International Journal of Infectious Diseases 139 (2024) 50–58

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Bridging the gap - estimation of 2022/2023 SARS-CoV-2 healthcare burden in Germany based on multidimensional data from a rapid epidemic panel

Manuela Harries[1,2,#,*], Veronika K. Jaeger[3,#], Isti Rodiah[1], Max J. Hassenstein[1], Julia Ortmann[1], Maren Dreier[2], Isabell von Holt[2], Melanie Brinkmann[2], Alex Dulovic[4], Daniela Gornyk[1], Olga Hovardovska[1], Christina Kuczewski[1], Marc-André Kurosinski[3], Maike Schlotz[5], Nicole Schneiderhan-Marra[4], Monika Strengert[1], Gérard Krause[1,6], Martina Sester[7], Florian Klein[5,8,9], Astrid Petersmann[10,11], André Karch[3,†], Berit Lange[1,6,†]

[1] Department of Epidemiology, Helmholtz Centre for Infection Research Braunschweig, Germany
[2] Institute for Epidemiology Social Medicine and Health Systems Research, Hannover Medical School (MHH) Hannover, Germany
[3] Institute of Epidemiology and Social Medicine, University of Münster, Germany
[4] NMI Natural and Medical Sciences, Institute at the University of Tubingen Reutlingen, Germany
[5] Laboratory of Experimental Immunology, Institute of Virology Faculty of Medicine and University Hospital Cologne University of Cologne Cologne, Germany
[6] German Center for Infection Research (DZIF), Braunschweig, Germany
[7] Department of transplant and infection immunology, Saarland University, Germany
[8] German Center for Infection Research, Partner site Bonn-Cologne Cologne, Germany
[9] Center for Molecular Medicine Cologne (CMMC), University of Cologne Cologne, Germany
[10] Institute of Clinical Chemistry and Laboratory Medicine, University Medicine Greifswald Greifswald, Germany
[11] Institute of Clinical Chemistry and Laboratory Medicine, University Medicine Oldenburg Oldenburg, Germany

ARTICLE INFO

Article history:
Received 26 June 2023
Revised 9 November 2023
Accepted 10 November 2023

Keywords:
SARS-CoV-2
SEIR
ODE Model
IGRA
Humoral immunity
Scenarios
Simulation
Seroepidemiological studies
Neutralizing antibodies

ABSTRACT

Objectives: Throughout the SARS-CoV-2 pandemic, Germany like other countries lacked adaptive population-based panels to monitor the spread of epidemic diseases.
Methods: To fill a gap in population-based estimates needed for winter 2022/23 we resampled in the German SARS-CoV-2 cohort study MuSPAD in mid-2022, including characterization of systemic cellular and humoral immune responses by interferon-γ-release assay (IGRA) and CLIA/IVN assay. We were able to confirm categorization of our study population into four groups with differing protection levels against severe COVID-19 courses based on literature synthesis. Using these estimates, we assessed potential healthcare burden for winter 2022/23 in different scenarios with varying assumptions on transmissibility, pathogenicity, new variants, and vaccine booster campaigns in ordinary differential equation models.
Results: We included 9921 participants from eight German regions. While 85% of individuals were located in one of the two highest protection categories, hospitalization estimates from scenario modeling were highly dependent on viral variant characteristics ranging from 30-300% compared to the 02/2021 peak. Our results were openly communicated and published to an epidemic panel network and a newly established modeling network.
Conclusions: We demonstrate feasibility of a rapid epidemic panel to provide complex immune protection levels for inclusion in dynamic disease burden modeling scenarios.

Introduction

During the first two pandemic years, Germany lacked rapid adaptive population-based panels for epidemic diseases [1] and the capacity for central modeling platforms to quickly integrate information from cross-sectional surveys [2–4]. Instead, several

* Corresponding author: Tel.: +49(0)531-6181-3126.
E-mail address: Manuela.Harries@helmholtz-hzi.de (M. Harries).
# These authors shared first authorship.
† These authors shared last authorship.

https://doi.org/10.1016/j.ijid.2023.11.014

population-specific and population-based seroprevalence studies were performed, and the results were not published fast enough and rarely used in model estimates or scenarios [5]. Modeling groups operated independently without a central platform for harmonization and integration of results [6].

By spring 2022, existing German seroprevalence studies [2–4,7–10] had largely ceased sampling and recruiting due to a lack of funding after the Omicron BA.1 and BA.2 waves. Changes in testing strategies and lifting of nonpharmaceutical interventions made it difficult to determine the extent of underdetection of notified infections in the German public health agencies. This led to modeling efforts with greater uncertainties regarding protection against severe disease or symptomatic infection by vaccination or previous infection for BA.5 and other variants.

Interpretation studies on population immunity for protection against infection or severe course have become more challenging with larger numbers of reinfections, varied vaccination schedules, potentially differential waning immunity, neutralization activity, and breakthrough infections [11] among different population groups [12]. Simple seroprevalence surveys lack sufficient information, while detailed immunological evaluations (i.e. T-cells, immune responses toward non-Spike [S] antigens) are not scalable to population-level studies.

However, estimates indicating protection against severe COVID-19 course and infection are necessary in each modeling study for each new variant using a combination of population-based information on vaccinations, (re)infections confirmed by humoral immunity and cellular immunity within various age groups. These parameters should be provided in a timely manner, even if their interpretation as protection against infection is not straightforward. Additionally, estimating contact frequency during a pandemic cannot rely on previous estimates and should be determined from current studies [13], as contact patterns undergo differential change across age groups.

During the past year, our involvement included linking new surveys on immunity-based protection levels against severe disease progression and infection in Germany and developing platforms to harmonize modeling studies that utilize these estimates in scenario modeling [14]. We transformed the “Multilocal and Serial Prevalence Study of Antibodies against SARS-CoV-2 in Germany” (MuSPAD) into a rapid, longitudinal, adaptive population-based epidemic panel capable of surveying and sampling within two months of the decision to sample.

We present estimates from this panel on vaccination coverage, reinfection incidence, cellular and humoral immunity, and contact frequency and intensity and discuss selected scenarios for winter 2022/23 in Germany using dynamic models informed by these estimates.

Methods

We conducted a resurvey of the MuSPAD cohort as previously described [3]. Originally, participants were invited in 2020 from randomly selected population registration offices in the study regions. In summer 2022, we amended the study protocol to allow rapid blood sampling and testing for various infectious diseases with plans for future resampling. Invitations were sent via letter or email to 33,426 original MuSPAD participants across eight regions to take part in the survey. Among them, 10,090 participants from three regions (Aachen, Magdeburg, and Hannover) were asked to provide blood samples onsite (Supplementary Figure 1).

