

## DELIVERABLE

WP5\_D5.8,

Incidence of Breakthrough Infections

Ludwig-Maximilians-Universität Munich (LMU)

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## Executive summary

This report contains preliminary results concerning the cumulative incidence of SARS-CoV-2 breakthrough infections of health care workers and staff of long-term care facilities as derived from the KoCoImpf study of the Division of Infectious Diseases and Tropical Medicine of the Munich University (LMU) Medical Centre. The period under consideration spans from the initial recruitment of study participants in June 2021 to the first follow-up in November 2021. 280 study participants (from 5762 recruited) were included in this initial analysis. Out of these, 16 participants (5.71%) showed serological patterns of a SARS-CoV-2-infection apparently undergone before their recruitment. In the first follow-up, 8 additional anti-nucleocapsid-positive participants could be identified corresponding to an overall cumulative incidence of 8.57% and an incidence during the period under consideration of about 2.86%.

Due to the relatively low sample size, which is a substantial limitation for the external validity of this study, the results presented here should be interpreted cautiously. Overall, the relatively low incidence in the period under consideration reflects the low prevalence in Bavaria during this period. Interestingly, the cumulative incidence of health care workers in this analysis is still substantially lower than the respective incidence in the general population of Munich possibly indicating a better preparedness and protection. However, our data show a higher breakthrough infection incidence compared to those reported in previous publications in HCWs in the first six months after the primary vaccination scheme.

