Evaluation of intrahospital test data as an indicator of SARS-CoV-2 incidence underreporting

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Abstract

The incidence has been widely used to assess the epidemiological situation during the COVID-19 pandemic and guide health policy. As testing requirements changed during the pandemic, more SARS-CoV-2 infections may have remained undetected. This study aims to evaluate the use of different indicators for estimating unreported SARS-CoV-2 infections. Monthly SARS-CoV-2 incidences in the general Bavarian population were compared with three indicators: incidence in healthcare workers (HCWs), incidence of patients, and incidence in visitors. Based on this, the number of unreported SARS-CoV-2 cases in the Bavarian population was estimated. The incidence from the visitors correlated moderately with the official incidences (r = 0.63). The general population incidence and the inpatient incidence are highly correlated (r = 0.91), as are the general population incidence and the HCWs incidence (r = 0.94). Between April 2020 and June 2023, the general population incidence was on average higher than the average incidence of the three indicators, after which the relationship reversed. The reversal of the relationship between the data series of the Bavarian population and the chosen indicators in June 2022 suggests that SARS-CoV-2 infections were underreported. Inpatient screening incidence and HCWs' incidence in settings with low-threshold test accessibility are suitable indicators of current epidemiology in the general population.

Introduction

Despite the decreased perception and actual disease burden, the risk of infection with COVID-19, which can also still cause severe courses, to the general population may rise again in the future.[1,2] Possible reasons for this compromise are mainly the continuing emergence of novel SARS-CoV-2 variants and the waning of immunity after vaccination or infection.[3,4] Specifically, older individuals, those with pre-existing medical conditions, or those with inadequate immune protection are at the highest risk of severe COVID-19.[5–7] To protect vulnerable individuals, ensure the optimal possible healthcare for the infected patients and simultaneously alleviate the burden of the healthcare system and Healthcare Workers (HCWs) during the acute phases of the pandemic, it was necessary to implement appropriate measures. Special health policy and pandemic management strategies in Germany have already been developed during the pandemic.[8–10]

To assess the epidemiological situation during the COVID-19 pandemic and to guide contemporary health policy measures, incidence has been one of the most frequently used indicators, although it is not optimal for monitoring disease spread.[11] To capture an accurate incidence, an appropriate testing strategy is necessary. Since the beginning of the COVID-19 pandemic, the accessibility, testing requirements, and willingness to test have regularly changed throughout the pandemic (Fig. 1).[12–14]

Due to fewer testing offers and less willingness to test, fewer infections are being recorded, especially asymptomatic ones. For this reason, an increasing number of SARS-CoV-2 infections may remain undetected.

There are currently few studies available that address the underreporting of SARS-CoV-2 cases. These estimate the number of unreported cases with data from blood donations or estimation models, for example, but mainly refer to the first waves of infection during the pandemic.[15–17] Therefore, the objective of this study was to estimate the rate of unreported SARS-CoV-2 infections in the population using test data from various indicators collected over a longer period and thus including multiple waves of infection.

Results

A total of 10,697 positive RT-PCR results from HCWs as well as patients were recorded in the database from 03/01/2020 to 30/04/2023 (Fig. 2). Excluding 942 external test results, this number was reduced to 9,754. 4,071 of these positive findings were from HCWs and 5,684 were from inpatients. The total number of HCWs comprises 7,456 individuals. Of the 5,684 positive inpatients, 45 duplicates were identified and removed. 840 positive tests from outpatients and patients with nosocomial infections were excluded. A total of 4,799 patient cases were included in this study. A total of 70,594 rapid tests were performed at the RDT diagnostic centre for visitors. Out of these, a total of 616 visitors were tested SARS-CoV-2 positive by RDT.

The average age of the tested HCWs was 39.4 years. Overall, there were more females (5,563; 72.8%) than males (2,083; 27.2%) in the group of HCWs (Fig. 3).

The infection waves are identifiable by the peaks in the graph, representing months in which the numbers of recorded SARS-CoV-2 cases were the highest compared to the months before and after. Incidences peaked in April and December 2020, April and November 2021, and most notably in March 2022 (Fig. 3). The highest values overall were recorded in March 2022.

The incidence calculated on the RDT diagnostic centre data (I) only correlates moderately with the official incidence ($r = 0.63$). There is a high correlation between the general population incidence and the inpatients incidence (II) ($r = 0.91$), as well as between the HCWs incidence (III) and the general population incidence ($r = 0.94$). The difference between the official incidence and indicators II and III decreases over time until the relationship reverses.