Onsite participants gave written informed consent and underwent blood collection (9-15 ml) through venepuncture using barcoded serum-gel and lithium-heparin monovettes. The collected samples were stored at 4-8°C until analysis. We measured receptor-binding domain (RBD) or nucleocapsid (NC) specific total immunoglobulin (Ig)Gs using the Elecsys® Anti-SARS-CoV-2 S or N Assays (Roche Diagnostics), respectively. Cell-mediated immunity (CMI) was conducted using the QuantiFERON SARS-CoV-2 assay® (QIAGEN) [15], which is a SARS-CoV-2 interferon (IFN) gamma-releasing assay (IGRA). Briefly, full blood from lithium-heparin monovettes was stimulated with S (RBD, S1, S2) and non-S peptides mix targeting full genome (spike (S), membrane (M), nucleocapsid (N) and Non-structural protein (NSP)) for 16-24 hours. Following stimulation, supernatants were isolated through centrifugation, and IFNγ was measured using enzyme-linked immunosorbent assay (ELISA) (QuantiFERON SARS-CoV-2 ELISA Kit: 626420), following the manufacturer’s instructions. SARS-CoV-2 neutralization potency of sera samples was measured by using lentiviral particles pseudotyped with the S protein of the Wuhan or the BA.5 isolate, respectively [16,17] (Supplementary Laboratory Analysis).

Data collection and management

We developed a questionnaire to collect updated demographic information, health status, SARS-CoV-2 vaccine history, known (re-)infections, and previous serologic testing. The questionnaire was compatible with the serohub minimal data set (www.serohub.net). In this way, it could be used within larger projects in Germany, linking data from various population panels within the IMMUNEBRIDGE project [14,18].

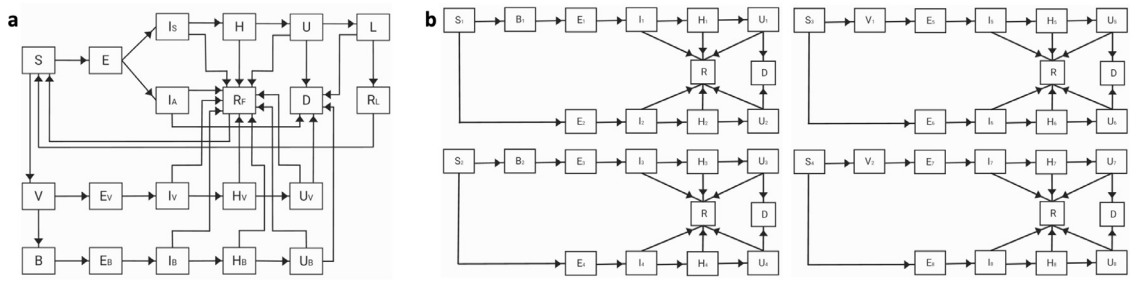
Immunity-based protection levels against infection and severe course of disease

We performed a literature review [15,19,20] focusing on studies with humoral immune markers reflecting protection against infection, hospitalization, and death for Omicron subvariant BA.5 (Supplementary Table 1). By considering the number of self-reported vaccine doses, the number of previous and recently reported SARS-CoV-2 infections, and humoral immunity correlates (confirmed exposures), we derived different immunity-based levels of protection against infection and severe course [14]. The protection levels are divided into no protection, low protection, moderate protection, and high protection, depending on the number of confirmed exposures (Supplementary Table 2). We additionally divided the levels of protection into positive or negative CMI responses using IGRAs.

High protection against severe COVID-19 course and infection requires four confirmed exposures, with one occurring in 2022 and confirmed by humoral immune correlates (referred to as 3 confirmed exposures + 1 confirmed exposure in 2022). Moderate protection is defined by three exposures with humoral immune correlates (referred to as 3 confirmed exposures). Low level of protection includes three exposures without immune correlate, or one to two exposures with or without immune correlate, or no exposures but immune correlate (referred to as 1 to <3 confirmed exposures). No protection against severe disease is defined as no reported exposures and no confirmed cellular and humoral responses (referred to as 0 exposure).

Data analysis

We present socio-demographic data, current vaccination coverage, and (re-)infection history and humoral and cellular immunity characteristics by standard descriptive statistics. We compared results from before 2022 analyzed with the MULTICOV-AB antibody binding assay, a multiplex assay based on the Luminex platform [21], to evaluate changes in prevalence and titer of IgG antibodies against S and NC over time. We described the level of immunity-based protection for adult age groups, sex, and underlying conditions. We summarized contact behavior and infection rate over time considering age and vaccination status. We conducted



c

Scenario	Transmissibility	Severity in comparison to BA.5	Immune evasion	Booster campaign of 5% per week from October 2022
Scenario A1	=	=	=	no
Scenario A2	=	=	=	yes
Scenario B1	1.3x	=	=	no
Scenario B2	1.3x	=	=	yes
Scenario C1	1.3x	2x	=	no
Scenario C2	1.3x	2x	=	yes
Scenario D1	1.3x	2x	++	no
Scenario D2	1.3x	2x	++	yes
Scenario E1	2x	2x	++	no
Scenario E2	2x	2x	++	yes

Figure 1. (a) Structure of the models based on officially recorded public health data. The compartments are classified either as susceptible (S), exposed (E), asymptomatically infectious (I_A), symptomatically infectious (I_S), hospitalized (H), in intensive care (U), suffering under long-COVID (L), fully recovered (R_F), recovered from long-COVID (R_L), dead (D), vaccinated (V), exposed after vaccination (E_V), infectious after vaccination (I_V), hospitalized after vaccination (H_V), in intensive care after vaccination (U_V), booster (B), exposed after booster (E_B), infectious after booster (I_B), hospitalized after booster (H_B), and in intensive care after booster (U_B). (b) Structure of the two models based on estimates from the population-based panel with humoral and cellular immunity. The compartments are classified either as susceptible (S), exposed (E), infectious (I), hospitalized (H), in intensive care (U), recovered (R), dead (D), vaccinated (V), and booster (B). (c) Designed scenarios to model the pandemic course for winter 2022/23 in Germany. Transmissibility is estimated by the basic reproduction number.

random-effect logistic and binomial regression models on the determinants of vaccination coverage, reinfections, and humoral and cellular immunity and exposure status. Analyses were performed using R Version 4.0.2.

Age-specific Susceptible-Exposed-Infectious-Recovered model

We applied a deterministic Susceptible-Exposed-Infectious-Recovered (SEIR) model with a realistic age structure and contact behavior based on a social contact matrix [13]. In the model, the transmission rate is modeled as the product of the contact rate and the risk of infection, and it governs the rate at which individuals move from the susceptible to the exposed. The model, which has been previously described [22] includes compartments for hospitalizations, patients in the intensive care unit (ICU), and deaths (Figure 1). In the model, the transmission rate is modeled as the product of the contact rate and the risk of transmission per contact, and it governs the rate at which individuals move from the susceptible to the exposed. In one version of this model, we divided the susceptible population into four groups based on the protection levels by humoral confirmation (Supplementary Table 2). In a third version, we further divided the susceptible into four groups based on IGRA positivity. We also incorporated estimates of confirmed exposure from our population-based study into each age group. Figure 1c provides an overview of the scenarios we designed: Scenario A1 stimulates a wave of a BA.5-like variant without (booster) vaccinations; Scenario A2 covers a BA.5-like variant with a booster campaign using an adapted vaccine. Scenario B models a new variant with BA.5-like capacities but higher transmissibility without (B1) and with a variant-adapted vaccine booster campaign (B2). Scenario C represents a new variant with higher severity and transmissibility without (C1) and with a booster campaign (C2). Scenario D and E model a new variant with higher transmissibility, severity, and immune evasion without (D1, E1) and with a booster (D2, E2). We used EPIFORGE [22,23] to describe the ordinary differential equation (ODE) model.

