Impact of the COVID-19 pandemic on influenza and respiratory syncytial virus antibody titres in the community: a prospective cohort study in Neustadt, Thuringia, Germany

Received: 8 May 2022
Accepted: 16 Sept 2022

To the Editor:

The coronavirus disease 2019 (COVID-19) pandemic, and the subsequent infection control measures, has led to a substantial shift in the spectrum of respiratory tract infections. In many regions, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was or still is the most common viral respiratory pathogen while the circulation of influenza and respiratory syncytial virus (RSV) was decreased [1–3]. There is some evidence from the past that an interruption of viral circulation for several years may reduce the immunity of the population and lead to a consecutive severe season, as observed in the 2017–2018 season that was dominated by influenza B lineage Yamagata, which was barely present in the previous 5 years [4, 5].

As was influenza, RSV was one of the most common viral pathogens in lower respiratory tract infections, not only in children but also in adults, before the pandemic [6]. In autumn 2020, a model was published that predicted larger RSV and influenza seasons after lifting infection control interventions when the pandemic ended [7]. At least for RSV, this model has proven true: in the northern hemisphere, a high disease burden of RSV infections was observed in summer 2021, especially among young children [8]. A striking observation was that this season did not peak in the first quarter of the calendar year as usual, but was delayed in comparison [8]. One of the main hypotheses to explain the observed severe RSV season and the expected severe influenza seasons was a decreasing immunity against these viral pathogens in the population [8]. However, this hypothesis has not yet been substantiated by longitudinal serological studies. Alternative to the hypothesis of declining overall immunity due to the lack of RSV circulation, it has been postulated that the primary RSV infection of infants who were born during the pandemic did not occur continuously, but was delayed and timely concentrated, after the measures were temporarily withdrawn in many regions after the first COVID-19 winter season [9].

To investigate the hypothesis of decreasing antibody-mediated immunity due to the lack of circulation of influenza and RSV during the pandemic, we performed an analysis of influenza and RSV antibody titres in a German community over 12 months.

We had the unique opportunity to investigate the seroprevalence of SARS-CoV-2, RSV and influenza in a population-based study from May 2020 to May 2021 in Neustadt am Rennsteig, a small rural town in Thuringia, Germany with 883 inhabitants [10]. During a COVID-19 outbreak in March and April of 2020, all inhabitants underwent obligatory PCR testing by local authorities and a total of 51 infected persons were identified in this municipality. 6 weeks after the outbreak, all inhabitants of Neustadt am Rennsteig were invited *via* mail to participate in this study. The study was conducted according to the current version of the Declaration of Helsinki and has been approved by the institutional ethics committees of the Jena University Hospital and the respective data protection commissioner (approval number 2020-1776) and the ethics committee of the Thuringian chamber of physicians. All participants were informed and gave written informed consent. All data were collected with unique pseudonyms on paper case report forms. These identifiers were later used to merge the questionnaire information with the laboratory information in an electronic study database. The study is registered at the German clinical trials register as DRKS00022416.

Shareable abstract (@ERSpublications)
The lack of circulation of influenza and RSV during the COVID-19 pandemic did not result in a substantial drop in respective antibody levels in the community over 12 months https://bit.ly/3qXVLId

Cite this article as: Pletz MW, Dürrwald R, Reiche J, *et al.* Impact of the COVID-19 pandemic on influenza and respiratory syncytial virus antibody titres in the community: a prospective cohort study in Neustadt, Thuringia, Germany. *Eur Respir J* 2022; 60: 2200947 [DOI: 10.1183/13993003.00947-2022].

626 of the 883 inhabitants participated in the initial visit of our study (CoVID-19 in Neustadt am Rennsteig: CoNAN). For the two follow-up visits, only participants with prior COVID-19 and age- and sex-matched non-infected controls were invited. Details and results of the CoNAN study have previously been published [10]. In October 2020 (CoNAN visit 6 months) and in May 2021 (CoNAN visit 12 months), blood sampling was repeated. Here, we report the anti-RSV and anti-influenza antibody course over 12 months (May 2020, October 2020, April 2021), which covers the missing 2020–2021 influenza and RSV season.

The study population of this substudy consisted of 189 participants (figure 1a). Due to insufficient sample volume, not all measurements were performed in all samples; in particular, there were fewer samples for the (interim) 6-month time point (figure 1a).

Subset population characteristics were as follows: median age 56 years (interquartile range 40.8–70.0 years); males 46.0%; co-morbidities: arterial hypertension 40.5%, chronic lung disease 5.8%, autoimmune disease 10.0%, diabetes mellitus 12.6%, chronic kidney disease 14.7%; current smokers or history of smoking 30.5%.

