Journal of Infection and Public Health 18 (2025) 102660

Contents lists available at ScienceDirect

Journal of Infection and Public Health

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

Original article

Impact of COVID-19 on testing, positive cases, patient characteristics, and hospital contacts for respiratory syncytial virus, influenza, and pneumococcus in Danish children

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ARTICLE INFO

Article history:
Received 21 October 2024
Received in revised form 6 January 2025
Accepted 7 January 2025

Keywords:
COVID-19
RSV
Influenza
Pneumococcus
Testing patterns

ABSTRACT

Background: Respiratory infections substantially impact pediatric health. The COVID-19 pandemic introduced widespread non-pharmaceutical interventions, which influenced the incidence of common respiratory infections. This comprehensive study investigates the impact of these interventions on the incidence of respiratory syncytial virus, influenza, and invasive pneumococcal disease in Danish children.
Methods: We conducted a descriptive study based on a cohort of 1,790,464 Danish children from 2012 to 2022. We analyzed data from microbiology tests and hospital contacts to assess infection rates and testing patterns before, during, and after the COVID-19 pandemic. The relationships between testing and sex, age groups, chronic disease status, and hospital contacts were analyzed.
Results: We observed a marked decrease in cases of respiratory syncytial virus, influenza, and pneumococcus disease during the lockdown period. Once restrictions were lifted, there was a substantial resurgence in these infections. The frequency of testing for respiratory pathogens increased over time, with a rising proportion of healthy individuals without underlying chronic disease being tested. The proportion of positive tests linked to hospital contacts varied: there was a notable decline for respiratory syncytial virus and influenza post-lockdown, while pneumococcus cases continued to be strongly linked to hospital contacts.
Conclusion: The study highlights the impact of COVID-19 interventions on the epidemiology of pediatric respiratory infections, revealing a pattern of decreased incidence during lockdowns followed by a resurgence. More tests were carried out among an increasing proportion of healthy individuals. Such changes in testing practices and changing characteristics of tested populations have implications for understanding post-pandemic infection trends and healthcare resource allocation.

Introduction

Respiratory infections are a leading cause of pediatric morbidity, hospitalization, and mortality worldwide [1]. Respiratory syncytial virus (RSV) is a major cause of infant hospitalizations, while influenza tends to affect toddlers and school-aged children more commonly [1]. Bacterial infections, though less frequent, remain a concern. Especially, children with complex chronic diseases are more susceptible to invasive infections caused by *Streptococcus Pneumonia*, known as invasive pneumococcal disease, which is a severe and potentially life-threatening condition [2]. Following hospitalization for a viral lower respiratory tract infection, the risk of developing a severe bacterial airway infection is increased. From 2019 to 2022, the COVID-19 pandemic introduced a novel viral pathogen, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which caused widespread lower respiratory tract infections [3]. Before the introduction of vaccines in 2021, non-pharmaceutical interventions (NPIs), including social distancing, lockdowns, and mask mandates, were introduced to limit transmission.

A potential consequence of these interventions has been the phenomenon known as "immunity debt", which refers to the reduction in population immunity due to lack of exposure to common pathogens during the pandemic. The concept of immunity debt has

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https://doi.org/10.1016/j.jiph.2025.102660

been hypothesized to explain the post-pandemic surge in respiratory infections, and the focus of this study is to present empirical data scrutinizing and quantifying these patterns [3–7].

While previous studies have reported a decrease in the incidence of common respiratory infections during the COVID-19 pandemic, there has been no comprehensive national-level analysis in Denmark that specifically examines how these changes have impacted the incidence of RSV, influenza, and invasive pneumococcal disease, as well as testing practices, hospitalizations, and underlying chronic disease in pediatric populations [5]. The post-pandemic surges in both viral and bacterial infections were explained theoretically to be due to immunity debt, as mentioned above [8]. Also, changes in testing frequencies were found to contribute to the higher detection rates of infections [9]. The full reference list of the papers found in a prior literature search is provided in the Supplementary Material (Appendix A) along with further relevant references (Appendix B).

This study provides a national, population-based analysis using a cohort of 1.79 million Danish children over a 10-year period (2012–2022), examining the impact of the COVID-19 pandemic and subsequent NPIs on the incidence of respiratory syncytial virus (RSV), influenza, and pneumococcus. Additionally, this study uniquely explores changes in testing behaviors, including variations in the proportion of healthy versus chronically ill children being tested, and the role of hospital contacts in these patterns. By offering a comprehensive, long-term view of multiple pathogens alongside test practices, we provide valuable insights into the broader implications for pediatric health during and after the pandemic.

Material and methods

Study population

We conducted a national study based on the cohort of all children born in Denmark aged 0–17 years between 1 January 2012 and 31 December 2022. Participants exited the cohort upon death, emigration, reaching their 18th birthday, or on 1 January 2023.

Outcomes

The outcomes of interest were the occurrences of tests for three different pathogens, specifically respiratory syncytial virus (RSV), influenza virus, and pneumococcus. Testing for COVID-19 was also included to provide context within the study period. Testing patterns were described based on both the absolute number of tests performed and the percentage of positive tests.

Data sources

Data on microbiology tests were obtained from the Danish Microbiology Database (MiBa) [10]. Since 2010, MiBa has registered all microbiology tests from all Danish patients with hospital in- or outpatient contact. While the majority of tests in MiBa come from hospital patients, tests collected from patients in general practice are also included. These tests are analyzed by the microbiology department at Statens Serum Institut [11]. COVID-19 test data were obtained from Statens Serum Institut (SSI) and Statistics Denmark [12]. Polymerase chain reaction (PCR) testing was the gold standard throughout the study period; however, antigen testing (for COVID-19) was introduced during the period and handled separately. Information on the background population, as described above, was extracted from the Danish Civil Registration System [13]. Additionally, the tests were linked to hospital contacts and severe chronic disease status using data from the Danish National Patient Register which contains complete information on inpatient and outpatient records for all Danish citizens [14,15].