Results

In June 2022, we invited all previous MuSPAD participants (n = 33,426) from eight regions in Germany, of whom 9921 (30%) completed the survey (Supplementary Figure 1). Among 10,090 participants from three regions (Aachen, Hannover, Magdeburg) we collected 3034 blood samples, of which 2955 completed the questionnaire. In a subgroup of 1038 individuals from two centers (Aachen, Magdeburg), IGRAs were performed, and in 1008 individuals we tested for SARS-CoV-2 neutralizing activity of serum IgG. Supplementary Table 1 in the supplement describes the study population's characteristics.

Population estimates of vaccination coverage, reinfections, humoral and cellular immunity, and contact frequency

Over 85% of 9921 respondents received at least three SARS-CoV-2 vaccine doses (Supplementary Table 3). Among those who reported positive polymerase chain reaction (PCR) tests (29.3%), 7.1% had a confirmed positive PCR test in 2020, 12.5% in 2021, and 80.4% in 2022. For self-reported reinfection, 1.7% of participants experienced reinfection, with 1.8% in 2020, 15.5% in 2021, and 82.7% in 2022. Mean number of contacts reported in summer 2022 was 3.1 within the household and 15.5 outside of the household (Table 1). In terms of blood samples, 99.3% had antibodies against the S-antigen and 36.0% had antibodies against the NC-antigen. Of the 1038 participants with IGRA results, 65.6% tested IGRA positive with one having an indeterminate result (0.1%). IGRA-positivity was lower in those > 65 years of age.

Confirmed exposure to SARS-CoV-2 infection or vaccination

When categorizing the population into four groups according to exposure and humoral immunity, 34.2% reported four exposures (including one in 2022) confirmed by humoral immunity (highest protection). This proportion was higher in those >65 years. Over 95.4% had at least three exposures confirmed by humoral immunity (moderate protection). Of those with at least four exposures with one in 2022 confirmed by humoral immune correlates, 24.5% did not show a positive IGRA, and this proportion increased with age (Supplementary Table 4, Figure 2).

Those with blood samples and those aged >80 years had three times the odds of having four exposures confirmed by humoral immune correlates (odds ratio [OR] 3.34; 95% CI: 1.92-5.80)

Table 1
Self-reported SARS-CoV-2 positive test history, vaccination status, confirmed humoral or cellular immunity test result (Spike and Nucleocapsid -antibodies, interferon-γ-release assay) and number of social contacts for defined age groups of "Multilocal and Serial Prevalence Study of Antibodies against SARS CoV-2 in Germany" participants by age group.

Age groups (years) Total	18-34 n = 1368	35-49 n = 1840	50-64 n = 3331	65-79 n = 2644	80+ n = 631	Overall n = 9921[a]
First positive PCR test result (self-reported) in year; n (%)						
2020	33 (5.6%)	44 (5.6%)	86 (8.7%)	35 (8.0%)	8 (9.8%)	206 (7.1%)
2021	64 (10.7%)	105 (13.3%)	116 (11.7%)	57 (13.1%)	20 (24.4%)	364 (12.5%)
2022	501 (83.8%)	642 (81.2%)	791 (79.7%)	343 (78.9%)	54 (65.9%)	2339 (80.4%)
Unknown / no reported positive PCR test	770 (56.3%)	1049 (57.0%)	2338 (70.2%)	2209 (83.5%)	549 (87.0%)	7012 (70.7%)
Second positive confirmed PCR test result (self-reported) in year; n (%)						
2020	0 (0%)	2 (3.5%)	1 (2.5%)	0 (0%)	0 (0%)	3 (1.8%)
2021	2 (5.1%)	7 (12.3%)	5 (12.5%)	7 (31.8%)	5 (71.4%)	26 (15.5%)
2022	37 (94.7%)	50 (87.7%)	34 (85.0%)	15 (68.2%)	2 (28.6%)	139 (82.7%)
Unknown	1329 (97.1%)	1781 (96.8%)	3291 (98.8%)	2622 (99.2%)	624 (98.9%)	9753 (98.3%)
Number of COVID-19 vaccine doses received; n (%)						
None	45 (3.5%)	97 (5.6%)	104 (3.2%)	55 (2.1%)	5 (0.9%)	308 (3.3%)
One-two	150 (11.6%)	179 (10.3%)	230 (7.1%)	81 (3.1%)	22 (3.7%)	662 (7.0%)
Three	1073 (83.0%)	1383 (79.5%)	2639 (82.0%)	1624 (63.0%)	243 (41.3%)	6982 (73.9%)
Four	25 (1.9%)	80 (4.6%)	247 (7.7%)	818 (31.7%)	318 (54.1%)	1491 (15.8%)
Unknown	75 (5.5%)	101 (5.5%)	111 (3.3%)	66 (2.5%)	43 (6.8%)	478 (4.8%)
Decision on further SARS-Cov-2 vaccination depending on STIKO recommendation; n (%)						
Yes	628 (45.9%)	737 (40.1%)	1321 (39.7%)	1117 (42.2%)	245 (38.8%)	4057 (41.2%)
No	740 (54.1%)	1103 (59.9%)	2010 (60.3%)	1527 (57.8%)	386 (61.2%)	5786 (58.8%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	78 (0.8%)
Decision on further SARS-Cov-2 vaccination depending on new available vaccine; n (%)						
Yes	70 (5.1%)	101 (5.5%)	293 (8.8%)	259 (9.8%)	76 (12.0%)	802 (8.2%)
No	1298 (94.9%)	1739 (94.5%)	3038 (91.2%)	2385 (90.2%)	555 (88.0%)	9041 (91.9%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	78 (0.8%)
Number of reported contacts						
Mean number of reported contacts (SD)[b]	20.2 (78.2%)	21.8 (85.1%)	20.1 (67.7%)	14.8 (43.5%)	16.6 (43.5%)	18.6 (66.0%)
Mean number of contacts in household (SD)[b]	3.33 (13.0%)	3.62 (9.1%)	3.09 (9.9%)	2.77 (10.8%)	2.72 (12.9%)	3.09 (10.7%)
Mean number of contacts outside of households (SD)[b]	16.8 (74.7%)	18.2 (84.2%)	17.0 (66.5%)	12.0 (41.5%)	13.9 (41.6%)	15.5 (64.4%)
Antibody results based on subgroup with blood samples						
SARS-CoV-2 Spike RBD antibody results (Total)	n = 278	n = 491	n = 1150	n = 887	n = 141	n = 3029
Negative	1 (0.4%)	4 (0.8%)	10 (0.9%)	4 (0.5%)	1 (0.7%)	22 (0.7%)
Positive	277 (99.6%)	487 (99.2%)	1140 (99.1%)	883 (99.5%)	140 (99.3%)	3007 (99.3%)
SARS-CoV-2 Nucleocapsid (NC) antibody result (Total)	n = 280	n = 491	n = 1151	n = 888	n = 141	n = 3033
Negative	153 (54.6%)	260 (53.0%)	744 (64.6%)	628 (70.7%)	110 (78.0%)	1941 (64.0%)
Positive	127 (45.4%)	231 (47.0%)	407 (35.4%)	260 (29.3%)	31 (22.0%)	1092 (36.0%)
SARS-CoV-2 IGRA test results (Total)	n = 122	n = 191	n = 307	n = 277	n = 88	n = 1038
Negative	32 (26.0%)	46 (23.8%)	88 (28.4%)	128 (45.6%)	50 (56.8%)	356 (34.3%)
Positive	91 (74.0%)	147 (76.2%)	222 (71.6%)	152 (54.1%)	38 (43.2%)	682 (65.6%)
Indeterminate	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)	0 (0%)	1 (0.1%)