Discussion

The data series of the three indicators show a moderate to good correlation with the data series of the general Bavarian population at least concerning the trend of infections. The monthly incidence remains slightly higher than the monthly incidence of the three indicators until June 2022. However, after that point, the relationship reverses. This suggests the presence of underreported cases of SARS-CoV-2 in the general population.

In our study, the incidences of visitors as well as HCWs, which we assume to be a representative sample of the healthy population, are proportionally higher than the incidences of the Bavarian population from

November 2022 onwards. This provides a further sign that the true incidence of the total population is probably higher. However, evidence has already been found in other modeling studies to suggest the presence of an underreporting of SARS-CoV-2 in the same period.[18] The number of infections increases with the number of tests performed, as symptom-free infections can also be identified. The number of tests fluctuated during the pandemic, especially after the elimination of mandatory testing (see also Fig. 1). Records of the number of official tests for SARS-CoV-2 performed show that this has consistently decreased over the period after March 2022.[19]

One possible reason for this could be the willingness to test, which has changed throughout the pandemic. There should be a willingness in the population to be tested for SARS-CoV-2.[12] A change in testing behaviour could already be observed during the pandemic. This influences the accuracy of the assessment of the epidemiological situation.[20] While people were respectful or even fearful of infection with SARS-CoV-2 during the acute phases of the pandemic, especially during the lockdown, willingness to test was rather high.[21] The more an individual is worried about being infected with COVID-19, the more the willingness to test increases.[22] SARS-CoV-2 protection regulations in Germany applied until 7/04/2023.[23] Due to the removal of COVID-19 regulations, official testing gradually became no longer required. Additionally, voluntary testing has steadily decreased, possibly due to diminishing concerns about the illness or transmission of the virus. This could also be attributed to the removal of COVID-19 regulations, which gave people a sense of normalcy. The option to be vaccinated against SARS-CoV-2 may also have had an impact on the number of tests performed in the population. Moreover, with 76.4% (status: 08/04/2023) a large part of the population in Germany has been vaccinated,[24] providing individuals with a sense of security from the protection offered by the COVID-vaccines. Furthermore, the fear of health implications and the impact of work absence due to illness was less pronounced, as it became evident during the pandemic that the Omicron variant caused milder symptoms.[25] Along with these changes, there were increasingly fewer opportunities to undergo official SARS-CoV-2 testing. Moreover, with the expiration of the COVID-19 regulations, official test centres that offer PCR or rapid tests for SARS-CoV-2 available to the general population vanished. In summary, with the change in testing strategy, the number of tests performed and thus the official incidence changed.

Insufficient testing can have varying degrees of consequences. An outbreak might not be detected as early. By the time countermeasures are taken, the pathogenic agent could have already spread significantly, according to its infectivity. Particularly in the event of an actual outbreak, when policy decisions become necessary, preventive measures might not be enacted due to falsely low numbers of cases which lead to misinterpretation of the current situation. Symptomless infections also pose a problem of insufficient testing. Infected individuals without symptoms assume they are healthy and may have close contacts. This can result in more individuals getting infected.

The indicator of HCWs (I) used for this study is suitable for this purpose because at least age groups 18 to 65 are approximately equally represented (Fig. 2). The distribution of age or gender of the positive tested hospitalised patients (II) or visitors who underwent testing in the RDT-diagnostic centre (III) is not determinable. The data used for this study are solely from one hospital, thus limiting the generalisability of findings to the general population. Furthermore, individuals with COVID-19 symptoms present themselves at the hospital (selection bias), resulting in a higher proportion of infected individuals in the group of hospitalised patients compared to the general population. As a result, the incidences could potentially be elevated. Among HCWs, the number of those tested positive for SARS-CoV-2 may be proportionally higher. This can be attributed to the fact that HCWs have been exposed to a greater risk of SARS-CoV-2 infection throughout the entire duration of the pandemic.

To conclude, based on the data of the three indicators until June 2023, the estimated underreported cases are higher than the official monthly incidence of SARS-CoV-2. The official incidence has been no longer representative. In principle, it is advised to not only rely on incidence alone but to use multiple parameters to assess the risk posed by SARS-CoV-2 to the population, particularly to vulnerable populations and the healthcare system. The implications of our findings are profound for public health strategies and decision-making. To avoid misguided policy decisions resulting in inappropriate resource allocation and an overburdened healthcare system, it is important to implement a robust surveillance system. This contains the inclusion of further indicators, such as the recorded cases from hospitals or other health service-providing institutions. More accurate knowledge of the actual incidence of the virus will allow public health authorities to adequately coordinate actions, efficiently (re-)allocate resources, and target high-risk areas for containment efforts.

