Unique Changes in the Incidence of Acute Chest Syndrome in Children with Sickle-Cell Disease Unravel the Role of Respiratory Pathogens: A Time-Series Analysis

Zein Assad, Zaba Valtuille, Alexis Rybak, Florentia Kaguelidou, Andrea Lazzati, Emmanuelle Varon, Luu-Ly Pham, Lea Lenglart, Albert Faye, Marion Caseris, et al.

Journal Pre-proof

Unique Changes in the Incidence of Acute Chest Syndrome in Children with Sickle-Cell Disease Unravel the Role of Respiratory Pathogens: A Time-Series Analysis

Zein Assad, MD, Zaba Valtuille, MSc, Alexis Rybak, MD, PhD, Florentia Kaguelidou, MD, PhD, Andrea Lazzati, MD, PhD, Emmanuelle Varon, MD, Luu-Ly Pham, MD, Lea Lenglart, MD, Albert Faye, MD, PhD, Marion Caseris, MD, Robert Cohen, MD, Corinne Levy, MD, Astrid Vabret, MD, PhD, Francois Gravey, MD, PhD, Francois Angoulvant, MD, PhD, Berengere Koehl, MD, PhD, Naim Ouldali, MD, PhD

PII: S0012-3692(23)05256-X

DOI: https://doi.org/10.1016/j.chest.2023.07.4219

Reference: CHEST 5826

To appear in: *CHEST*

Received Date: 23 May 2023

Revised Date: 27 July 2023

Accepted Date: 30 July 2023

Please cite this article as: Assad Z, Valtuille Z, Rybak A, Kaguelidou F, Lazzati A, Varon E, Pham LL, Lenglart L, Faye A, Caseris M, Cohen R, Levy C, Vabret A, Gravey F, Angoulvant F, Koehl B, Ouldali N, Unique Changes in the Incidence of Acute Chest Syndrome in Children with Sickle-Cell Disease Unravel the Role of Respiratory Pathogens: A Time-Series Analysis, *CHEST* (2023), doi: https://doi.org/10.1016/j.chest.2023.07.4219.

Word counts: abstract 334.Text 3451.

Title: Unique Changes in the Incidence of Acute Chest Syndrome in Children with Sickle-Cell Disease Unravel the Role of Respiratory Pathogens: A Time-Series Analysis

Short title: Role of Respiratory Pathogens in Pediatric Acute Chest Syndrome

Author list:
Zein Assad, MD[1,2]; Zaba Valtuille, MSc[3,4]; Alexis Rybak, MD, PhD[5,6,7]; Florentia Kaguelidou, MD, PhD[3,4]; Andrea Lazzati, MD, PhD[8]; Emmanuelle Varon, MD[9]; Luu-Ly Pham, MD[2,10]; Léa Lenglart, MD[11]; Albert Faye, MD, PhD[1,6]; Marion Caseris, MD[1]; Robert Cohen, MD[7,12]; Corinne Levy, MD[7,12]; Astrid Vabret, MD, PhD[13,14]; François Gravey, MD, PhD[14]; François Angoulvant, MD, PhD[15]; Bérengère Koehl, MD, PhD[16,17]; and Naïm Ouldali, MD, PhD[1,2,6].

Authors' affiliations:
[1] Department of General Pediatrics, Pediatric Infectious Disease and Internal Medicine, Robert Debré University Hospital, Assistance Publique-Hôpitaux de Paris, Paris, France.

[2] Paris Cité University, INSERM UMR 1137, Infection, Antimicrobials, Modelling, Evolution (IAME), Paris, France.

[3] Paris Cité University, EA7323 Perinatal and Pediatric Pharmacology and Therapeutic Assessment, Paris, France.

[4] Centre d'Investigation Clinique, INSERM CIC1426, Robert Debré University Hospital, Assistance Publique-Hôpitaux de Paris, Paris, France.

[5] Urgences Pédiatriques, Hôpital Trousseau, Assistance Publique-Hôpitaux de Paris, Sorbonne Université, Paris, France.

[6] Paris Cité University, INSERM UMR 1123, ECEVE, Paris, France.

[7] Association Clinique et Thérapeutique Infantile du Val-de-Marne (ACTIV), St Maur-des-Fossés, France.

[8] Department of General Surgery, Centre Hospitalier Intercommunal de Créteil, Créteil, France.

[9] National Reference Center for Pneumococci, Centre de Recherche Clinique et Biologique, Centre Hospitalier Intercommunal de Créteil, Créteil, France.

[10] Department of General Pediatrics, Jean Verdier University Hospital, Assistance Publique-Hôpitaux de Paris, Bondy, France.