Study size

The flow diagrams (Figs. 1–3 in the Results section) illustrate how the study size was arrived at. The background population consisted of 1,843,739 individuals born in Denmark between 1994 and 2022. Individuals who died or emigrated before 1 January 2012 were excluded, resulting in 1,790,464 individuals available for analysis and linkage to microbiology test data.

Variables and definitions

In addition to the unique personal identifier enabling linkage with routinely collected national register data, the MiBa dataset included the following variables: tested pathogen (influenza types A, B or C; RSV; and pneumococcus), test result (positive, negative, or inconclusive), test date, location (microbiology department), and sample material (primarily nasopharyngeal secretions collected by suction or swab, or blood). Samples analyzed at Statens Serum Institut were excluded i.e., samples analyzed at hospital microbiology departments were retained. COVID-19 test data included test date, result (positive or negative, we classified inconclusive results as negative), test center status (yes or no), responsible institution (e.g., SSI), and case definition (PCR or antigen).

Statistical methods

The monthly occurrence of tests for the different pathogens was presented over the study period 2012–2022. In the last three calendar years of the study period after COVID-19 had emerged, COVID-19 test data were compared with testing for, RSV, influenza, and pneumococcus to illustrate how the presence of COVID-19 affected the occurrence of the three other pathogens. The study period was divided into three subperiods: pre-lockdown (1 January 2012 to 11 March 2020), full and partial lockdown (12 March 2020 to 21 May 2021), and post-lockdown (22 May 2021 to 31 December 2022) [16]. This was done by splitting the analysis time scale.

Incidence rates were calculated as the number of positive test cases per 100,000 person-years at risk. The period-specific incidence rates were obtained by fitting Poisson regression models with the logarithm of the number of person-years as offsets (Appendix C). Incidence rates were further presented by sex, severe chronic disease status, and age group (0 years, 1 year, 2–6 years, and 7–17 years) [17]. For the age variable this procedure required a split of the transformed time scale to allocate the person-time to the age groups in question. After back-transforming the time scale to calendar time, chronic disease status was ascertained at every incident event time.

In addition to incidence rates, the number of tests performed over time was reported. Positive test results were also presented based on whether they occurred in connection with a hospital contact (defined as occurring between 2 days before and 5 days after the positive test). Hospital contacts were classified as any contact, or those lasting at least 6 or 12 hours. Due to the implementation of a new version of the Danish National Patient Register in 2019, hospitalization data were only assessed for the period 1 January 2019 to 31 December 2022 to ensure comparability [18].

Two sets of comparisons by lockdown status were performed. First, the incidence rates of RSV, influenza and pneumococcus were compared before, during and after the defined lockdown period using a Bayesian Poisson regression model [19,20]. Second, the proportions of positive RSV and influenza linked to a hospital contact were compared before and after lockdown using a Bayesian logistic regression model. Both models were based on a normal prior distribution. The model robustness to changes in the variance parameter was assessed. The posterior distributions were estimated based on 10,000 one-chained Monte Carlo simulations.