Methods

For this study, data on SARS-CoV-2 cases were collected from 03/01/2020 to 30/04/2023 from the general Bavarian population as well as from a tertiary care hospital in the federal state of Bavaria in southern Germany.[26]

The data of reported monthly SARS-CoV-2 cases in the Bavarian population were retrieved from the Robert Koch Institute (RKI) on 13/05/2023. The monthly incidence for Bavaria was calculated using data of positive tested individuals from the Federal Statistical Office, for the aforementioned period.[26]

These incidence data were subsequently compared with additional three indicators:

I) Incidence in healthcare workers of a large tertiary care hospital in Bavaria with low-threshold access to real-time reverse transcriptase-polymerase chain reaction (RT-PCR) tests:

Information from HCWs of the study site, who tested positive for the SARS-CoV-2 by RT-PCR was collected in a Microsoft Access database (Microsoft, Redmond, USA), using data from the hospital's virological laboratory. The documentation of those cases was conducted by the Department of Infection Control and Antimicrobial Stewardship Unit over three years, during the entire study period. Since March 2020, healthcare workers in a tertiary hospital with low-threshold access to RT-PCR tests for SARS-CoV-2 have been obliged to carry them out if at least one of the following criteria applies: a positive rapid antigen test, COVID-19-specific symptoms, outbreaks in the respective work area, if they had contact with a person infected with SARS-CoV-2, or if they were on leave for more than three days (until November 2022). HCWs who tested processing in the hospital's diagnostic were included. To calculate the monthly incidence, the number of newly positive tested employees was divided by the official number of HCWs from the annual report of the hospital. In addition, information on age and gender was collected for infected HCWs.

II) Incidence of inpatients of the universal admission screening of this hospital:

Patients' positive test results for SARS-CoV-2 by RT-PCR during their stay in the hospital were collected in the same database as HCWs during the entire study period. SARS-CoV-2 RT-PCR tests were used as universal screening for all patients as described before.[27] For this study, only inpatients who tested positive by RT-PCR in the tertiary hospital admission screening were included. Information on the total number of inpatients per month was retrieved from the hospital administration system SAP ERP 6.0 (SAP, Walldorf, Germany). Using the total number of inpatients, the monthly incidence was calculated. Monthly incidences were calculated assuming an average duration for RT-PCR positivity of 18 days since the onset of SARS-CoV-2 infection.[28]

IIIIncidence in a SARS-CoV-2 rapid antigen test (RDT) diagnostic centre for visitors:

The RDT diagnostic centre was open to visitors from 01/01/2022 to 28/02/ 2023. The monthly incidence was calculated using the number of individuals who tested positive for SARS-CoV-2 by RDT, as well as the total number of individuals tested. Values were also calculated according to the average duration of 18 days that an RT-PCR has been positive since the onset of SARS-CoV-2 infection[28]. Additionally, the latter were corrected and extrapolated according to the limited sensitivity of RDTs. As the same RDTs were used in the visitor testing centre as analysed for their sensitivity in screening use in a previous study, the incidence was corrected for the average RDT sensitivity of 38.5%.[29]

Data were calculated and analysed using Microsoft Excel (Redmond, USA). Correlations were calculated between the data series of the monthly incidences of the Bavarian population and those of the monthly incidences of the three indicators. An indication of the point in time (June 2022) at which the incidence of the Bavarian population no longer shows the actual incidence was obtained. Up to this point, the respective monthly deviations between the data series of the three indicators and the data series of the Bavarian population were averaged. The resulting values were then used as a baseline for the estimation of the underreporting of SARS-CoV-2 cases. Based on the above data, a bar chart was created showing the incidence of the three different indicators over time. The monthly incidence of the Bavarian population and the estimated incidence of undetected SARS-CoV-2 cases over time were inserted into the graph as a line (see also Fig. 4). Using the age data of HCWs, an age and gender distribution was depicted.

All methods used for this study were conducted in accordance with the regulations of the University Hospital of Würzburg and the guidelines of good scientific practice. According to Bavarian State law (Art. 27 BayKrG, Bavarian Hospital Act), no explicit informed consent was necessary as the anonymized data used for this study. The ethics committee of the University of Würzburg waived the need to formally apply for ethical approval after viewing the study design since anonymized routine data from the clinical information system were retrospectively evaluated for this study (file number 20230113 01).