[11] Service d'Accueil des Urgences Pédiatriques, Robert Debré University Hospital, Assistance Publique-Hôpitaux de Paris, Paris Cité University, Paris, France.

[12] Centre Hospitalier Intercommunal, Research Centre, Université Paris Est, IMRB-GRC GEMINI, Créteil, France.

[13] Department of Virology, Caen University Hospital, Caen, France.

[14] Univ Caen Normandie, Univ Rouen Normandie, INSERM UMR 1311, DYNAMICURE, Caen, France.

[15] Paris Sorbonne University, Centre de Recherche des Cordeliers, INSERM UMRS 1138, Paris, France.

[16] Department of Child Hematology, Reference Center for Sickle-Cell Disease, Robert Debré University Hospital, Assistance Publique-Hôpitaux de Paris, Paris, France.

[17] Paris Cité University, INSERM UMR S1134, Integrated Biology of Red Blood Cells, Paris, France.

Corresponding author information:
Zein Assad, MD, Department of General Pediatrics, Pediatric Infectious Disease and Internal Medicine, Robert Debré University Hospital, Assistance Publique-Hôpitaux de Paris, F-75019 Paris, France; Email: zein.assad@aphp.fr

Conflicts of Interest Disclosures: NO reports travel grants from GSK, Pfizer, and Sanofi. AR reports travel grants from Pfizer and AstraZeneca and personal fees from MSD outside the submitted work. AV reports personal fees from Sanofi, Moderna, GSK, and MSD. RC reports speaking and lecture fees from Pfizer, Sanofi, GSK, and MSD, funding and travel grants from Pfizer. EV reports grants from Santé Publique France, Pfizer, and MSD. FA reports honoraria from Pfizer, GSK, MSD, and Sanofi outside the submitted work. All other authors have no potential conflicts of interest to disclose.

Acknowledgements:

Guarantor statement: NO and ZA take responsibility for the content of the manuscript, including the integrity of the data and the accuracy of the data analysis.

Author Contributions: ZA, NO, FA, BK, and AF made substantial contributions to the conception or design of the work. ZA and NO drafted the manuscript. ZA, FK, ZV, AL, FG, AV, BK, AF, FA, and NO were involved in the acquisition, analysis, or interpretation of data. All authors provided critical revision of the manuscript for important intellectual content.

Funding/Support: NO was supported by an ESPID (European Society of Pediatric Infectious Diseases) 2021–2023 Fellowship Award and the 2022 ISPPD (International Symposium on Pneumococci and Pneumococcal Diseases) Robert Austrian Research award. This study received support from the ATIP-Avenir partnership between the National Institute for Health and Medical Research (Inserm) and the French National Center for Scientific Research (CNRS) and La Foundation de France as part of the alliance Tous unis contre le virus.

Role of the Funder/Sponsor: The study sponsors had no role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

Other contributions: We are grateful to the medico-university department of pediatrics, Robert Debré Hospital, APHP, Paris, France, for its support.

Prior abstract presentation: European Society for Pediatric Infectious Diseases (ESPID) 2023, 8-12 June 2023, Lisbon, Portugal.

Unique Changes in the Incidence of Acute Chest Syndrome in Children with Sickle-Cell Disease Unravel the Role of Respiratory Pathogens: A Time-Series Analysis

Keywords

Acute chest syndrome, sickle-cell disease, child, COVID-19 pandemic, non-pharmaceutical interventions, respiratory pathogens, pneumococcus, influenza, attributable fraction, time-series analysis.

Abbreviations list

ACS: acute chest syndrome
COVID-19: coronavirus disease 2019
hAdV: human adenovirus
hEV: human enterovirus
hMPV: human metapneumovirus
hRV: human rhinovirus
hPIV: human parainfluenza virus
ICD-10: International Statistical Classification of Diseases, Tenth Revision
NPIs: non-pharmaceutical interventions
PCV13: 13-valent pneumococcal conjugate vaccine
PMSI: Medicalization of Information Systems Program
PPSV23: 23-valent-pneumococcal polysaccharide vaccine
RSV: respiratory syncytial virus
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2
SCD: sickle-cell disease
VOC: vaso-occlusive crisis

Abstract

BACKGROUND. Acute chest syndrome (ACS) is a life-threatening complication of sickle-cell disease (SCD). Although respiratory pathogens are frequently detected in children with ACS, their respective role in triggering the disease is still unclear. We hypothesized that ACS incidence followed the unprecedented population-level changes in respiratory pathogens dynamics following the COVID-19-related non-pharmaceutical interventions (NPIs).

RESEARCH QUESTION. What is the respective role of respiratory pathogens in ACS epidemiology?