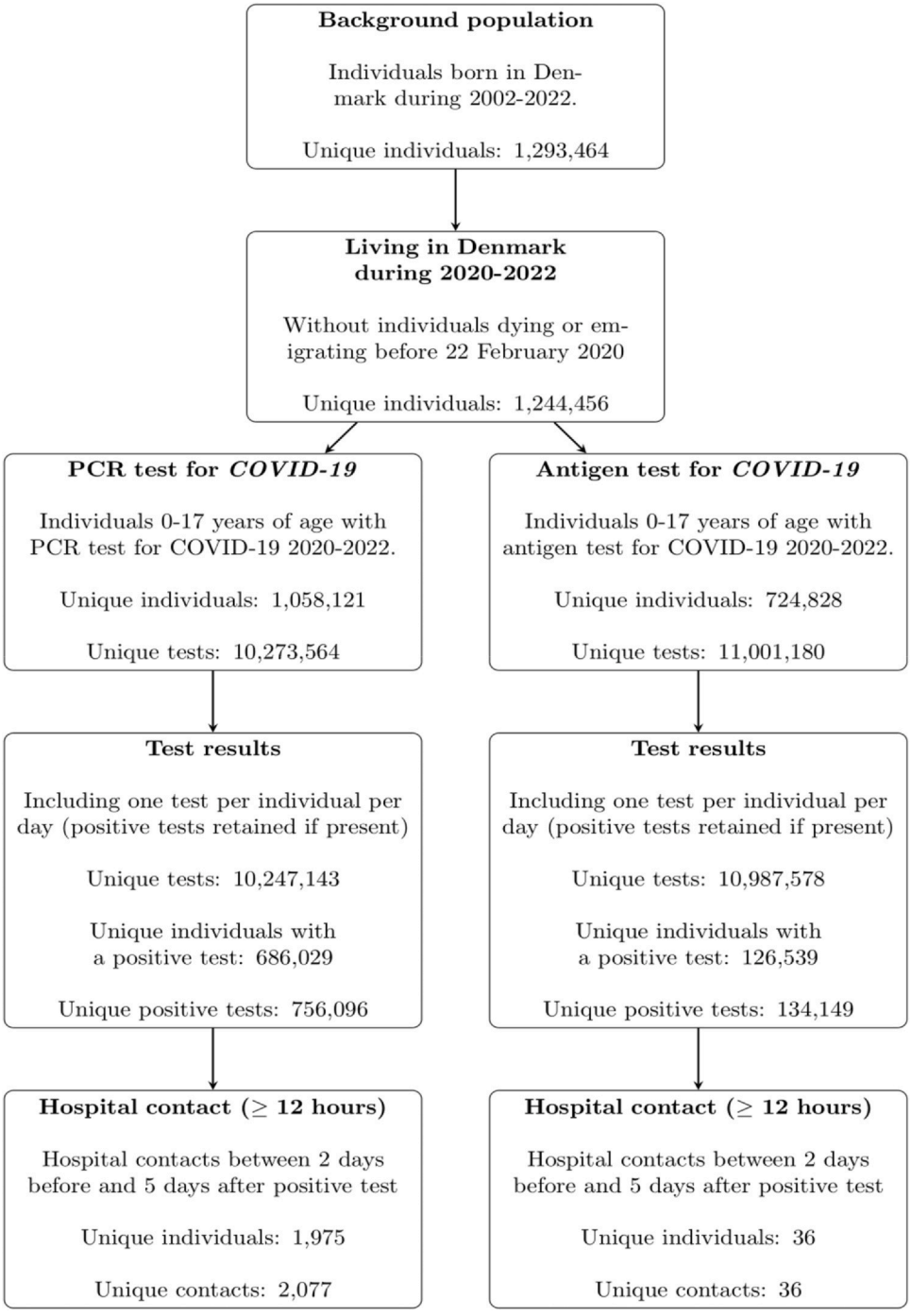

Fig. 1. Flow diagram 1. Danish children aged 0–17 years tested for COVID-19, 2020–2022.

Data management and analyses were performed using StataNow/SE 18.5.

Role of the funding source

No specific funding for this study.

Ethical considerations

The study relied solely on register data, and thus, no ethical approval was necessary according to Danish law [21].

Results

The study enrolled a total of 1,790,464 unique individuals aged 0–17 years, residing in Denmark during 1 January 2012 to 31 December 2022. These individuals contributed a total of 11,963,512 person-years at risk. After the COVID-19 outbreak, 1,244,456 unique individuals remained at risk, contributing 3,055,064 person-years. The study populations are illustrated in three flow diagrams (Figs. 1–3).

Fig. 1 shows that during the period impacted by COVID-19 (2020–2022), the majority of children were tested at least once for COVID-19. After removing duplicates, a total of 10,247,143 PCR tests and 10,987,578 antigen tests were conducted in this population, averaging 9.7 and 15.2 tests per child, respectively, among those

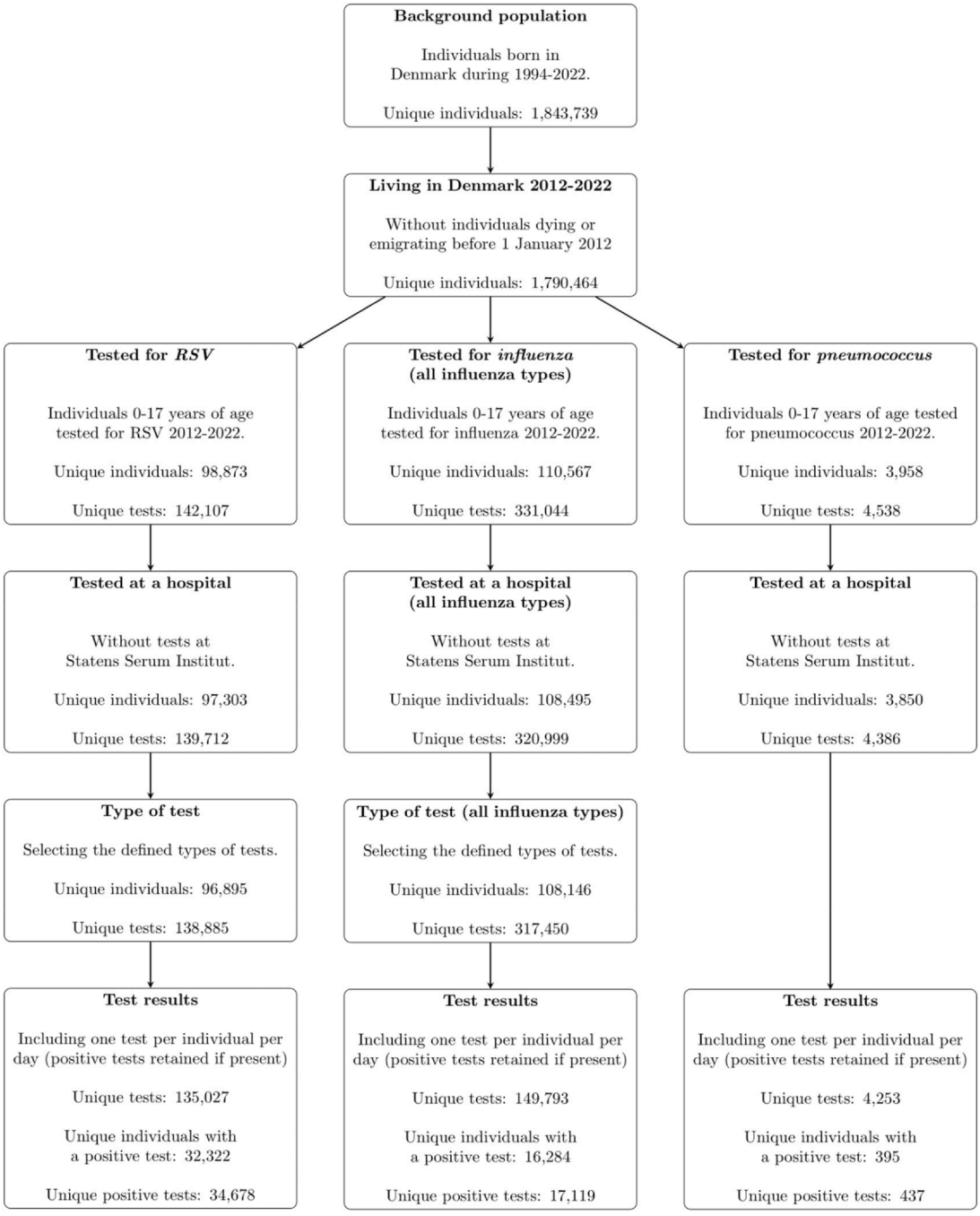

Fig. 2. Flow diagram 2. Danish children aged 0–17 years tested for RSV, influenza, and pneumococcus (full study period 2012–2022).