Artificial intelligence (AI) was used for language improvement purposes only. The tools ChatGPT (OpenAI, San Francisco CA, USA) and DeepL (DeepL SE, Cologne, Germany) were used. The actual writing of the manuscript was carried out solely by the authors mentioned by name.

Declarations

Data availability: Additional data that underlie the results reported in this article, after de-identification (text, tables, figures, and appendices) as well as the study protocol, statistical analysis plan, and analytic code is made available to researchers who provide a methodologically sound proposal to achieve aims in the approved proposal on request to the corresponding author.

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Conflict of interest: Manuel Krone receives honoraria from Abbott, GSK, and Pfizer outside the submitted work. All other authors declare no potential conflicts of interest.

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Authorship and manuscript preparation: All authors had unlimited access to all data. JM and MK take responsibility for the integrity of the data and the accuracy of the data analysis.

Epidemiological investigations: JM, VR, JR, ME, MK

Data collection: JM, VR, TP, AH, SE, NR, ME, MK

Methodology: JM, MK

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The manuscript was reviewed and approved by all the authors.

References

1. *Risikobewertung zu COVID-19*, <https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Risikobewertung.html?nn=2386228> (2022).
2. Zhu, N. *et al.* A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med* **382**, 727-733, doi:10.1056/NEJMoa2001017 (2020).
3. Tolksdorf, K. *et al.* ICD-10 based syndromic surveillance enables robust estimation of burden of severe COVID-19 requiring hospitalization and intensive care treatment. *medRxiv*, 2022.2002.2011.22269594, doi:10.1101/2022.02.11.22269594 (2022).
4. Reusch, J. *et al.* Influencing factors of anti-SARS-CoV-2-spike-IgG antibody titers in healthcare workers: A cross-section study. *J. Med. Virol.* **95**, e28300, doi:https://doi.org/10.1002/jmv.28300 (2023).
5. Treskova-Schwarzbach, M. *et al.* Pre-existing health conditions and severe COVID-19 outcomes: an umbrella review approach and meta-analysis of global evidence. *BMC Med.* **19**, 212, doi:10.1186/s12916-021-02058-6 (2021).
6. Biswas, M., Rahaman, S., Biswas, T. K., Haque, Z. & Ibrahim, B. Association of Sex, Age, and Comorbidities with Mortality in COVID-19 Patients: A Systematic Review and Meta-Analysis. *Intervirology*, 1-12, doi:10.1159/000512592 (2020).
7. Koppe, U. *et al.* COVID-19-Patientinnen und -Patienten in Deutschland: Expositionsrisiken und assoziierte Faktoren für Hospitalisierungen und schwere Krankheitsverläufe. *Bundesgesundheitsblatt - Gesundheitsforschung - Gesundheitsschutz* **64**, 1107-1115, doi:10.1007/s00103-021-03391-0 (2021).
8. Stratil, J. M. *et al.* Non-pharmacological measures implemented in the setting of long-term care facilities to prevent SARS-CoV-2 infections and their consequences: a rapid review. *Cochrane Database Syst. Rev.* **9**, Cd015085, doi:10.1002/14651858.CD015085.pub2 (2021).
9. Grote, U. *et al.* [Measures to cope with the COVID-19 pandemic in Germany: nonpharmaceutical and pharmaceutical interventions]. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz* **64**, 435-445, doi:10.1007/s00103-021-03306-z (2021).
10. Bozorgmehr, K. *et al.* Covid-19 pandemic policy monitor (COV-PPM) - European level tracking data of non-pharmaceutical interventions. *Data in Brief* **39**, 107579, doi:https://doi.org/10.1016/j.dib.2021.107579 (2021).
11. *Coronavirus SARS-CoV-2, Antworten auf häufig gestellte Fragen zur COVID-19-Pandemie*, <https://www.rki.de/SharedDocs/FAQ/NCOV2019/FAQ-Liste-COVID-19-Pandemie.html> (2023).
12. Vandrevala, T., Montague, A., Terry, P. & Fielder, M. D. Willingness of the UK public to volunteer for testing in relation to the COVID-19 pandemic. *BMC Public Health* **22**, 565, doi:10.1186/s12889-022-12848-z (2022).