# Core content

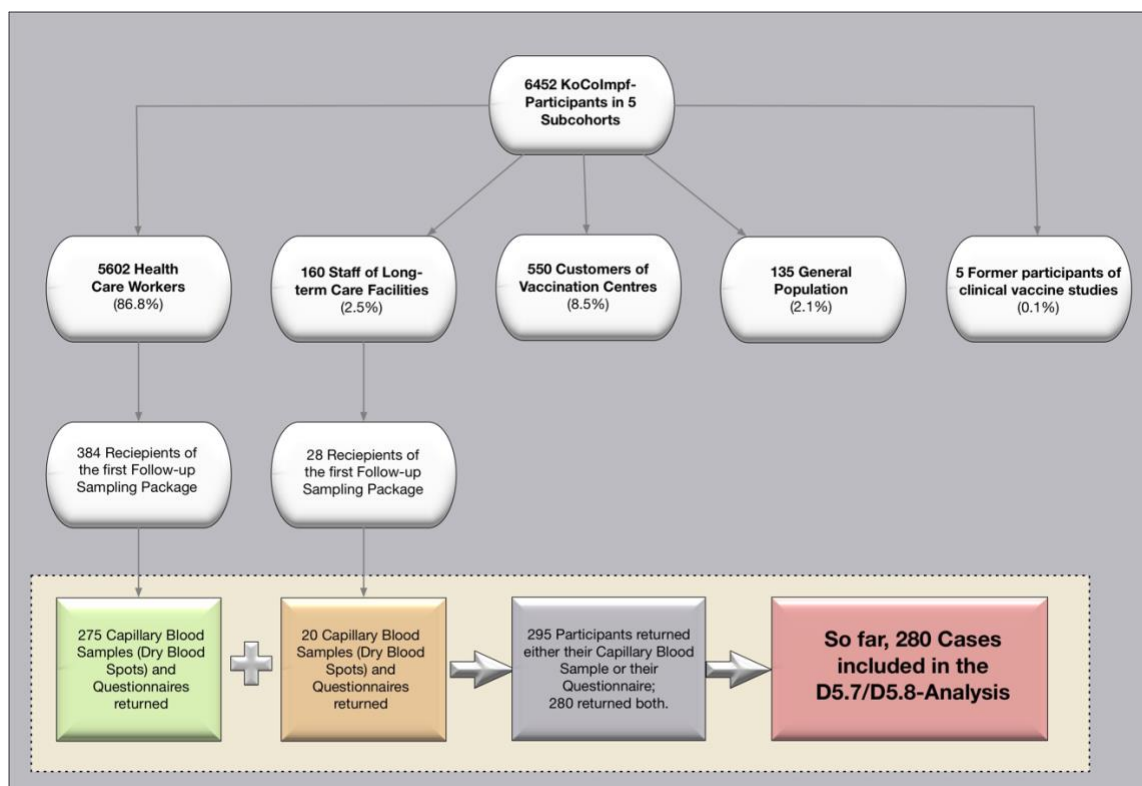
## 1. Cohorts and Study Profile

### KoColmpf Study: Prospective COVID-19 Post-Immunization Cohort in Munich

The aim of this study is to understand the serological short-, medium- and long-term immune response as well as the patterns of breakthrough infections in vaccinated individuals with focus on healthcare workers in the greater Munich area.

Detailed objectives are

- the determination of the baseline immune status and the prevalence of individuals (silently and symptomatically) infected before vaccination
- the follow-up of SARS-CoV-2-antibody dynamics over time and in relation to the vaccine they received, pre-existing immunity, and other covariates
- the determination of relative risks of post-immunization infections with SARS-CoV-2 in relation to antibody titres at the time of infection and other covariates.



**Figure 1:** The KoColmpf-cohort with its current contribution to D5.8

## 2. Methods Brief

Capillary blood samples were analysed for SARS-CoV-2 antibodies using the Elecsys® Anti-N SARS-CoV-2 (Roche) test. Antibody follow-ups were conducted in the beginning of November 2021 based on participants self-sampled capillary blood (Dry Blood Spot). Anti-S antibodies were additionally measured to quantify the overall serological response. Newly Anti-N positive participants without anti-S in the initial serological analysis were considered naturally infected (e.g., those recruited on the day of their first vaccination). Newly anti-N positive cases with anti-S antibodies in the initial round were considered breakthrough infections. Details concerning vaccinations and infections were based on questionnaire data.

The primary COVID-19 vaccination for study participants took place between December 2020 and July 2021. Participants were enrolled from from 15th June until 15th August 2021. After enrolment, the first follow-up took place in November and December 2021 with a second DBS sample and a questionnaire. The individual follow-up interval varies between two to six months because the timing of follow-ups was guided rather regarding the local epidemiological situation than a fixed period after recruitment. In case of breakthrough infections, participants' self-reporting of positive SARS-CoV-2 RT-PCR results were collected until February 2022 and led to another blood sampling for further serological and questionnaire-based investigations.

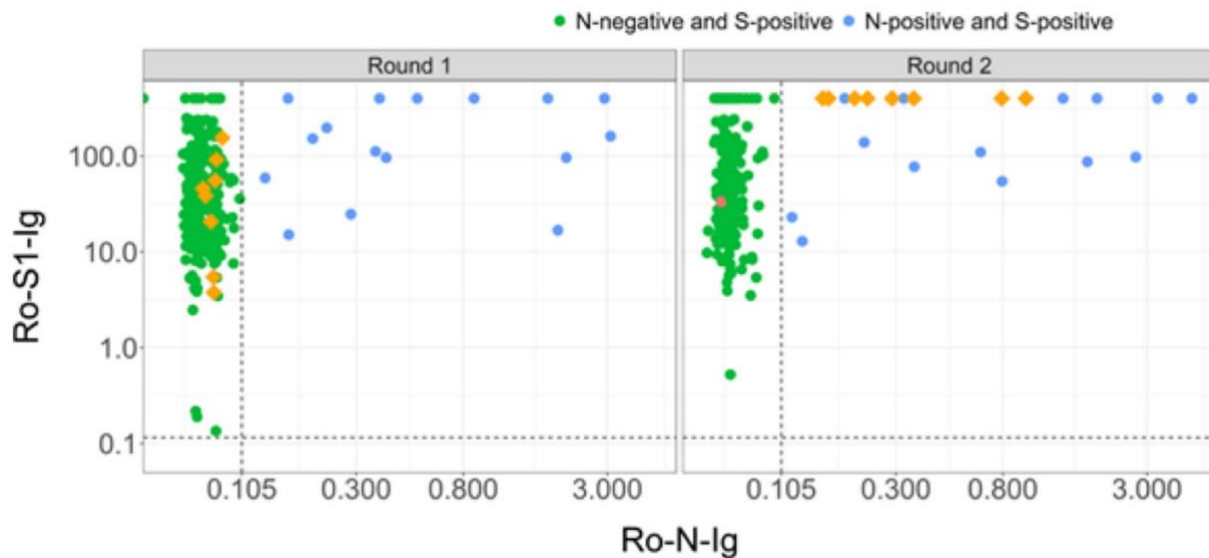
## 3. Incidence of breakthrough infections