Serum samples were analysed at the "National Influenza Centre and the Consultant Laboratory for RSV, parainfluenza virus and human metapneumovirus" at the Robert Koch Institute in Berlin, Germany.

Antibodies against RSV were determined using anti-RSV ELISA (IgG) (Euroimmun, Germany). Antibodies against influenza were measured for strains H1N1 (A/Guangdong-Maonan/SWL1536/2019 H1N1 and A/Victoria/2570/2019), H3N2 (A/Hong Kong/2671/2019 H3N2), B Yamagata (B/Phuket/3073/2013 B-Yam) and B Victoria (IS B/Washington/2/2019 B-Vic) with a haemagglutination inhibition test. All antibodies were analysed by linear mixed models with random intercept for the clustering within participants and fixed time effects (either linear or as three categories for the three time points).

Anti-RSV antibodies were determined in 189 participants (figure 1a). In seven participants, no anti-RSV antibodies were detected at any of the three CoNAN visits. The mixed model showed a small monthly decrease of −0.60 relative units (RU) per mL (95% CI −0.94 to −0.26 $RU \cdot mL^{-1}$; p=0.001). In line with this, we observed evidence for a decrease between the first and the third measurements (−6.39 $RU \cdot mL^{-1}$, 95% CI −9.99 to −2.79 $RU \cdot mL^{-1}$; p<0.001) (figure 1c). This decrease was considered minor because a decrease of more than two-fold was observed in 12 (7%) participants only. In a further seven participants (4%) an increase of RSV-antibodies by more than two-fold of baseline (first visit) was observed. For all other samples, changes were less prominent.

Anti-influenza antibodies were determined in 185 participants (figure 1a). 32 patients were vaccinated during the study and excluded from further analysis. Since the haemagglutination inhibition test delivers titres and not concentrations, only strain-specific influenza seroprevalence is provided (figure 1d). The mixed model revealed no evidence for a decrease in antibody titres against the different influenza strains tested with point estimates ranging between 0.01 (B-Jam) and 0.22 (H1N1-Victoria) for a linear time trend of log2 antibody titres per month (figure 1e–i).

To date, these data are the first to describe the impact of the missing circulation of RSV and influenza in the 2020–2021 season on respective antibody titres in a prospective cohort. A potential bias could be conferred by the (unavoidable) exclusion of influenza-vaccinated subjects, since they could possibly have an increased likelihood for declining immunity.

After an outage of one influenza/RSV season, we did not observe evidence for a relevant decline of anti-RSV antibodies and no evidence for a decline of anti-influenza antibodies over the 12-month observation period.

Our results strengthen the abovementioned hypothesis, that the observed severe RSV seasons in 2021 in young children may be mainly explained by a time-pressed catch-up of the initial infection rather than a general substantial decline of immunity in the overall population. For influenza, the lack of evidence for a decrease in serological immunity makes the likelihood of a large upcoming influenza season in adults seem lower, but the time-pressed catch-up of an initial infection in infants born during the pandemics, as seen for RSV in 2021, may occur also for influenza in the upcoming season. In line with this, the Australian Department of Health and Aged Care reports that the weekly number of notifications of laboratory-confirmed influenza reported in Australia has exceeded the 5-year average, with people aged 5–9 years, children aged younger than 5 years, and people aged 10–19 years having the highest notification