13. Richter-Kuhlmann, E. & Maybaum, T. *Neue Testverordnung: PCR-Test nur noch nach positivem Antigenschnelltest*, <https://www.aerzteblatt.de/archiv/223425/Neue-Testverordnung-PCR-Test-nur-noch-nach-positivem-Antigenschnelltest> (2022).
14. *Coronavirus-Pandemie: Was geschah wann?*, <https://www.bundesgesundheitsministerium.de/coronavirus/chronik-coronavirus> (2023).
15. Offergeld, R. *et al.* Monitoring the SARS-CoV-2 Pandemic: Prevalence of Antibodies in a Large, Repetitive Cross-Sectional Study of Blood Donors in Germany—Results from the SeBluCo Study 2020–2022. *Pathogens* **12**, 551 (2023).
16. Lohse, S. *et al.* German federal-state-wide seroprevalence study of 1st SARS-CoV-2 pandemic wave shows importance of long-term antibody test performance. *Communications Medicine* **2**, 52, doi:10.1038/s43856-022-00100-z (2022).
17. Rodiah, I. *et al.* Age-specific contribution of contacts to transmission of SARS-CoV-2 in Germany. *Eur. J. Epidemiol.* **38**, 39-58, doi:10.1007/s10654-022-00938-6 (2023).
18. Sigal, A., Milo, R. & Jassat, W. Estimating disease severity of Omicron and Delta SARS-CoV-2 infections. *Nature Reviews Immunology* **22**, 267-269, doi:10.1038/s41577-022-00720-5 (2022).
19. *Tabellen zu Testzahlen, Testkapazitäten und Probenrückstau pro Woche (2.2.2023)*, <https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Daten/Testzahlen-gesamt.html> (2023).
20. Tolksdorf, K., Loenenbach, A. & Buda, S. *Dritte Aktualisierung der "Retrospektiven Phaseneinteilung der COVID-19-Pandemie in Deutschland""*, <https://www.rki.de/DE/Content/Infekt/EpidBull/Archiv/2022/Ausgaben/38_22.pdf?__blob=publicationFile> (2022).
21. Jones, E. A. K., Mitra, A. K. & Bhuiyan, A. R. Impact of COVID-19 on Mental Health in Adolescents: A Systematic Review. *Int. J. Environ. Res. Public Health* **18**, doi:10.3390/ijerph18052470 (2021).
22. Thunström, L., Ashworth, M., Shogren, J. F., Newbold, S. & Finnoff, D. Testing for COVID-19: willful ignorance or selfless behavior? *Behavioural Public Policy* **5**, 135-152, doi:10.1017/bpp.2020.15 (2021).
23. *Corona-Schutzmaßnahmen sind ausgelaufen*, <https://www.bundesregierung.de/breg-de/themen/coronavirus/ende-corona-massnahmen-2068856> (2023).
24. *Übersicht zum Impfstatus - COVID-19-Impfung in Deutschland bis zum 8. April 2023*, <https://impfdashboard.de/> (2023).
25. Zhang, J. *et al.* Clinical Characteristics of COVID-19 Patients Infected by the Omicron Variant of SARS-CoV-2. *Front Med (Lausanne)* **9**, 912367, doi:10.3389/fmed.2022.912367 (2022).
26. *COVID-19 Datenhub*, <https://npgeo-corona-npgeo-de.hub.arcgis.com/> (2022).
27. Krüger, S. *et al.* Performance and feasibility of universal PCR admission screening for SARS-CoV-2 in a German tertiary care hospital. *J. Med. Virol.* **93**, 2890-2898, doi:10.1002/jmv.26770 (2021).

28. Okita, Y., Morita, T. & Kumanogoh, A. Duration of SARS-CoV-2 RNA positivity from various specimens and clinical characteristics in patients with COVID-19: a systematic review and meta-analysis. *Inflamm. Regen.* **42**, 16, doi:10.1186/s41232-022-00205-x (2022).
29. Wagenhäuser, I. *et al.* Virus variant–specific clinical performance of SARS coronavirus two rapid antigen tests in point-of-care use, from November 2020 to January 2022. *Clin. Microbiol. Infect.*, doi:https://doi.org/10.1016/j.cmi.2022.08.006 (2022).