[a] Unknown age n = 107;
[b] During summer 2022.
IGRA = interferon-gamma (IFN-γ) release assay response to SARS-CoV-2; PCR, polymerase chain reaction; RBD, receptor-binding domain; SD, standard deviation; STIKO, Standing Committee On Vaccination At The Robert Koch Institute.

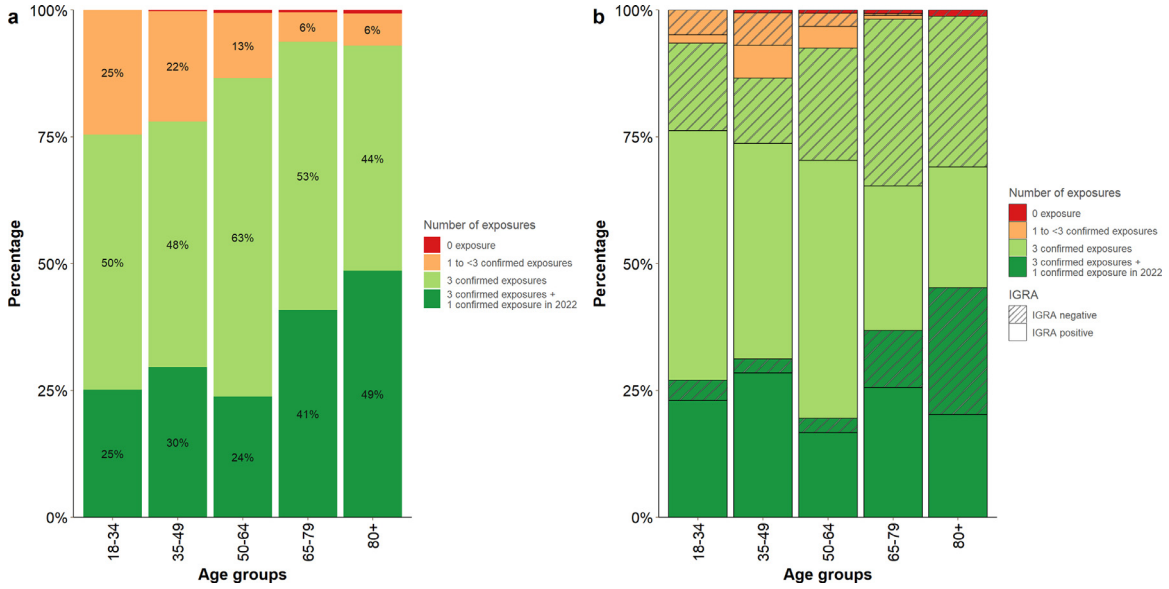


Figure 2. Immunity-based protection levels representing numbers of exposures by infection or vaccination with corresponding humoral immune response stratified by (a) age and further stratified by (b) IGRA positivity. Note: (a) is based on all participants with information on the protection levels (number of exposures) and age (n = 3209) and (b) is based on all participants with information on the protection levels (number of exposures), age, and IGRA (n = 974).
IGRA, interferon-γ-release assay.

(Supplementary Table 5). Employment in the medical field or the education sector and having 1-2 children were also associated with having higher odds of having had four exposures, respectively. Those over 80 years had lower odds of having a positive IGRA (OR 0.30; 95% CI: 0.14-0.65). Having a chronic lung disease was associated with lower odds of having a positive IGRA (OR 0.45; 95% CI: 0.27-0.78) while current smoking had higher odds for IGRA positivity (OR 2.30; 95% CI: 1.32-4.01) (Supplementary Table 5).

Correlation of neutralization versus BA.5 with protection level

The SARS-CoV-2 neutralizing antibody (NAb) response was higher in participants with three or more exposures confirmed by humoral response. Participants showed higher NAb activity against parental Wu01 variant compared to BA.5 variant (Supplementary Figure 2). Most individuals had high S-reactive IgG levels, which correlated with the number of exposures. Anti-NC-antibody titers varied across the different protection levels.

Previous infection confirmed by NC antibodies modified the decreasing trend in NAb titers against BA.5 and Wu01 with increasing time since the last vaccination seen in those without NC antibodies. In contrast to participants without previous infection, there was no decreasing trend in participants with NC antibodies. Participants with more than 150 days since the last vaccination had lower neutralization activity than participants with vaccinations in the last 50 days in the absence of NC antibodies. Participants with confirmed infection (positive NC antibodies) showed a clear downward trend of neutralization activity over time (Figure 3). This trend was less evident for interferon-gamma-release (Supplementary Figure 3) and for both exposures together (Supplementary Figure 4).

Vaccinations, (re)infections, contact frequency, and immunity markers over time

Supplementary Figure 4 summarizes findings related to seropositivity estimates, proportions of individuals with previous SARS-CoV-2 infection based on NC-antibody positivity, self-reported infections, and reinfections based on reported dates, and proportions of individuals with 1-4 vaccine doses and contact frequency over time.

Potential healthcare burden during winter 2022/23 in Germany based on ODE models

We analyzed five scenarios (A-E) with and without booster campaigns (Figure 1c), examining peak general ward hospitalizations and peak ICU hospitalizations. Figures 4a-e show the modeling of infections, hospitalizations, and ICU hospitalizations (Supplementary Figure 5) for each scenario using three different compartmental models.

In a base case scenario of variants with properties similar to BA.5, all models showed peak hospitalizations for children and adults below 50% of those in winter 2022 during the BA1/2 wave. A standard wild-type vaccination campaign would not reduce hospitalizations by more than 20% as hospitalizations were predicted to mainly happen in the remaining weeks of 2022.

In a second scenario, with a new SARS-CoV-2 variant with 1.3 times the transmissibility of BA.5, but equal pathogenicity and immune evasion, we found similar peaks of hospitalizations at the beginning of 2023 in adults and children as seen during BA1/BA 2 in all three models. A vaccination campaign in our model was able to reduce overall hospitalizations by up to 25% (Supplementary Table 6).

In a third scenario with transmissibility increased as in Scenario B but additionally increased pathogenicity, all models predicted a surpassing of peaks seen during the BA1/BA2 wave to slightly different degrees and a reduction of overall hospitalizations with a vaccination campaign of about a third.