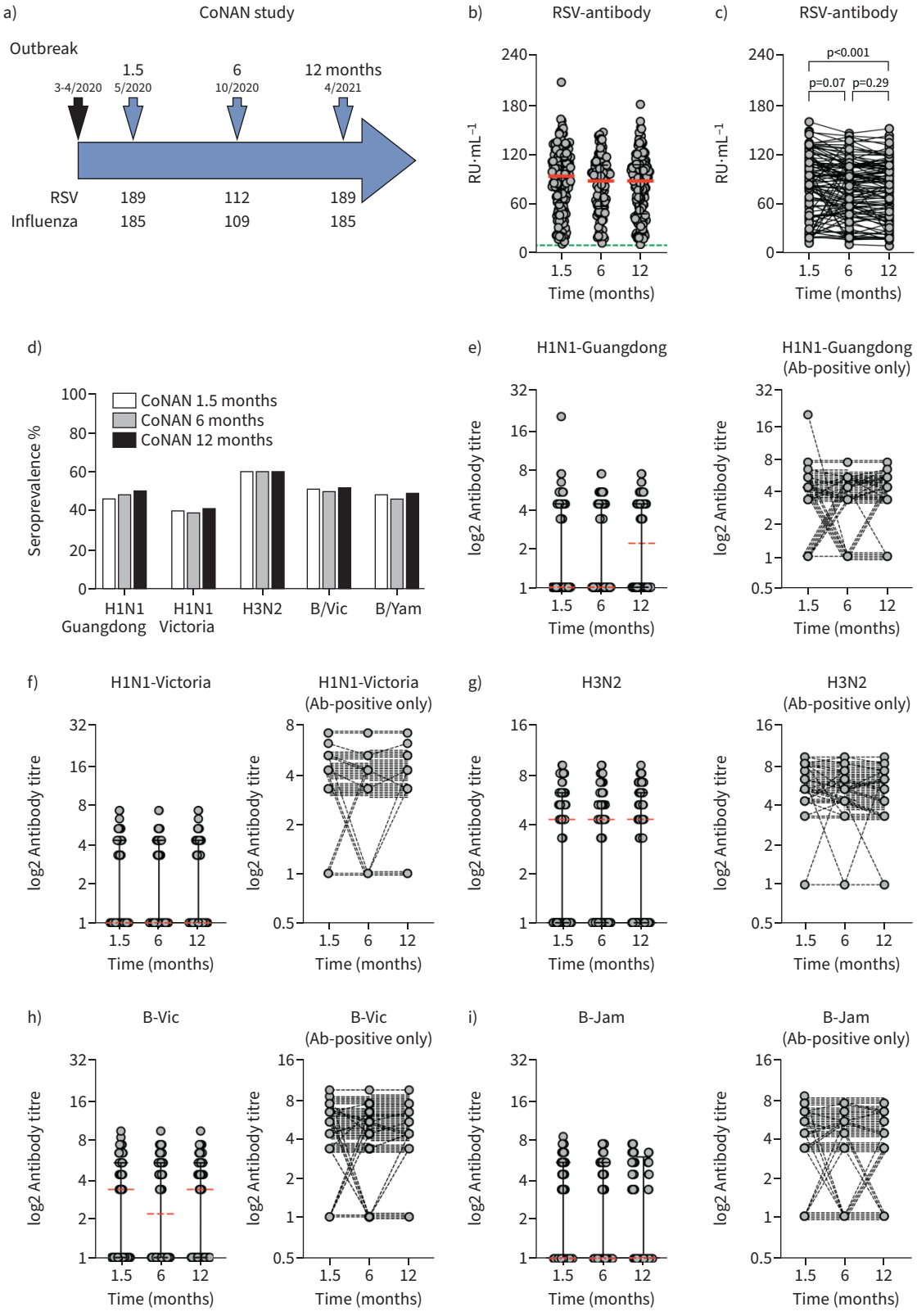

FIGURE 1 a) Flow chart of the CoNAN (CoVID-19 in Neustadt am Rennsteig) study with included participants in this substudy. Concentration of respiratory syncytial virus (RSV) antibodies shown b) at the three time points and c) as spaghetti plot in all participants with three measurements (n=106). Dashed line represents cut-off values. d) Seroprevalence (in % of study participants) of antibodies against five different influenza strains for all three study visits. e–i) log2 antibody titres against individual influenza strains as indicated, shown for all participants with three measurements (left panels) and for participants with positive antibody titres only (right panels). Each dot represents one individual participant. RU: relative units.

rates [11]. Thus, influenza vaccination in general and particularly of these infants will be of great importance in the upcoming season.

Mathias W. Pletz[1,2], Ralf Dürrwald[3], Janine Reiche[3], Norman Rose[1], André Scherag[2,4] and Sebastian Weis[1,5] for the CoNAN study group

[1]Institute of Infectious Diseases and Infection Control, Jena University Hospital—Friedrich Schiller University, Jena, Germany. [2]Center for Sepsis Care and Control (CSCC), Jena University Hospital—Friedrich Schiller University, Jena, Germany. [3]Department of Infectious Diseases, Unit 17, Influenza and Other Respiratory Viruses, National Influenza Centre and Consultant Laboratory for RSV, PIV and HMPV, Robert Koch Institute, Berlin, Germany. [4]Institute of Medical Statistics, Computer and Data Sciences, Jena University Hospital—Friedrich Schiller University, Jena, Germany. [5]Leibniz Institute for Natural Product Research and Infection Biology, Hans Knöll Institute (HKI), Jena, Germany.