tested. As shown in Fig. 1, most tests were negative (92.6 % for PCR), and only a small fraction of positive cases were linked to a hospital contact exceeding 12 hours (0.27 % for PCR).

Fig. 2 presents the number of individuals in the study population tested for RSV, influenza, or pneumococcus during the entire study period (2012–2022). After removing duplicate tests, 96,895 individuals were tested for RSV, 108,146 for influenza, and only 3,850 for pneumococcus. The total number of tests performed for RSV, influenza, and pneumococcus were 135,027, 149,793, and 4,253, respectively. Of these, 34,678 RSV tests (25.7 %), 17,119 influenza tests (11.4 %), and 437 pneumococcus tests (10.3 %) returned positive results (Fig. 2).

Fig. 3 follows the same structure as Fig. 2, albeit with two key differences. First, Fig. 3 focuses on the study period from 2019 to 2022, which was partly impacted by the COVID-19 pandemic. Second, this period coincided with the introduction of the new version of the National Patient Register (DNPR3). Fig. 3 also links positive tests for the three pathogens to hospital contacts lasting more than 12 hours. During the period from 2019 to 2022, there were 22,533 positive tests for RSV, 10,957 for influenza, and 125 for pneumococcus. Of these, 8,044 RSV cases, 1,200 influenza cases, and 107 pneumococcus cases were associated with hospital contacts lasting more than 12 hours. Thus, the proportion of positive cases linked to prolonged hospital contacts was 35.7 % for RSV, 11.0 % for influenza, and 86.0 % for pneumococcus. This aspect of hospital contacts is discussed in more detail in later sections of the manuscript.

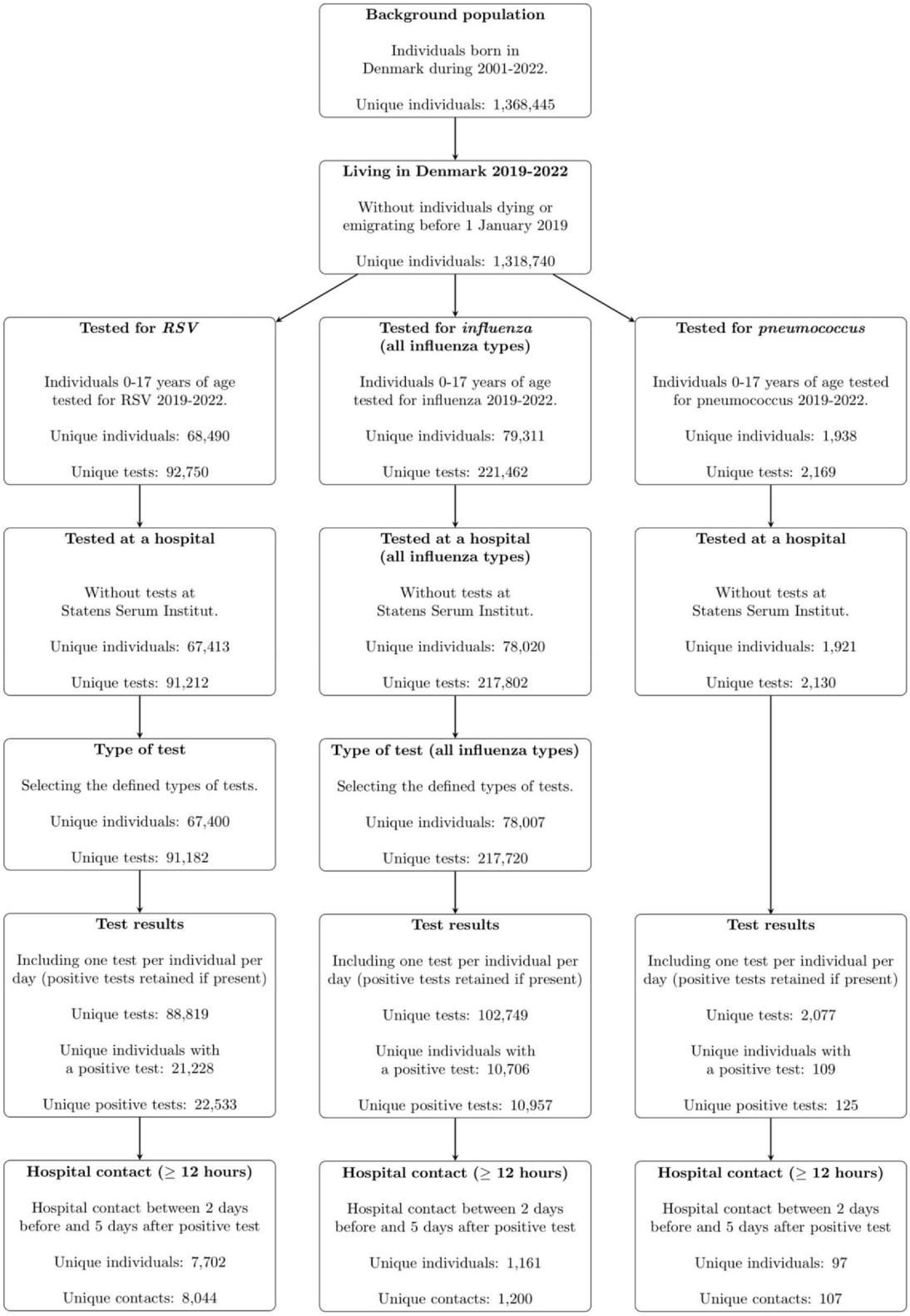

Fig. 3. Flow diagram 3. Danish children aged 0–17 years tested for RSV, influenza, and pneumococcus with hospital contact data (end of study period 2019–2022).