Figures

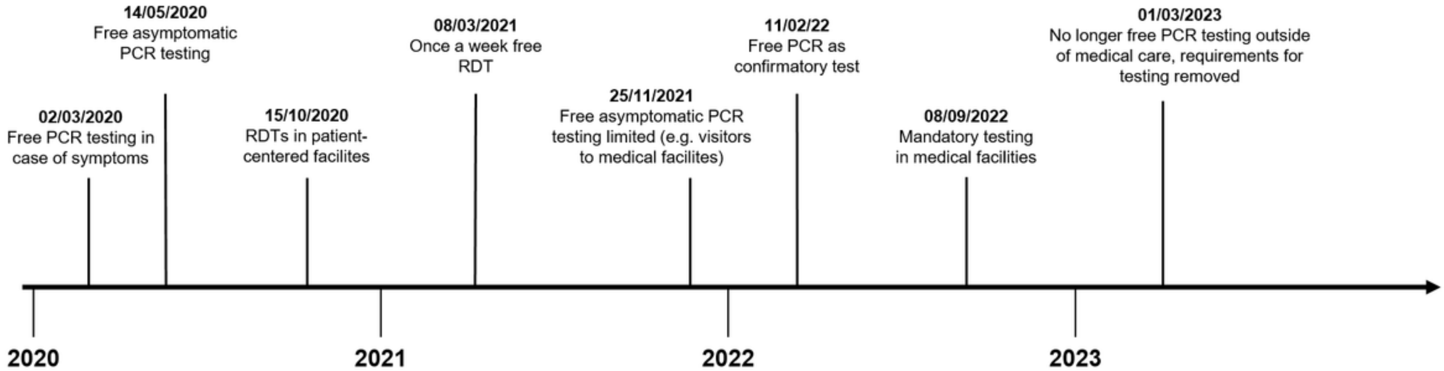

Figure 1

Timeline with information on the adjustments to the regulations for testing for SARS-CoV-2.[14]