In scenarios D-E, higher peaks of hospitalizations were possible in the models (up to 300% of BA1/2) for adults and children if transmissibility or immune evasiveness of variants relevantly raised. Vaccination and/or booster campaigns could reduce overall hospitalizations by up to 40% (Supplementary Table 6).

The model based on data from the population panel predicted slightly lower and slower peaks in comparison to the model using public health surveillance data. In the third model integrating cellular immunity estimates from IGRA measurements, peaks

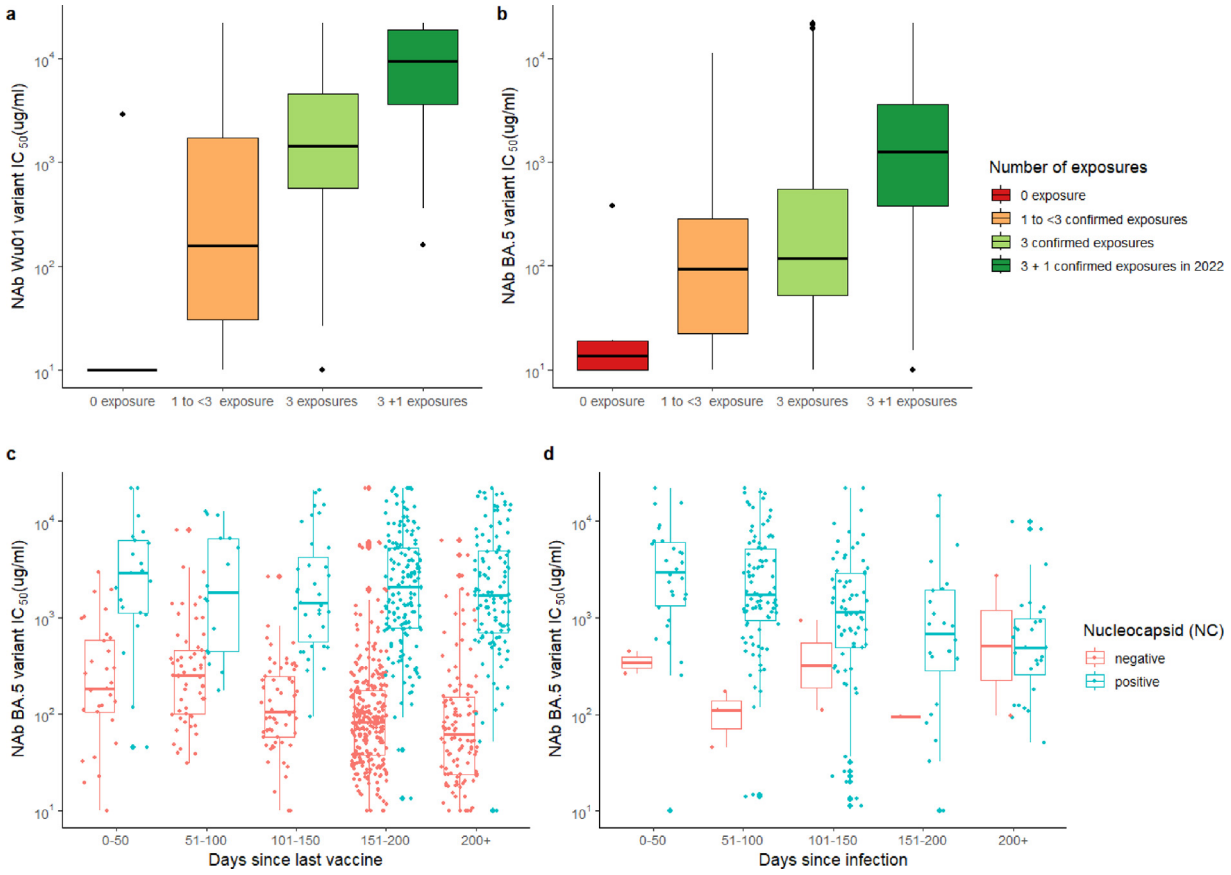


Figure 3. MuSPAD participants neutralizing antibody responses to variants (a) Wu01 and (b) BA.5 over immunity-based protection level (combined categories based on the number of exposures) in 2022; (c) A boxplot of BA.5 neutralizing antibody response by time since last SARS CoV-2 vaccination, and (d) last SARS-CoV-2 infection stratified by nucleocapsid antibody response (NC with ≥0.8 BAU/ml cut-offs for seropositivity). Protection levels: no protection (0 exposure), low (1 to <3 confirmed exposures), moderate (3 confirmed exposures), and high (3 confirmed exposures +1 confirmed exposure in 2022).
MusPAD, "Multilocal and Serial Prevalence Study of Antibodies against SARS CoV-2 in Germany".

and the number of hospitalizations increased compared to the model based on humoral immunity but remained lower than in the model based on surveillance data.

We performed sensitivity analyses assessing the effect of varying age-specific hospitalization risks, contact rates in the elderly in autumn, and susceptibility of the elderly population, and found only small changes because of the different assumptions when looking at the comparison of projected and actual hospitalization numbers during winter 2022/2023 (Supplementary Figure 7). In a second set of sensitivity analyses, we introduced a new protection level into the population-based models after both the summer and autumn waves in 2022 to assess the effect on infection dynamics projections in comparison to analysis without these additional levels. Adding this additional protection level resulted in a trajectory of cases and hospitalizations in the simulations that resembled more closely reported data, indicating that this assumption set is most critical for our modeling study (Supplementary Figures 8 and 9). Since this is also the assumption set that we targeted with the addition of population-based primary study data, sensitivity analysis results underline the importance of incorporating high-quality data in the parametrization of the respective variables.

Discussion

In this study, we showed how a rapid population-based panel from June/July 2022 in Germany could be used to derive and validate proxies for protection from a severe COVID-19 course, and how this additional knowledge affected modeling studies aiming at an ad-hoc estimation of healthcare burden for the approaching winter.

Most adults (95%) in this study had more than three exposures to either the SARS-CoV-2 virus or vaccination with humoral immune correlates, respectively. In total, 68.3% of those aged >65 years and 45.9% of those >80 years had not yet had a fourth vaccination. Over 90% of people in our sample express willingness to be vaccinated or receive a booster in fall. When evaluating booster campaigns' impact, we found that initiating them in October at a 5% rate of the population per week could lead to decreased hospitalizations by up to 40% in specific scenarios, especially those involving more pathogenic SARS-CoV-2 variants.

Over 34% in all age groups had four exposures to SARS-CoV-2 (infection/vaccination) and confirmed humoral immune correlates, one of which occurred in 2022. This group was expected to have the highest protection against severe COVID-19 course and at least some protection against reinfection based on the literature [24]. However, we found that even in this group, 24.5% did not have interferon-gamma release after stimulation with S-specific antigens, as detected by SARS-CoV-2 specific IGRA. The same was true for 36.7% of those with least three exposures with confirmed humoral immunity. IGRAs positivity was age-dependent, with those >80 years having lower odds of positivity due to age-dependent immune waning effect [25]. Overall, 65.7 % of participants tested IGRA positive. Previous studies showed high sensitivity of IGRA to detect recent infections, with 100% directly post-exposure and declining to 79.5% after 10 months [26].