### 3.1 Breakthrough infections by self-reported positive PCR-results

In the period between recruitment and the first follow-up (cut-off date December 1<sup>st</sup>, 2021), study participants reported in total 24 breakthrough infections (out of 1708 health care workers plus staff of nursing homes) through positive PCR-results. For these cases, however, it is difficult to determine a risk-associated denominator since the recruitment of new study participants was ongoing until December 2021 and, therefore, the individual “time under risk” differed extremely. Further, there is a high likelihood of underreporting due to the requirement of actively reporting infections on the part of the participants (as opposed to a regular recall system on the part of the study team, which is not part of the study design). Therefore, the incidence of self-reported breakthrough infections in the time period under consideration (24 cases out of 1708 study participants equals 1.4%) is substantially lower than the serological “incidence” reported in the following section.

### 3.2 Breakthrough infections detected through N-seroconversions

The assessment of breakthrough infections in KoCoImpf relies mainly on the detection of anti-nucleocapsid-seroconversions (anti-N-seroconversion) during short-term follow-up periods (2-6 months) thereby covering both symptomatic and asymptomatic breakthrough infections and overcoming most of the limitations described in the preceding paragraph (see 3.1). The substantial contribution of asymptomatic and oligosymptomatic infections in the transmission of SARS-CoV-2 infections has been estimated in several publications (1-4).



**Figure 2:** The four-quadrant-approach: 8 study participants that showed vaccination titres (anti-S1-antibodies without anti-N in the first round (orange rhombuses) shifted to a positive anti-S1/anti-N-pattern in the second round thereby indicating a breakthrough infection

The first KoCoImpf recruitment period took place between June and August 2021. Only those 412 study participants (healthcare workers and staff of long-term care facilities, see fig. 1) that were recruited until August 15<sup>th</sup>, 2021 were considered for the first follow-up sent out on October 31<sup>st</sup>, 2021 since, by study design, the minimal follow-up period is to be two months. The 280 participants that returned both the questionnaire and the capillary blood sample (DBS, dry blood spot) were included in this initial D5.8 analysis. This number corresponds to a return rate of 67.9% (280 out of 412).

In the initial serological analysis (performed immediately after recruitment), 16 out of the 280 study participants included in the current analysis showed positive anti-nucleocapsid antibodies corresponding to a baseline cumulative incidence of 5.71%. By the end of the first follow-up period, that is, in the capillary blood samples collected until December 1<sup>st</sup>, 2021, positive anti-nucleocapsid antibodies were found in 24 out of 280 samples indicating an increase of the

overall cumulative incidence to 8.57% or an incidence during the period under consideration of about 2.86%, respectively.

Based on the questionnaire results, however, out of these eight new N-seropositive study participants, only five had reported symptoms and the same five had a positive PCR-test in the relevant period of time.