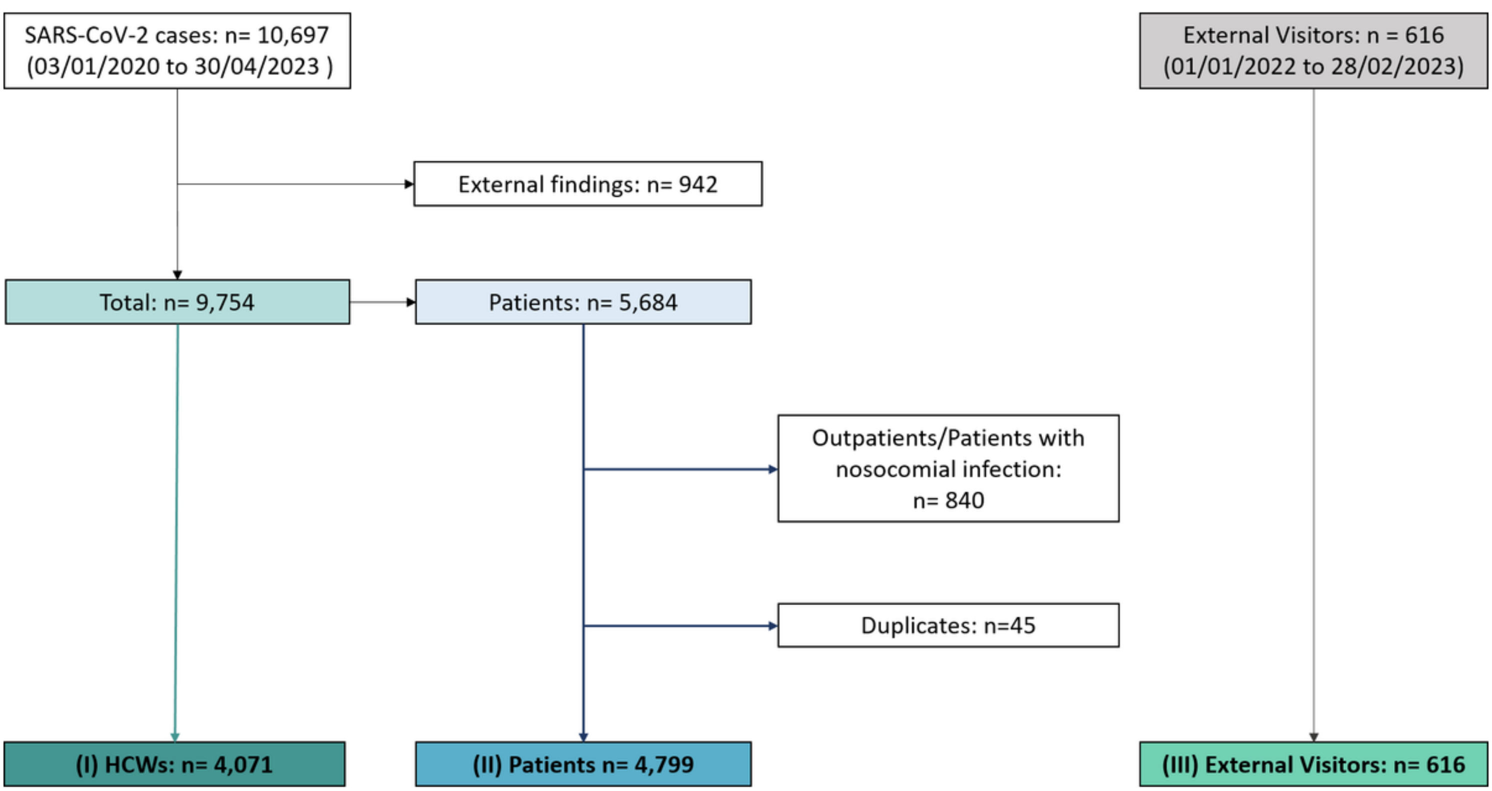

Figure 2

Data Setting Flow-Chart with (I) HCWs tested positive with PCR, (II) Patients tested positive by PCR and (III) External Visitors, tested positive with RDT.

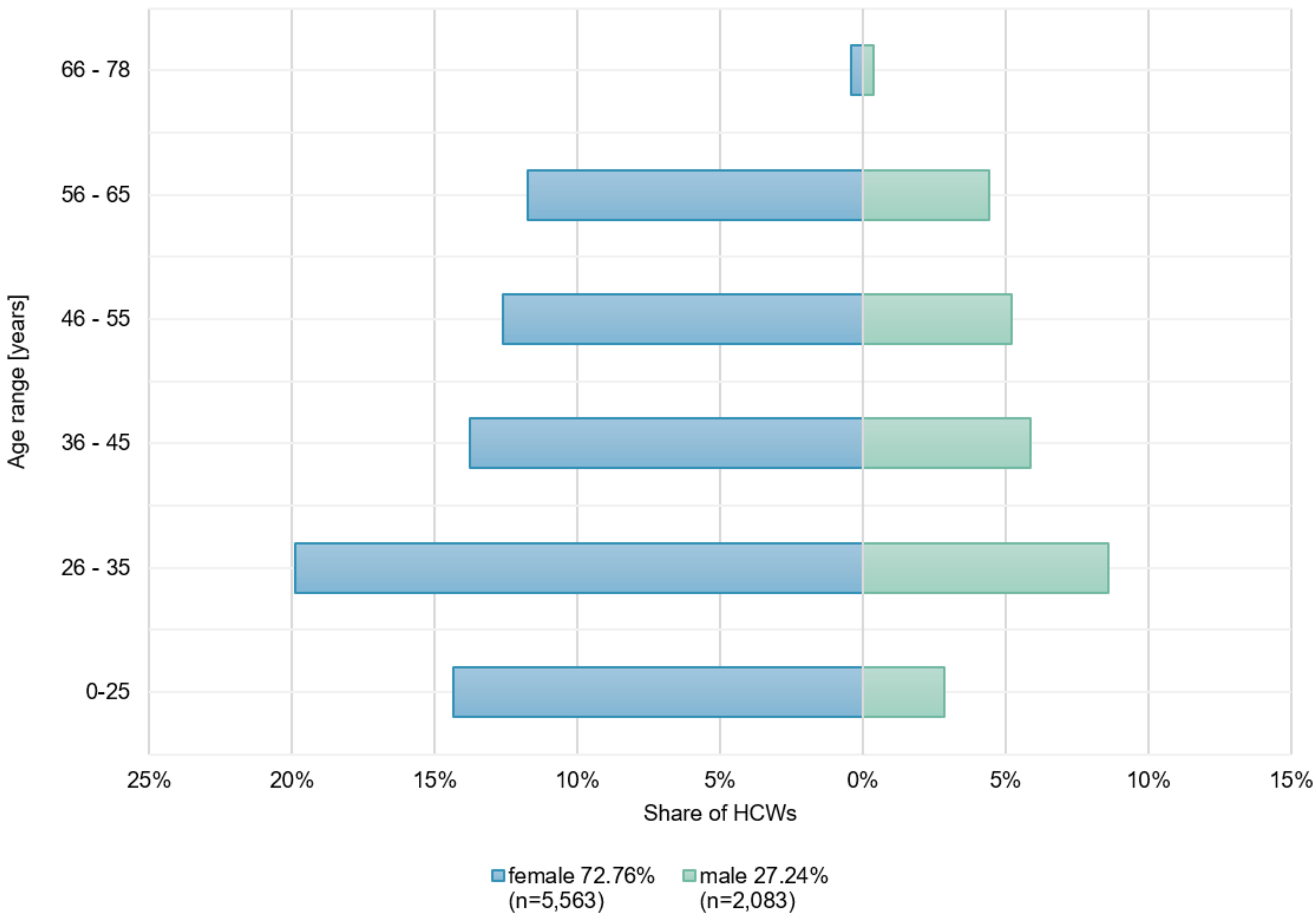

Figure 3

Age and sex distribution of HCWs that tested positive for SARS-CoV2. Female HCWs were indicated in blue, and males in green.