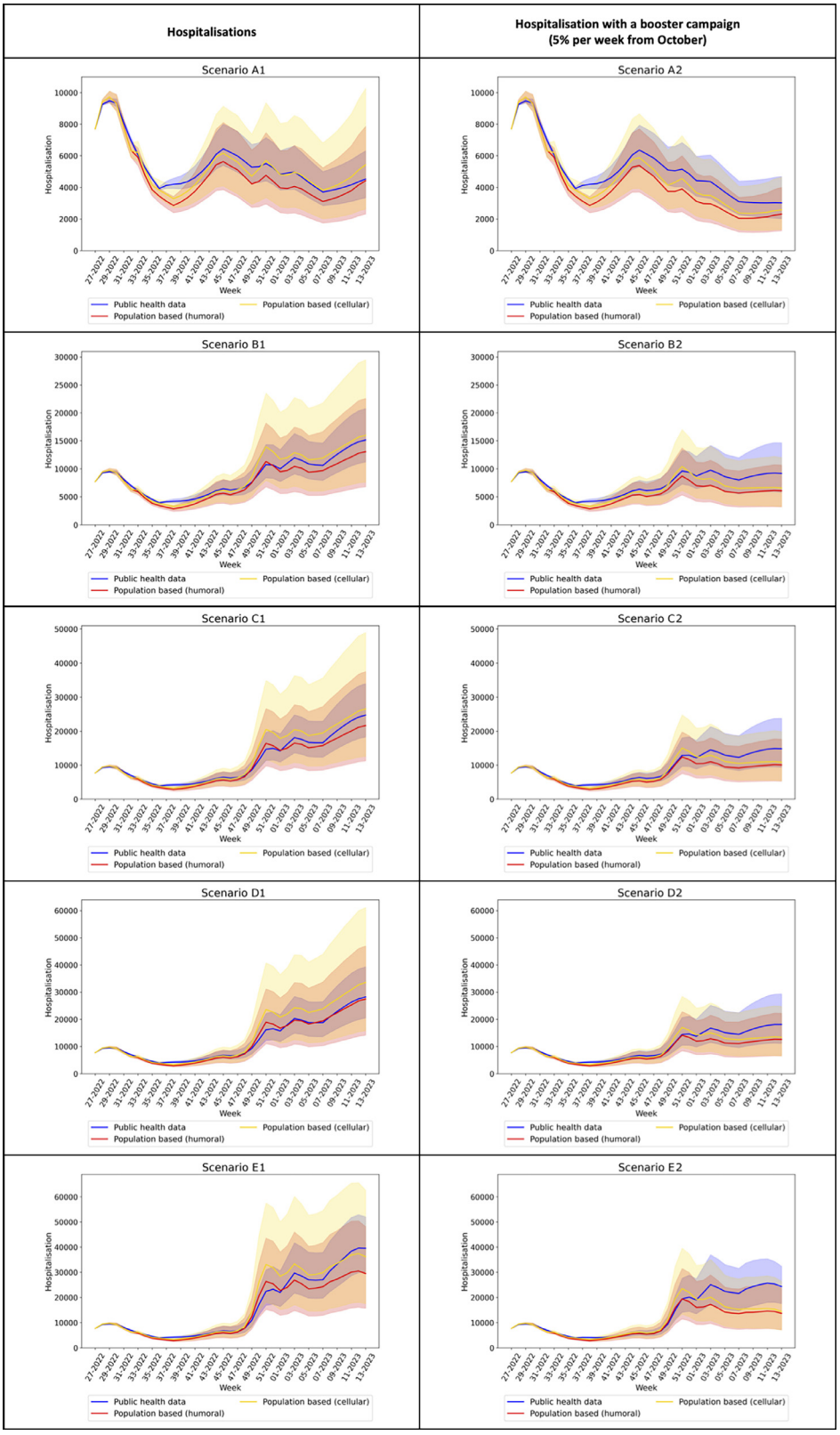


Figure 4. Scenarios A (variant similar to BA.5), B (new variant with higher transmissibility), C (new variant with higher severity, and transmissibility), D and E (new variant with higher transmissibility, severity, and immune evasion) and associated hospitalization rates based on public health data, population-based estimates (humoral and cellular) without (1) and with (2) booster campaigns in 2022/23 in Germany.

Assessing different scenarios of SARS-CoV-2 variants and vaccination strategies with three compartmental models using population-based estimates, we found that hospitalization peaks during the BA1/2 wave in January and February would not be surpassed without the introduction of a new variant or significant immune waning (Scenario A). Scenarios considering new variants with higher transmissibility, higher pathogenicity, and higher immune evasiveness suggest the possibility of surpassing previous hospitalization peaks seen in previous winter waves. The results were consistent with modeling studies conducted before the BA.5 summer wave in the UK [24] and consistent with most models in a statement from Germany's central modeling network (MONID) in 09/2022, which this group also contributed to (14).

While the overall prediction that no surpassing of clinical capacities would take place in Scenario A was correct, both our model and those from other modeling groups underestimated the height of the first hospitalization peak seen within a second BA.5 wave in calendar weeks 39-44 by 30-40%. In contrast, the total number of hospitalizations (Supplementary Figure 5) in autumn/winter 2022/23 was not largely underestimated. This was likely due to the assumption of a prolonged second wave and a similar age-specific distribution of infections compared to the first BA.5 wave. However, the actual second BA.5 wave had short and steep dynamics, with a higher proportion of cases among older age groups, resulting in a higher overall hospitalization risk per case. More accurate use of estimates of age-specific underdetection during the BA.5 summer wave might have helped to predict the larger contribution of the elderly during the second BA.5 wave [22]. Adding additional levels of protections to our original protection level framework after the summer wave informed by population-based data resulted in more realistic projections as shown by the trajectory of hospitalizations and cases in one set of sensitivity analyses (Supplementary Figures 8 and 9), resembling more closely the actual reported data. These sensitivity analyses show the potential of integrating population-based data in this format into models both for projections and potentially in the future to assess protection correlates.

Our decision to use immunity-based protection levels against infection and severe disease progression based on literature is supported by the finding that there is a clear trend toward lower neutralizing activity in the lower protection level than at the higher level. For this category, we designed the highest protection to be at least four exposures, one of which (vaccination/infection) occurred in 2022, which is also supported by a clear trend toward higher neutralizing activity among those with recent infections.

The benefit of including neutralization titers or indirect correlates like IGRAs for assessing complex models' usable levels of protection against severe disease and infection is unclear. IGRAs, a tool established for measuring the immune response to *Mycobacterium tuberculosis* [19] are now being explored for specific immune cell response to SARS-CoV-2. IGRAs have shown clinical capacity for the assessment of specific T cell immunity immediately after vaccination [20]. This is especially true for immune-compromised patients [20,27]. However, it remains unclear whether IGRA measurement in population-based studies can accurately predict the risk of severe disease [26,28,29].