COVID-19: PCR and antigen tests

The first recorded COVID-19 test for Danish children aged 0–17 years was performed on 22 February 2020. The number of daily tests and the number of positive results, from this date through 31 December 2022, is presented by test type (PCR or antigen) in Fig. 4.

PCR tests peaked in January 2022, with 1,261,143 tests conducted and 27 % testing positive (Supplementary Table 1). The positivity rate reached its highest point the following month, approaching 40 %, just before COVID-19 cases began to diminish in Denmark (Fig. 1). Earlier monthly positivity rates remained below 6.5 %. The number of antigen tests peaked in May 2021 at 1,979,837 tests, but with a much lower positivity

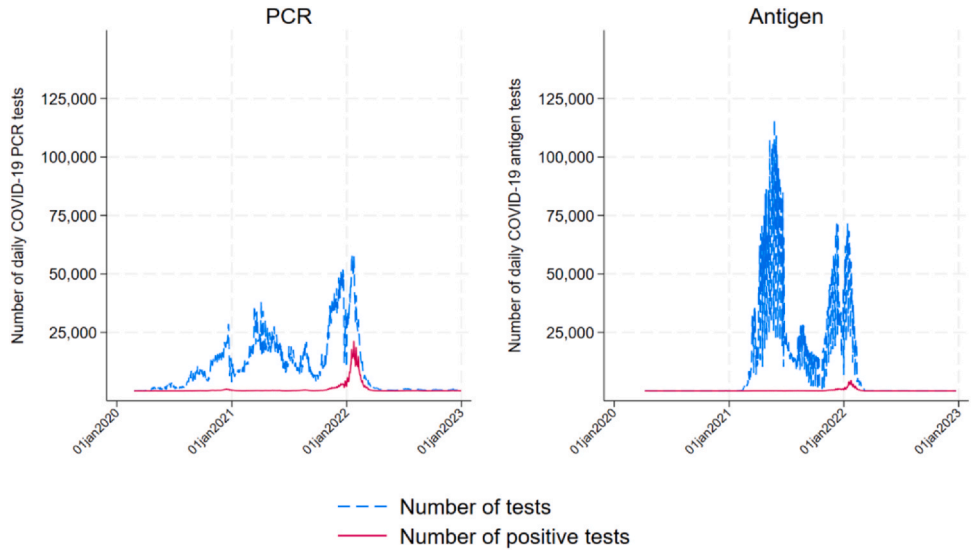

Fig. 4. PCR and antigen tests for COVID-19 in Danish children aged 0–17 years.

percentage of 0.08 % during this month. Until January 2022, the monthly positivity percentages for antigen tests ranged between 0.04 % and 1.73 %. The incidence of COVID-19 cases, defined as the number of positive tests per 100,000 person-years at risk, is shown in Supplementary Figure 1. Additionally, the incidence rates by subgroups defined by sex (male or female), chronic disease status (yes or no), and age groups (0 years, 1 year, 2–6 years, and 7–17 years) are also illustrated in Supplementary Figure 2 and presented in Supplementary Table 2.

Incidences of RSV, influenza, and pneumococcus versus COVID-19

The incidences of RSV, influenza, and pneumococcus over time are presented in Fig. 5. This figure also highlights the timing of the COVID-19 lockdown alongside the incidence of COVID-19 cases measured by PCR tests.

Caption Fig. 5: The cases per 100,000 person-years were calculated within each month during the follow-up. The shaded area shows the incidence of COVID-19 standardized to the range of the y-axis.

Fig. 5 clearly shows that the typical seasonal patterns for RSV, influenza, and pneumococcus were disrupted during the lockdown period, with virtually no cases observed around January 2021. RSV epidemics peaked each January before the lockdown, with rates showing a consistent seasonal pattern. The resurgence of RSV cases was notable during the summer of 2021, coinciding with the end of the lockdown period, even though this period is usually considered the off-season for RSV (Table 1). In contrast, the incidence of influenza virus remained low throughout the summer of 2021 but emerged as an epidemic in January 2022, staggered relative to the COVID-19 incidence at that time.

