b2
- No significant waning after 1st booster
- Beneficial effect of booster vaccines

Tri-VOICE plus



- No significant antibody waning
- 1st BNT162b2 booster induces increased antibody titers compared to after ChAdOx1 primo-vaccination
- 2nd booster did not further increase humoral immune response

REAL-V



- >90% of the cancer patients is able to mount a detectable antibody response after primo-vaccination
- No significant antibody waning
- Each booster dose increases SARS-CoV-2 anti-S1 IgG antibody titers compared to prior vaccine administration

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ACKNOWLEDGEMENTS

We kindly thank the B-VOICE, Tri-VOICE plus and REAL-V participants for study participation, the staff members of the Biobank Antwerp and all recruiting physicians. In addition, we thank the B-VOICE, Tri-VOICE plus and REAL-V study teams from all recruiting centers for patient inclusion and sample collection and the clinical biology study team for performing serological analysis.

This research was funded by the Belgian Federal Government through Sciensano and Kom op Tegen Kanker.

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Predictive model for BNT162b2 vaccine response in cancer patients treated with anti-neoplastic drugs based on blood cytokines and growth factors

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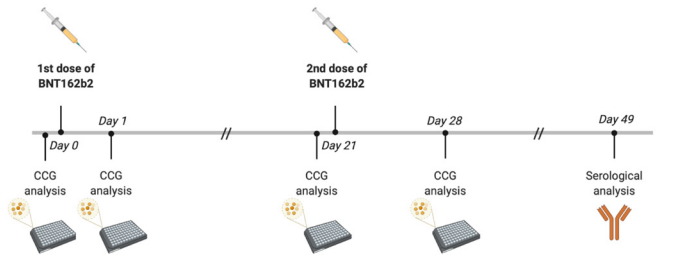
Conclusions

- BNT162b2 vaccine administration altered levels of several cytokines, chemokines and growth factors (CCG) in cancer patients linked with **anti-viral response induction** despite being treated with anti-cancer treatments
- The CCG profiles were **not significantly different** in patients receiving **different anti-cancer treatments**
- We identified a **unique signature based on 4 CCGs** (CRP, IL-15, IL-18 and PIGF) that could be utilised as a **predictive marker of a diminished immune response** to vaccination in cancer patients

Patients with cancer, especially hematological malignancies, are at increased risk for breakthrough COVID-19 infection. Here, we studied the possible mechanisms that could determine the quality and quantity of immunological responses in this patient population.

Methods



Meso-scale Discovery assays for the analysis of cytokines, chemokines and growth factors (CCGs)

In-house ELISA for anti-RBD IgGs developed by Sciensano

Results

- We observed a significant alteration of 23 CCGs after administration of the BNT162b2 vaccine in cancer patients under active treatment, including 11 altered after the administration of the primer dose and 14 altered after the administration of the booster dose (**Figure 1**)
- After classifying cancer patients into serologically good (≥ 200 IU/mL) and poor (< 200 IU/mL) responders to the BNT162b2 vaccine, we identified upregulated inflammatory marker CRP as the best predictor of serological response prior to vaccine administration, followed by IL-15, PIGF, IL-6, IL-18, and serum amyloid A (SAA) (**Figure 2A**)
- Using machine learning algorithms, we identified the signature consisting of CRP, IL-15, IL-18, and PIGF, which differentiated good from poor anti-SARS-CoV-2 BNT162b2 vaccine responders with more than 80% accuracy (**Figure 2B**)

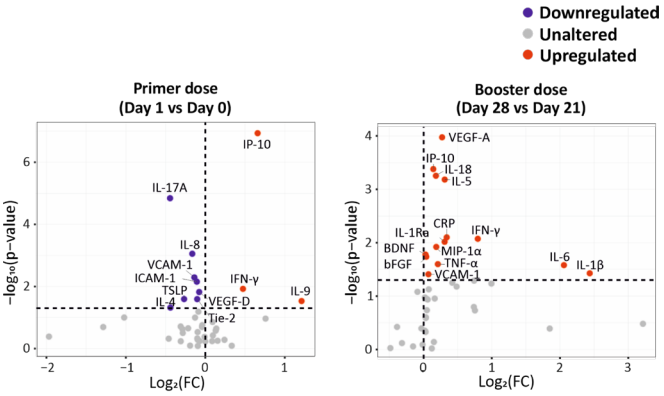


Figure 1. CCG alterations as a response to primer and booster dose vaccinations in cancer patients. Differentially expressed CCGs after the administration, compared to the CCG levels prior to vaccine administration. P-values were calculated using paired t-test. The vertical dotted line represents no change. The horizontal dotted line represents a p-value of 0.05.

A

Area under the ROC curve

	Day 0	Day 1	Day 21	Day 28
CRP	0.71*	0.71*	0.66*	0.65*
IL-15	0.67*	0.67*	0.62*	0.61*
PlGF	0.67*	0.64*	0.62*	0.62*
IL-18	0.66*	0.68*	0.70*	0.64*
SAA	0.62*	0.61*	0.60*	0.60*
IL-6	0.67*	0.61*	0.60	0.61
IL-1Ra	0.61*	0.60*	0.58	0.58*
IP-10	0.62*	0.55	0.58	0.55
IFN-γ	0.65	0.51	0.61	0.58
BDNF	0.60	0.54	0.58*	0.61*

B

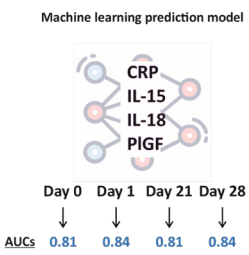


Figure 2. Prediction models for BNT162b2 immune response in cancer patients. (A) Area Under the Receiver Operating Characteristic (AUROC) values for 10 predictors of the binary IgG response as good or poor responders at day 0, day 1, day 21, and day 28. * Denotes significant p-values of at least < 0.05. (B) Random Forest Classifier predicted a model where a combination of CRP, IL-15, IL-18, and PlGF levels measured right before vaccine administration (day 0) and at day 1, day 21, and day 28 after the primer dose predicted good and poor responders with high accuracy (AUCs depicts averages of 10 individually constructed ROC curves).

ACKNOWLEDGEMENTS

We thank all the laboratory personnel, the nurses, and the study participants for their availability, flexibility and dedication.

FUNDING

This research was funded by the Belgian Federal Government through Sciensano, ORCHESTRA project, which has received funding from the European Union's Horizon 2020 research and innovation program and University of Antwerp-GOA grant.

Manuscript published in Frontiers in Immunology

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