In our modeling study, we compare a simple model parametrized based on public data allowing little differentiation with respect to protection through natural or vaccine-induced immunity to a more complex model parametrized based on specifically collected population data which allows exactly this differentiation. In general, more complexity in a model does not automatically result in better model projections, especially when data for the parametrization are sparse. We argue in our case that the added complexity is necessary for answering the underlying public health question as the introduction of exposure categories informed by primary data in an age-specific way allows a more realistic simulation of infection dynamics, especially in those age groups, that are most vulnerable. Our results, especially in the most realistic Scenario B1 and sensitivity analyses provide empirical evidence that the deviation from the true winter epidemic is indeed smaller when adding this level of complexity.

Future research will investigate ways to improve the modeling of protection by considering various protection levels for each SARS-CoV-2 wave, higher protection levels for individuals vaccinated with NC, incorporating a waning function based on last vaccination for those without NC antibodies, and incorporating estimates from cellular immunity. Such combined protection correlates including cellular immunity may be more appropriate for elderly individuals as they may have decreased IGRA positivity and lower assumed protection.

Limitations of our study include the exclusion of children and underrepresented groups, regional limitations, and omitting of underdetection and incidental hospitalizations during the BA.1/2 wave in the model.

Despite these limitations, our study demonstrates the efficacy of rapid, adaptive population panels using immunity-based protection levels for parametrizing scenarios and forecast models during epidemics in Germany. The data from our study along with other studies [18] have been made available to a central modeling platform [14] allowing other modeling groups to utilize it for their models.

Conclusion

Although we show protection in most of the population against severe course of disease measured by at least three exposures or vaccination and confirmed by humoral immune correlates, even quite moderate changes in transmissibility or pathogenicity of new SARS-CoV-2 variants could lead to relevant hospital burden surpassing previous waves if no remedial action is taken. Future epidemic panels and modeling efforts should prospectively evaluate combined surrogates for protection levels against SARS-CoV-2 infection and severe course of disease.

Declaration of competing interest

The authors have no competing interests to declare.

CRediT authorship contribution statement

Conceptualization: A.K., B.L.; Data quality: M.J.H., J.O., V.J., M.H., MA.K.; Formal analyses: M.H., V.J, I.R., M.J.H, B.L., A.K. M.D., I.v.H., M.B; Visualization: M.H., V.J., I.R; Project administration: C.K., D.G., M.H., M.S.; Laboratory analysis: A.P., F.K., M.S, A.D., N.S., M.S.; Evidence synthesis: B.L., M.D., I.v.H., M.B., O.H.; Writing-original draft: M.H., V.J., B.L., A.K., I.R.; Funding acquisition: B.L., A. K., G.K.; Writing-review & editing: M.S., M.J.H., J.O., V.J., MA.K, C.K., D.G., M.H., B.L., A.K., F.K., M.S., I.R., A.P., A.D., N.S.,O.H., G.K., M.D., I.v.H., M.B. All authors have read and agreed to the published version of the manuscript.

Funding

This work was supported by The Helmholtz Association (SO-096HZEPiAdHoc & LOKI: KA1-Co-08), European Union's Horizon 2020 research and innovation program (grant number 101003480; grant number: 10107382; grant number: 101095606), the Federal Ministry of Education and Research (BMBF) as part of the Network University Medicine (NUM) via the egePan Unimed project (grant number: 01KX2021), the IMMUNEBRIDE project (grant number: 01KX2121), the COVIM project (grant number: 01KX202) and

the PREPARED project (grant number: 01KX2121), the Federal Ministry of Education and Research (BMBF) via the RESPINOW (grant number: MV2021-012) and OptimAgent (grant number: MV2021-014) projects, by the German Research Foundation (DFG) via the SpaceImpact (grant number: 492390948) and EpiAdaptDiag (grant number: 458526380) projects and by intramural HZI funds.

Ethical approval

Ethics committee of Hannover Medical School (9086_BO_S_2020 for MuSPAD).

Acknowledgments

We appreciate all MuSPAD participants supporting and endorsing our study. We are grateful to our colleagues in Oldenburg (especially Heike Adam) and Cologne for the laboratory analyses. We thank BOS112 (Tim Balz), NAKO (in particular Sabrina Sistig), and Barbora Kessel (former HZI) for collaborating with us. We thank IPSOS for great technical appointment management and HUB MHH for the sample bio banking.

Data sharing statement

The anonymized data for this study will be made available to other academic researchers. The minimal dataset includes study site information, assay information, sample type, demographic information, self-administered diagnostic anamneses, and lab results (NC, Spike, IGRA, and NAb). For further details contact muspad@helmholtz-hzi.de. Institutions can apply for the data via serohub@helmholtz-hzi.de. The Modeling code is under https://github.com/hzi-braunschweig/Scenario-Modeling HZI GitHub available.

Informed consent statement

Before study participation, all participants provided signed informed consent.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2023.11.014.

References

[1] Ward H, Atchison C, Whitaker M, Donnelly CA, Riley S, Ashby D, et al. Increasing SARS-CoV-2 antibody prevalence in England at the start of the second wave: REACT-2 Round 4 cross-sectional study in 160,000 adults. medRxiv 22 July 2021. https://www.medrxiv.org/content/10.1101/2021.07.21.21260926v1 [accessed 27 July 2022].

[2] Klein C, Borsche M, Balck A, Föh B, Rahmöller J, Peters E, et al. One-year surveillance of SARS-CoV-2 transmission of the ELISA cohort: a model for population-based monitoring of infection risk. *Sci Adv* 2022;**8**:eabm5016. doi:10.1126/sciadv.abm5016.

[3] Gornyk D, Harries M, Glöckner S, Strengert M, Kerrinnes T, Heise J-K, et al. SARS-CoV-2 seroprevalence in Germany: a population-based sequential study in seven regions. *Dtsch Arztebl Int* 2021;**118**:824–31. doi:10.3238/arztebl.m2021.0364.

[4] Eichner FA, Gelbrich G, Weißbrich B, Dölken L, Kurzai O, Deckert J, et al. Seroprävalence of COVID-19 and psychosocial effects in the general population: results of the STAAB-COVID-One program. *Gesundheitswesen* 2021;**83**:965–75. doi:10.1055/a-1630-7601.

[5] Neuhauser H, Buttmann-Schweiger N, Ellert U, Fiebig J, Hövener C, Offergeld R. Seroepidemiological studies on SARS-CoV-2 in samples from the general population and blood donors in Germany–findings up to August 2021. *Epidemiol Bull* 2021;**37**:3–12.

[6] Beermann S, Dörr M, Grill E, Karch A, Lange B, Zeeb H. Coronapandemie: die Rolle epidemiologischer Forschung. *Gesundheitskrisen* 2022;**119**:753–6.

[7] Armann JP, Kirsten C, Galow L, Kahre E, Haag L, Dalpke A, et al. SARS-CoV-2 transmissions in students and teachers: seroprevalence follow-up study in a German secondary school in November and December 2020. *BMJ Paediatr Open* 2021;**5**:e001036. doi:10.1136/bmjpo-2021-001036.