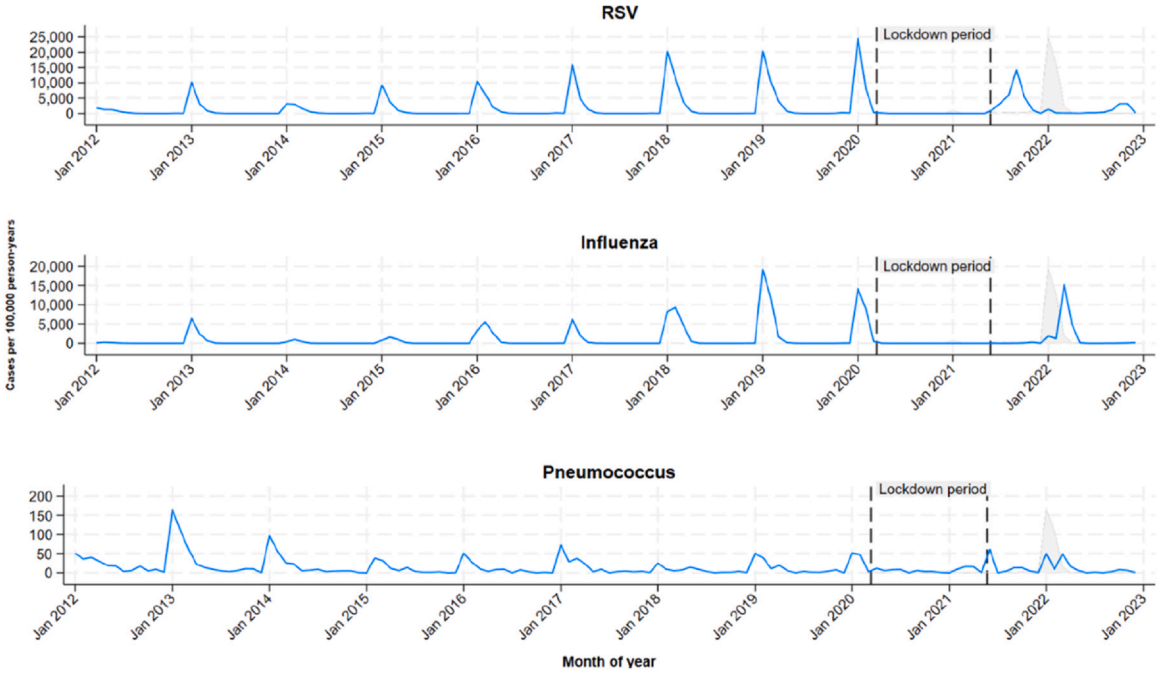

Fig. 5. RSV, influenza, pneumococcus, and COVID-19 in Danish children aged 0–17 years, 2012–2022.

Table 1
Comparison of disease incidences in Danish children aged 0–17 years: pre-lockdown, during lockdown, post-lockdown. Cases per 100,000 person-years.

	Incidence			Incidence rate ratio (95 % credible interval)	
Disease	**Pre-lockdown**	**During lockdown**	**Post-lockdown**	**During vs. pre-lockdown**	**Post vs. pre-lockdown**
RSV	205	21	926	0.10 (0.09–0.11)	4.51 (4.41–4.60)
Influenza	122	23	337	0.19 (0.17–0.21)	2.75 (2.67–2.83)
Pneumococcus	4	2	3	0.60 (0.39–0.85)	0.83 (0.62–1.09)

The comparisons were based on a Bayesian Poisson model with a normal prior distribution. The model was robust to changes in the variance parameter.

Incidences by sex, age, and chronic disease status

The incidence of RSV, influenza, and pneumococcus over time was calculated by sex, chronic disease status, and age group, as shown in Supplementary Fig. 3–5. Notably, while children with severe chronic diseases were associated with higher rates of all three pathogens in the beginning of the study period (Supplementary Table 3), this pattern was not sustained for RSV. Over time, the difference in RSV incidence between children with and without chronic disease diminished (Supplementary Fig. 4). In 2013, the RSV incidence rate ratio between children with and without chronic disease was 3.23. From 2014 to 2019, the yearly incidence rate ratios ranged from 1.59 to 1.93. After 2019, the ratios decreased to a range of 1.08–1.52. Further information on the subgroups can be found in the Supplementary Material (Supplementary Figs. 1–5 and Appendix C).

Number of tests over time for RSV and influenza

Fig. 6 presents the daily number of RSV and influenza tests and the corresponding positive test counts. A figure illustrating pneumococcus tests was omitted due to the low number of daily tests; however, trends are described below.

An increasing trend in RSV and influenza testing was observed. In January 2012, only 318 RSV tests were performed, which gradually increased to 2,931 tests by January 2020. The number of positive tests also increased, with monthly positivity rates peaking between 23 % and 47 % during the epidemic periods. The trend of higher testing volumes on specific dates was particularly notable for RSV in the years preceding the COVID-19 outbreak (Fig. 6). Notably, while virtually no cases of RSV or influenza were recorded during the lockdown period, the number of daily tests showed an increasing trend throughout this period of time. On a calendar year basis, 2021 showed by far the highest percentage of positive RSV cases, while the opposite trend was observed for influenza, with 2021 having the lowest percentage of positive influenza cases (Supplementary Table 4). For pneumococcus, the annual number of tests also demonstrated an upward trend, increasing from 372 tests in 2012 to 638 in 2022. However, the yearly positivity percentage of pneumococcus tests declined from 20 % and 25 % in 2012 and 2013 to between 5 % and 7 % during 2018–2022.

Hospital contacts versus the number of positive tests

Fig. 6 presents the daily number of tests and positive tests for RSV and influenza. To further investigate the relationship between positive tests and hospital contacts, Fig. 7 presents the number of positive tests linked to a hospital contact for the period from 2019 onwards. As with Fig. 6, pneumococcus tests were omitted from Fig. 7 due to low numbers.