STUDY DESIGN AND METHODS. We performed an interrupted time-series analysis of patient records from a national hospital-based surveillance system. All children < 18 years of age with SCD hospitalized for ACS in France between January 2015 and May 2022 were included. The monthly incidence of ACS per 1000 children with SCD over time was analyzed using a quasi-Poisson regression model. The circulation of 12 respiratory pathogens in the general pediatric population over the same period was included in the model to assess the fraction of ACS potentially attributable to each respiratory pathogen.

RESULTS. Among the 55,941 hospitalizations of children with SCD, 2306 episodes of ACS were included (median [IQR] age, 9 [5-13] years). We observed a significant decrease in ACS incidence after NPI implementation in March 2020 (-29.5%; 95% CI, -46.8% to -12.2%; *P* = .001) and a significant increase after lifting of the NPIs in April 2021 (24.4%; 95% CI, 7.2% to 41.6%; *P* = .007). Using population-level incidence of several respiratory pathogens, we found that *Streptococcus pneumoniae* accounted for 30.9% (95% CI, 4.9% to 56.9%; *P* = .02) of ACS incidence over the study period and influenza 6.8% (95% CI, 2.3% to 11.3%; *P* = .004), whereas other respiratory pathogens had only a minor role.

INTERPRETATION. NPIs were associated with significant changes in ACS incidence concomitantly with major changes in the circulation of several respiratory pathogens in the general population. This unique epidemiological situation allowed to unravel the contribution of these respiratory pathogens, in particular *S. pneumoniae* and influenza, to the burden of childhood ACS, highlighting the potential benefit of vaccine prevention in this vulnerable population.

Sickle-cell disease (SCD) is one of the most common hemoglobinopathies worldwide, with approximately 300,000 new cases each year globally.[1,2] More than 5000 children with SCD lived in France in 2019.[3] Acute chest syndrome (ACS) is a potentially life-threatening complication of SCD, affecting more than half of patients with SCD in the first decade of life. ACS requires mechanical ventilation in 10% of cases and leads to death in 3% of children. Preventing ACS is crucial to reducing the mortality of individuals with SCD.[4,5]

Based on microbiological studies, respiratory pathogens are suspected of playing a role in pediatric ACS.[5] Indeed, the identification of respiratory viruses has been frequently reported for children with ACS, with a predominance of human rhinovirus (hRV), respiratory syncytial virus (RSV), and human adenovirus (hAdV).[6,7] However, as some of these pathogens are frequently found in heathy children,[8] their detection in children with ACS does not imply their involvement in the disease. Similarly, *Streptococcus pneumoniae*, which is frequently responsible for respiratory infection in children with SCD,[9] is frequently carried in healthy young children.[10] As this pathogen is rarely isolated in blood culture,[11] it is highly challenging to distinguish carriage from involvement in ACS based on microbiological studies.[5] Thus, the respective role of these respiratory pathogens in triggering ACS is still unclear.

Since March 2020, unprecedented non-pharmaceutical interventions (NPIs) have been implemented to contain the coronavirus disease 2019 (COVID-19) pandemic (i.e., national lockdown followed by various mitigation strategies as night curfew, school closures, bans on public events, social distancing, and wearing of face masks). These NPIs have strongly affected the epidemiology of respiratory pathogens. Indeed, an unprecedented decrease in respiratory viruses and pneumococcal infections was observed in 2020.[10,12] Following the progressive lifting of NPIs in 2021, outbreaks of several respiratory viruses (in particular RSV, influenza, hRV, and hAdV)[13] and pneumococcal infections[14,15,16] were observed, with different timing

and magnitude. These unique changes in respiratory pathogen dynamics offer the opportunity to unravel their respective role in ACS epidemiology.

We aimed to assess the temporal association of the national ACS incidence with the implementation and lifting of NPIs, and use the population-level changes in several respiratory pathogens circulation to analyze their respective role of in pediatric ACS epidemiology.

Methods

Study design

We conducted a population-based interrupted time-series analysis of patient data from a hospital-based French national surveillance system over seven years (January 2015 to May 2022). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were followed to report this study.