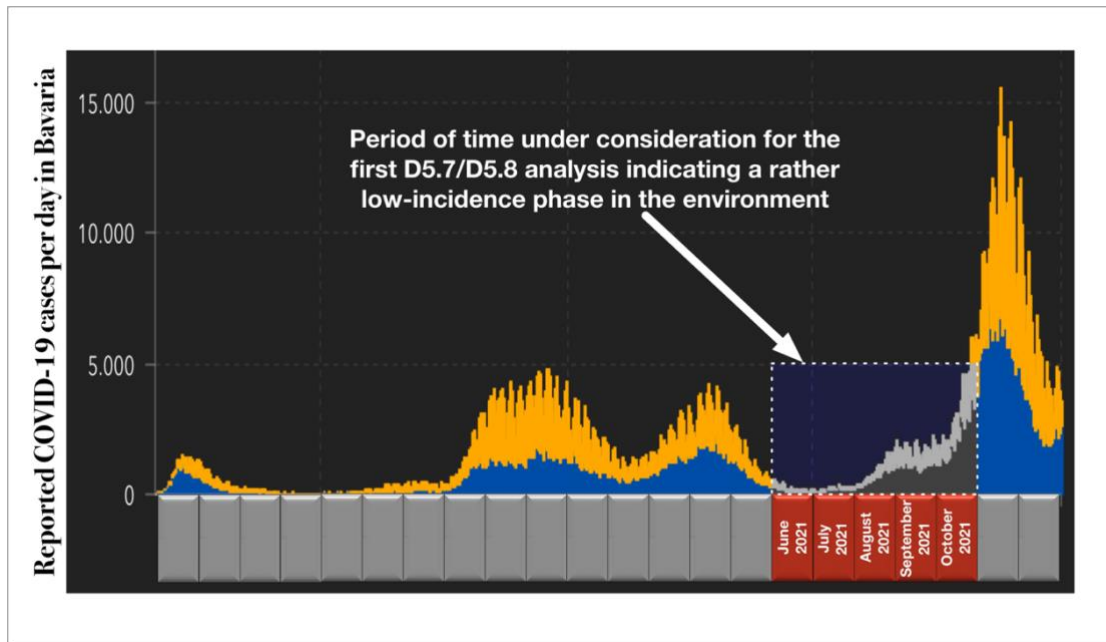
## 4. Discussion

The rather low SARS-CoV-2-incidence in the period between recruitment (June to August 2021) and the first follow-up (November 2021) corresponds to a general low-incidence in Bavaria during this period (see figure 3). However, both the initial and the follow-up cumulative SARS-CoV-2-incidence in our health care workers' (plus nursing care) cohort are substantially lower than the cumulative incidence in the general Munich population shown by our working group in the representative KoCo19-study during respective periods of time. So far, however, the sample size is too small to decide whether this finding indicates an epidemiological effect (e.g., a better pandemic preparedness and protection of Munich health care workers) or just an artefact (e.g., a selection bias due to a non-representative sampling among the health care workers). Consequently, these results should be considered preliminary.

However, this study will increase its power substantially: Further follow-ups, then based on the power derived from more than 6.000 Munich health care workers, will not only allow the assessment of incidence rates corresponding to a quantifiable time under risk (e.g., new cases per person week) but also the inference of differences between the health care worker subgroups and the Munich population. However, even the current results underscore the importance of serological data to detect all relevant breakthrough infections. Compared to previous publications (6,7) that reported incidences between 0.1-1.1% in the first six months after the first COVID-19 immunisation, our preliminary data indicate a higher breakthrough infection incidence in HCWs. However, several factors like sample size, time from primary immunisation, vaccination scheme, dominating SARS-CoV-2 variants, reporting bias, "booster" vaccinations, and SARS-CoV-2 detection strategies may have influenced (and diverted) COVID-19 breakthrough infection incidence reported in this study.

In the small sample that was analysed for this report, almost half of the breakthrough infection cases would have been missed by relying on participants-reported data exclusively. The role of asymptomatic breakthrough infection cases (here 3 out of 8 equals 37.5%) could still be highly relevant for the outbreak dynamics. Before COVID-19 vaccines had been available, a modelling study found that asymptomatic/presymptomatic persons could transmit 59% of SARS-CoV-2 infections (3). Additionally, a large retrospective HCW-cohort from Israel showed 38.7% asymptomatic infections in a two-month period (4).





**Figure 3:** The Bavarian environmental incidence during the period under consideration

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