Corresponding author: Mathias W. Pletz (mathias.pletz@med.uni-jena.de)

The project was carried out in cooperation with the district administration and the health department of the Ilm district. CoNAN study group: Technische Universität Ilmenau, Ilmenau, Germany: Thomas Hotz; local cooperation partners: Petra Enders, Renate Koch, Steffen Mai and Matthias Ullrich. Institute of Clinical Chemistry and Laboratory Diagnostics and Integrated Biobank Jena (IBBJ), Jena University Hospital—Friedrich Schiller University, Jena, Germany: Cora Richert, Cornelius Eibner, Bettina Meinung, Kay Stötzer, Julia Köhler and Michael Kiehntopf. Children's Hospital, Jena University Hospital—Friedrich Schiller University, Jena, Germany: Hans Proquitté, Hans Cipowicz and Christine Pinkwart. Department of Anesthesiology and Intensive Care Medicine Jena University Hospital—Friedrich Schiller University, Jena, Germany: Michael Bauer, Petra Dickmann, Annika Licht, Juliane Scholz and Wibke Wetzker. Institute for Infectious Disease and Infection Control, Jena University Hospital—Friedrich Schiller University, Jena, Germany: Anita Hartung, Daniel Weiss, Lara Thieme, Gabi Hanf, Clara Schnizer, Jasmin Müller, Jennifer Kosenkow, Franziska Röstel, Joel Guerra, Stefan Hagel, Christina Forstner, Steffi Kolanos, Clara Schnizer, Juliane Ankert and Aurelia Kimmig. Institute of Immunology, Jena University Hospital—Friedrich Schiller University, Jena, Germany: Raphaela Marquardt. Institute of Medical Microbiology, Jena University Hospital—Friedrich Schiller University, Jena, Germany: Stefanie Deinhardt-Emmer, Sebastian Kuhn, Bettina Löffler and Michael Baier.

The study is registered at the German Clinical Trials Register: DRKS00022416.

Conflicts of interest: The authors declare that they do not have any competing interests.

Support statement: This research was funded by the Thuringian Ministry for Economic Affairs, Science and Digital Society: Thüringer Corona-Pandemie-Hilfsfonds, SV-Kapitel 82 30, Titel 68205 #5526/32-4-2. Funding information for this article has been deposited with the Crossref Funder Registry.

References

1 Groves HE, Piché-Renaud P-P, Peci A, *et al.* The impact of the COVID-19 pandemic on influenza, respiratory syncytial virus, and other seasonal respiratory virus circulation in Canada: a population-based study. *Lancet Reg Health Am* 2021; 1: 100015.

2 Dähne T, Bauer W, Essig A, *et al.* The impact of the SARS-CoV-2 pandemic on the prevalence of respiratory tract pathogens in patients with community-acquired pneumonia in Germany. *Emerg Microbes Infect* 2021; 10: 1515–1518.

3 Oh D-Y, Buda S, Biere B, *et al.* Trends in respiratory virus circulation following COVID-19-targeted nonpharmaceutical interventions in Germany, January–September 2020: analysis of national surveillance data. *Lancet Reg Health Eur* 2021; 6: 100112.

4 Rößler S, Ankert J, Baier M, *et al.* Influenza-associated in-hospital mortality during the 2017/2018 influenza season: a retrospective multicentre cohort study in central Germany. *Infection* 2021; 49: 149–152.

5 Nielsen J, Vestergaard LS, Richter L, *et al.* European all-cause excess and influenza-attributable mortality in the 2017/18 season: should the burden of influenza B be reconsidered? *Clin Microbiol Infect* 2019; 25: 1266–1276.

6 Shi T, Denouel A, Tietjen AK, *et al.* Global disease burden estimates of respiratory syncytial virus-associated acute respiratory infection in older adults in 2015: a systematic review and meta-analysis. *J Infect Dis* 2020; 222: Suppl. 7, S577–S583.

7 Baker RE, Park SW, Yang W, *et al.* The impact of COVID-19 nonpharmaceutical interventions on the future dynamics of endemic infections. *Proc Natl Acad Sci USA* 2020; 117: 30547–30553.

8 Williams TC, Sinha I, Barr IG, *et al.* Transmission of paediatric respiratory syncytial virus and influenza in the wake of the COVID-19 pandemic. *Euro Surveill* 2021; 26: 2100186.

9 Zheng Z, Pitzer VE, Shapiro ED, *et al.* Estimation of the timing and intensity of reemergence of respiratory syncytial virus following the COVID-19 pandemic in the US. *JAMA Netw Open* 2021; 4: e2141779.

10 Weis S, Scherag A, Baier M, *et al.* Antibody response using six different serological assays in a completely PCR-tested community after a coronavirus disease 2019 outbreak – the CoNAN study. *Clin Microbiol Infect* 2021; 27: 470.e1–470.e9.

11 The Department of Health and Aged Care. Australian Influenza Surveillance Report and Activity Updates – 2022. Report number 8. Available from: www1.health.gov.au/internet/main/publishing.nsf/Content/cda-ozflu-2022.htm