[8] Aziz NA, Corman VM, Echterhoff AKC, Müller MA, Richter A, Schmandke A, et al. Seroprevalence and correlates of SARS-CoV-2 neutralizing antibodies from a population-based study in Bonn, Germany. *Nat Commun* 2021;**12**:2117. doi:10.1038/s41467-021-22351-5.

[9] Geis T, Brandstetter S, Toncheva AA, Laub O, Leipold G, Wagner R, et al. Serum neurofilament light chain (sNfL) values in a large cross-sectional population of children with asymptomatic to moderate COVID-19. *J Neurol* 2021;**268**:3969–74. doi:10.1007/s00415-021-10554-1.

[10] Wagner M, Tiffe T, Morbach C, Gelbrich G, Störk S, Heuschmann PUSTAAB-Consortium. Characteristics and course of heart failure stages A–B and determinants of progression – design and rationale of the STAAB cohort study. *Eur J Prev Cardiol* 2017;**24**:468–79. doi:10.1177/2047487316680693.

[11] Möhlendick B, Čiučiulkaitė I, Elsner C, Anastasiou OE, Trilling M, Wagner B, et al. Individuals with weaker antibody responses after booster immunization are prone to omicron breakthrough infections. *Front Immunol* 2022;**13**:907343. doi:10.3389/fimmu.2022.907343.

[12] Chou J, Thomas PG, Randolph AGJNi. Immunology of SARS-CoV-2 infection in children. *Nat Immunol* 2022;**23**:177–85. doi:10.1038/s41590-021-01123-9.

[13] Tomori DV, Rübsamen N, Berger T, Scholz S, Walde J, Wittenberg I, et al. Individual social contact data and population mobility data as early markers of SARS-CoV-2 transmission dynamics during the first wave in Germany-an analysis based on the COVIMOD study. *BMC Med* 2021;**19**:271. doi:10.1186/s12916-021-02139-6.

[14] Lange B, Jaeger VK, Harries M, Rücker V, Streeck H, Blaschke S, et al. Estimates of protection levels against SARS-CoV-2 infection and severe COVID-19 in Germany before the 2022/2023 winter season: the IMMUNEBRIDGE project. *Infection* 2023. doi:10.1007/s15010-023-02071-2.

[15] Fernández-González M, Agulló V, Padilla S, García JA, García-Abellán J, Botella Á, et al. Clinical performance of a standardized SARS-CoV-2 interferon-γ release assay for simple detection of T-cell responses after infection or vaccination. *Clin Infect Dis* 2022;**75**:e338–46. doi:10.1093/cid/ciab1021.

[16] Vanshylla K, Di Cristanziano V, Kleipass F, Dewald F, Schommers P, Gieselmann L, et al. Kinetics and correlates of the neutralizing antibody response to SARS-CoV-2 infection in humans. *Cell Host Microbe* 2021;**29**:917–29 e4. doi:10.1016/j.chom.2021.04.015.

[17] Crawford KHD, Eguia R, Dingens AS, Loes AN, Malone KD, Wolf CR, et al. Protocol and reagents for pseudotyping lentiviral particles with SARS-CoV-2 spike protein for neutralization assays. *Viruses* 2020;**12**:513. doi:10.3390/v12050513.

[18] Lange B, Jäger V, Rücker V, Hassenstein MJ, Harries M, Berner R, et al. Interimsanalyse des IMMUNEBRIDGE-Projektes zur Kommunikation von vorläufigen Ergebnissen an die Modellierungskonsortien der BMBF-geförderten Modellierungsplattform. Zenodo. 08 August 2022. https://doi.org/10.5281/zenodo.6968574 . [accessed 12 September 2022].

[19] Pai M, Denkinger CM, Kik SV, Rangaka MX, Zwerling A, Oxlade O, et al. Gamma interferon release assays for detection of Mycobacterium tuberculosis infection. *Clin Microbiol Rev* 2014;**27**:3–20. doi:10.1128/CMR.00034-13.

[20] Lange A, Borowik A, Bocheńska J, Rossowska J, Jaskuła EJV. Immune response to COVID-19 mRNA vaccine-a pilot study. *Vaccines (Basel)* 2021;**9**:488. doi:10.3390/vaccines9050488.

[21] Becker M, Strengert M, Junker D, Kaiser PD, Kerrinnes T, Traenkle B, et al. Exploring beyond clinical routine SARS-CoV-2 serology using MultiCoV-Ab to evaluate endemic coronavirus cross-reactivity. *Nat Commun* 2021;**12**:1152. doi:10.1038/s41467-021-20973-3.

[22] Rodiah I, Vanella P, Kuhlmann A, Jaeger VK, Harries M, Krause G, et al. Age-specific contribution of contacts to transmission of SARS-CoV-2 in Germany. *Eur J Epidemiol* 2023;**38**:39–58. doi:10.1007/s10654-022-00938-6.

[23] Pollett S, Johansson MA, Reich NG, Brett-Major D, Del Valle SY, Venkatramanan S, et al. Recommended reporting items for epidemic forecasting and prediction research: the EPIFORGE 2020 guidelines. *PLoS Med* 2021;**18**:e1003793. doi:10.1371/journal.pmed.1003793.

[24] Hansen CH, Friis NU, Bager P, Stegger M, Fonager J, Fomsgaard A, et al. Risk of reinfection, vaccine protection, and severity of infection with the BA.5 omicron subvariant: a Danish Nation-Wide population-based study. *Lancet Infect Dis* 2023;**23**:167–76. doi:10.1016/S1473-3099(22)00595-3.

[25] Patalon T, Saciuk Y, Peretz A, Perez G, Lurie Y, Maor Y, et al. Waning effectiveness of the third dose of the BNT162b2 mRNA COVID-19 vaccine. *Nat Commun* 2022;**13**:3203. doi:10.1038/s41467-022-30884-6.

[26] Murugesan K, Jagannathan P, Altamirano J, Maldonado YA, Bonilla HF, Jacobson KB, et al. Long term accuracy of SARS-CoV-2 interferon-γ release assay and its application in household investigation. *Clin Infect Dis* 2022;**75**:e314–21. doi:10.1093/cid/ciac045.

[27] Krasselt M, Wagner U, Nguyen P, Pietsch C, Boldt A, Baerwald C, et al. Humoral and cellular response to COVID-19 vaccination in patients with autoimmune inflammatory rheumatic diseases under real-life conditions. *Rheumatology (Oxford)* 2022;**61**:SI180–8. doi:10.1093/rheumatology/keac089.

[28] Tarke A, Coelho CH, Zhang Z, Dan JM, Yu ED, Methot N, et al. SARS-CoV-2 vaccination induces immunological T cell memory able to cross-recognize variants from Alpha to Omicron. *Cell* 2022;**185**:847–59 e11. doi:10.1016/j.cell.2022.01.015.

[29] Malipiero G, Moratto A, Infantino M, D'Agaro P, Piscianz E, Manfredi M, et al. Assessment of humoral and cellular immunity induced by the BNT162b2 SARS-CoV-2 vaccine in healthcare workers, elderly people, and immunosuppressed patients with autoimmune disease. *Immunol Res* 2021;**69**:576–83. doi:10.1007/s12026-021-09226-z.