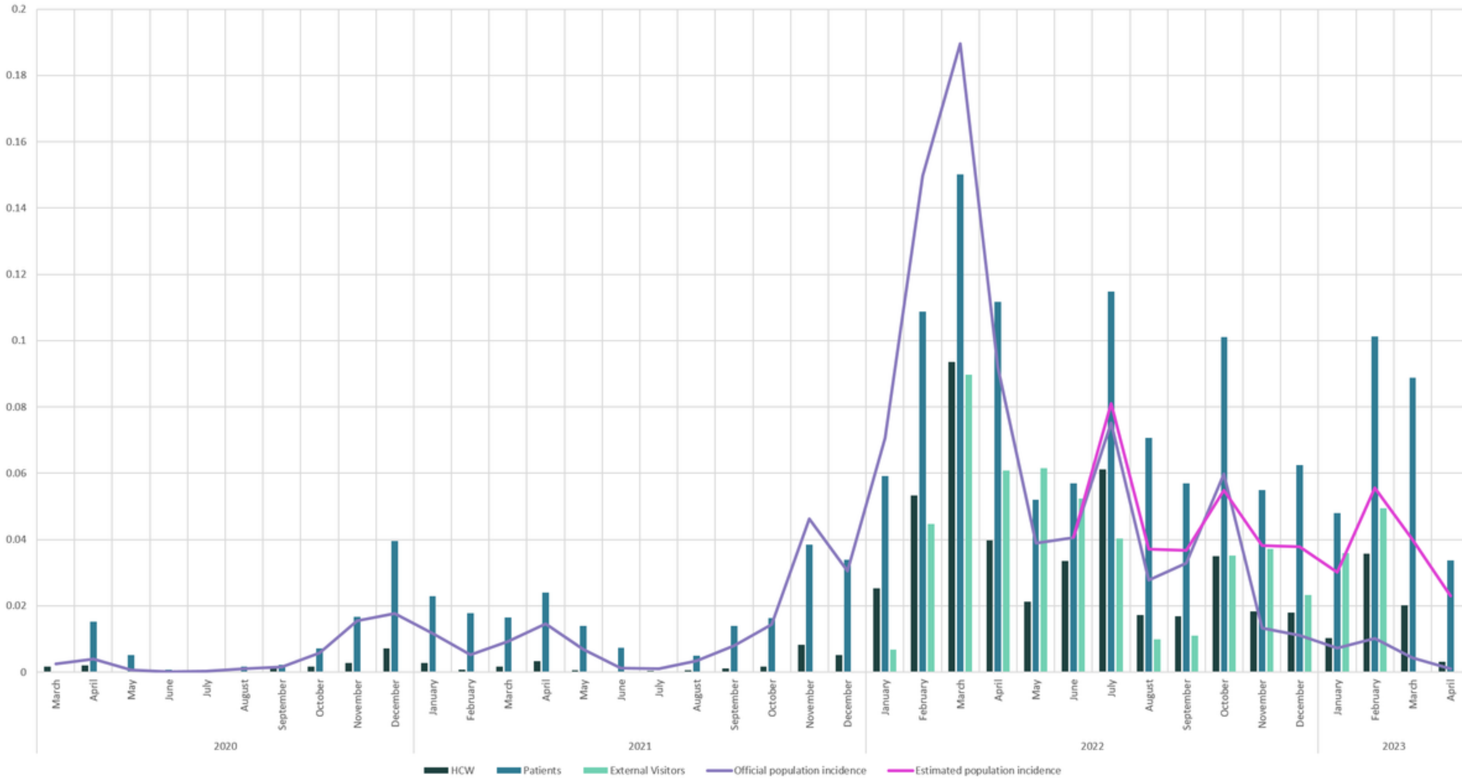

Figure 4

Regional official monthly SARS-CoV-2 incidence (purple) in comparison to the incidence derived from HCWs testing (dark green), patient screening (turquoise), and visitor testing (light green). Population incidence extrapolated from HCWs testing and patient screening (from June 2022) (pink)