Before the COVID-19 lockdown, 28 % of RSV cases were not linked to a hospital contact within two days before to five days after the positive test (Fig. 7 (blue area) and Supplementary Table 5). This pattern persisted during the first post-lockdown RSV epidemic, although some periods showed even lower linkage and an increased proportion of hospital contacts lasting less than six hours (left panel Fig. 7). During the second post-lockdown RSV epidemic, which began in late 2022, 18 % of positive tests were not linked to hospital contacts. However, there was a sustained notable increase in shorter hospital stays (green area of Fig. 7) and, overall, the proportion of

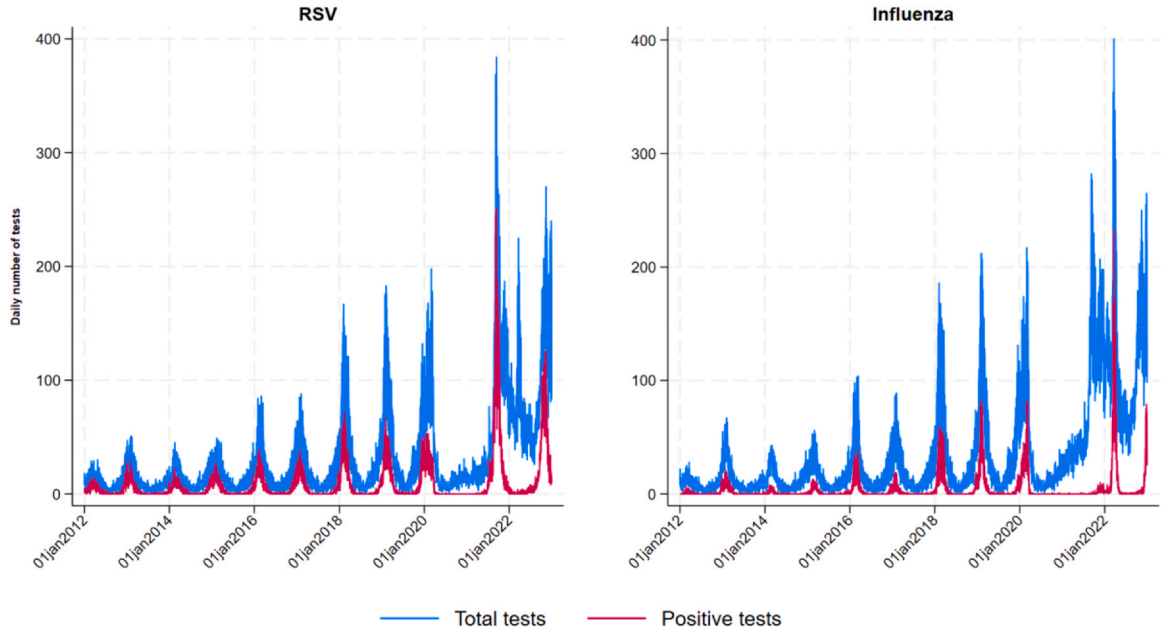

Fig. 6. Daily number of RSV and influenza tests in Danish children aged 0–17 years, 2012–2022.

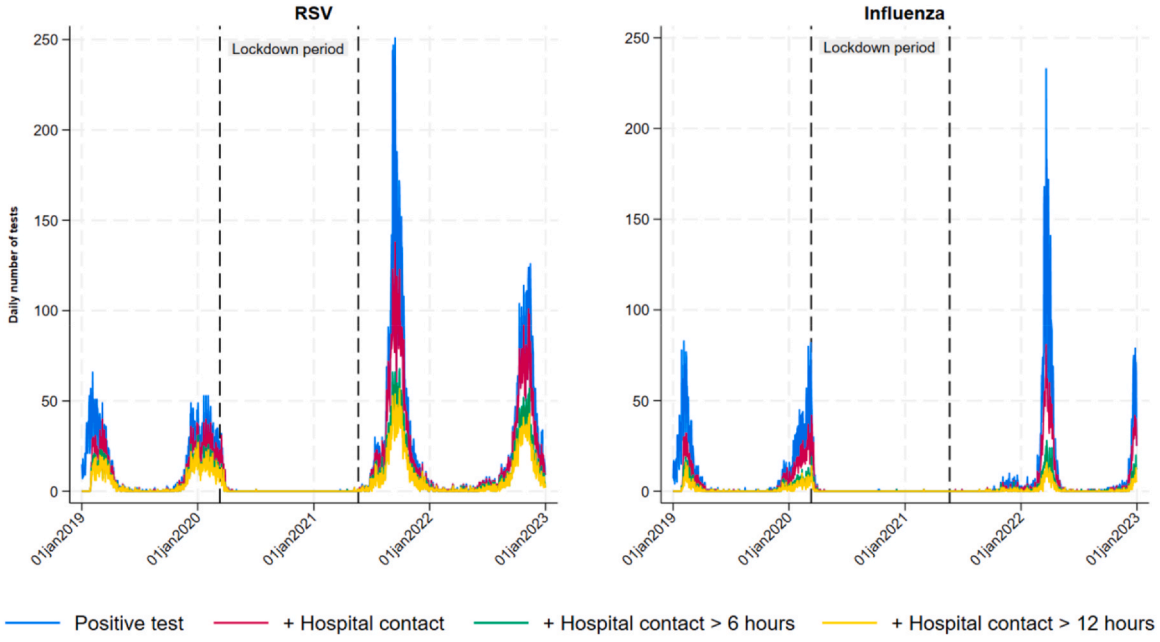

Fig. 7. Daily number of RSV/influenza cases linked to hospital contacts in Danish children aged 0–17 years, 2019–2022.

positive tests linked to a hospital contact was higher post-lockdown (Table 2). Comparable trends were observed for influenza, although the proportion of influenza cases linked to hospital contacts was more similar before and after lockdown. For pneumococcus, the majority of positive tests during 2019–2022 (86 %) were linked to a hospital contact lasting at least 12 hours (Fig. 2).

Discussion

This population-based study of 1.79 million Danish children from 2012 to 2022 utilized comprehensive data on COVID-19, RSV, influenza, and pneumococcus tests, along with hospital contacts, to explore how potential immunity debt and changes in testing behavior have impacted infectious disease epidemiology. The NPIs for COVID-19 not only limited the spread of the targeted virus but also substantially decreased the incidence of RSV, influenza, and pneumococcus. The subsequent lifting of restrictions led to a notable resurgence of these infections, likely attributable to immunity debt arising from reduced pathogen circulation.

Following this post-COVID19 infectious disease resurgence, the epidemiological trends appeared to stabilize. However, the high number of positive tests for common pathogens may also reflect factors beyond immunity debt. Notably, there was a steady increase in testing for all three pathogens even before the COVID-19 pandemic, followed by a substantial rise after the lockdown. The post-lockdown increase in testing may be attributed to public health awareness, leading to higher rates of healthcare utilization. Additionally, we observed a notable shift in the tested populations. Initially, individuals with chronic diseases were highly represented; however, over time, the proportion of healthy individuals tested for RSV steadily increased. The pattern of increasing relative proportions of health service utilization among otherwise healthy children has been observed in other contexts and should raise concerns about public health resource allocation [14].

Our findings align with reports such as Lomholt et al. [6], who documented a resurgence of RSV cases in Denmark following the easing of restrictions, indicating that NPIs have substantially altered the epidemiological landscape [5,9,22–24]. Further references are provided in Appendix A and Appendix B from the supplementary material. These studies highlight how the COVID-19 pandemic influenced respiratory disease patterns beyond the specific virus itself. Leung et al. (2024) reported post-pandemic immunity debt contributing to influenza resurgence in the US and England, while Cohen et al. (2022) examined various types of infections in France, reinforcing the idea that reductions in pathogen circulation during NPIs likely led to this resurgence of respiratory infections [8,25]. On the other hand, Petros et al. (2024) emphasized how changes in testing behaviors contributed to the surge in RSV infections, specifically pointing to the role of increased testing rates among pediatric populations, which may have led to overdiagnosis and unnecessary healthcare utilization [9]. While other studies have documented testing for both viral and bacterial pathogens, to our knowledge, this is the first study to examine the impact of testing behavior on the characteristics of populations tested in relation to chronic disease and hospital contact status [26]. During the widespread antigen testing for COVID-19, positive results remained below 2 %, raising ongoing questions about the utility and implications of these tests. These trends corroborate earlier findings regarding immunity debt and the resurgence of common infections post-COVID, while also highlighting a pronounced rise in pediatric microbiological testing, which may raise concerns about overdiagnosis and healthcare resource allocation [27].

Table 2
Proportion of RSV and influenza tests linked to hospital contacts in Danish children aged 0–17 years: pre-lockdown and post-lockdown.

Disease	Pre-lockdown, 1 Jan 2019 to 11 Mar 2020			Post-lockdown, 21 May 2021 to 31 Dec 2022			Post- vs. pre-lockdown
	Positive tests	With hospital contact	% positive tests linked with hospital contact	Positive tests	With hospital contact	% positive tests linked with hospital contact	Odds ratio (95 % credible interval)
RSV	6009	3906	65.00	15,989	12,247	76.60	1.76 (1.65–1.87)
Influenza	5123	2392	46.69	5826	2867	49.21	1.10 (1.03–1.19)

The implications of our study are important for healthcare practitioners and policymakers. The increasing number of tests among healthy children necessitates a re-evaluation of diagnostic practices, as there is a risk of overdiagnosis that could result in unnecessary treatments and healthcare costs. Clinicians should exercise caution in interpreting rising test positivity rates, particularly considering the changing demographics of those being tested. Furthermore, our findings emphasize the importance of implementing strategies that not only monitor respiratory infections but also inform healthcare providers about appropriate testing practices to ensure efficient use of healthcare resources.

The strengths of this study include the fact that the population was based on all Danish children and adolescents, comprehensive data collection, and the use of national registers, which ensured high data completeness and reliability. This approach also facilitated the identification of children with chronic diseases and examined the relationship between pathogenic testing and hospital contacts. The focus on both common respiratory pathogens, such as RSV and influenza, and rare conditions like invasive pneumococcal disease, provides a thorough perspective on the epidemiological changes during and after the COVID-19 pandemic.

Limitations include the lack of the most recent data, which may affect current applicability of our findings. Future studies should investigate the long-term trends in the epidemiological landscape. Additionally, while this study focused on RSV, influenza, and pneumococcus, it did not include other respiratory pathogens that could provide a more complete picture of the epidemiological landscape. Finally, reliance on national registers precluded detailed clinical assessments, potentially hiding variations in infection severity. Regarding the interpretation of the findings, it is also worth noting that immunity debt could be associated with many factors including, but not limited to NPIs.

Future research should investigate the long-term health outcomes of children affected by the changes in infectious disease patterns, explore the mechanisms underlying immunity debt, and develop evidence-based guidelines that balance public health interventions with the prevention of infectious diseases. Continuing to monitor these trends and their implications will help us better prepare for future respiratory disease outbreaks and optimize healthcare resource allocation. It is also worth mentioning that potential new prophylactic strategies against RSV would be expected to impact the future disease epidemiology in Denmark.

In summary, our study comprehensively described the impact of behavioral changes and immunity debt on infectious disease epidemiology. The rising number of tests among healthy children contributes to ongoing discussions regarding overdiagnosis and the implications for healthcare policy.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Not applicable.

Contributors

AJ and LGS designed the study. AJ provided data management and statistical analysis. AJ and LGS drafted the manuscript in collaboration.

Data sharing

The data are stored within the secure environment of Statistics Denmark. These data are only accessible to researchers who are affiliated with an institution and have been granted specific permission by Statistics Denmark. For further details on data access, please visit the Statistics Denmark Research Services webpage (https://www.dst.dk/en/TilSalg/Forskningsservice/Dataadgang).

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jiph.2025.102660.

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