Study data and settings

The data were obtained from the French Medicalization of Information Systems Program (PMSI), which is an exhaustive national database that contains all hospital discharge records from public and private hospitals in France. Diagnoses related to the hospitalizations were recorded according to the International Statistical Classification of Diseases, Tenth Revision (ICD-10). Details of the PMSI coding system have been published previously.[3]

Incidence of Acute Chest Syndrome in Children with Sickle-Cell Disease

We included all children aged less than 18 years with SCD hospitalized for ACS between January 2015 and May 2022. As previously published,[3] based on the national Technical Agency for Hospital Information (ATIH) guidelines,[17] ACS was defined as the combination of the ICD-10 discharge diagnosis code for SCD with crisis (D570 or D572) and one of several ICD-10 codes for respiratory impairment (J960, J189, I269). All children aged younger than 18 years with SCD hospitalized for pneumonia, vaso-occlusive crisis (VOC), or acute pyelonephritis were also recorded. HbS/ß0-thalassemia and HbS/ß+-thalassemia were not included. The details of ICD-10 diagnosis codes are presented in eTable 1 in the Supplement. We calculated the incidence per 1000 children with SCD using the monthly number of ACS episodes as the numerator and

the number of children with SCD under 18 years of age living in France as the denominator for each year of the study (eFigure 1). This information was provided by the National Health Insurance Scheme database.[18]

Incidence of Respiratory Pathogen Infections in the General Population

We correlated the incidence of ACS in children with SCD to the population-level circulation of selected respiratory pathogens. To assess respiratory pathogen dynamics in the general population, we recorded all children aged younger than 18 years hospitalized for RSV, influenza, human parainfluenza virus (hPIV), human metapneumovirus (hMPV), hAdV, hRV, human enterovirus (hEV), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), *S. pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae* infection based on the ICD-10 codes. The details of the ICD-10 diagnosis codes are presented in eTable 2. Multiplex polymerase chain reaction (PCR) was used to detect respiratory viruses, *M. pneumonia* and *C. pneumoniae*; and blood, cerebrospinal fluid, and pleural fluid cultures or PCR were used for the diagnosis of *S. pneumoniae* and *H. influenzae* infections. We used the age-specific French population demographics obtained from the National Institute for Statistics and Economic Studies[19] as the denominator to calculate the monthly incidence of each respiratory pathogen infection per 100,000 children (eFigure 2).

Non-Pharmaceutical COVID-19-related Interventions

From early March 2020, population-level NPIs to reduce SARS-CoV-2 transmission were introduced in many countries affected by COVID-19. In France, a national lockdown was officially started on March 17th, 2020, and gradually followed by various mitigation strategies. Given the progress against the COVID-19 pandemic, the implementation of immunization

programs, and the introduction of mandatory COVID-19 certification,[20] French authorities partially lifted the restrictive measures since April, 2021. Details on the measures and their timing were provided by the European Centre for Disease Prevention and Control (eTable 3).[21]

Study periods

We organized the study into three periods: (1) the "pre COVID-19" period, from January 2015 to March 2020, (2) the "NPI" period, from April 2020 to March 2021, during which stringent measures were implemented, and (3) the "NPI lifting" period, from April 2021 to May 2022, during which control measures were partially lifted, as reflected by the decrease in the national COVID-19 stringency index.[22,23]

Outcome Measures

The main outcomes were the monthly incidence of ACS per 1000 children with SCD in France and the estimated fraction of ACS attributable to a range of respiratory pathogens. Secondary outcomes were the monthly incidence of ACS among different age groups (0 to 5 years, 6 to 10 years, 11 to 14 years, 15 to 17 years) and the monthly incidence of pneumonia and VOC per 1000 children with SCD.

As a control outcome, we analyzed the monthly incidence of acute pyelonephritis per 1000 children with SCD over the same period to assess the risk of bias due to potential hidden cointerventions, mainly a potential change in hospital admission capacities during the COVID-19 pandemic.[24] To assess potential changes in nationwide respiratory virus testing practices during the study period, hospitalizations for "undocumented pneumonia" (pneumonia without detection of respiratory pathogen, eTable 2) in the general population were also

recorded to calculate the proportion of undocumented pneumonia among all pneumonia cases over time.

Statistical analysis

First, we built a quasi-Poisson regression model to estimate the changes in ACS incidence following NPI implementation in March 2020 and the lifting of NPIs in April 2021. This model accounted for temporal trends before and after these interventions and for seasonality by using harmonic terms (sines and cosines with 6-month and 12-month periods). We hypothesized that the introduction and discontinuation of NPIs would have an immediate impact on ACS incidence.[25] We, therefore, included dummy variables in the model to estimate the immediate change after the interventions.[26]. The time unit was one month.[27]

Then, we estimated the fraction of ACS incidence potentially attributable to a range of respiratory pathogens. Thus, we modelled the ACS incidence using a seasonally adjusted quasi-Poisson regression model that included all respiratory pathogens as explanatory variables (RSV, influenza, hPIV, hMPV, hAdV, hRV, hEV, SARS-CoV-2, *S. pneumoniae*, *H. influenzae*, *M. pneumoniae*, and *C. pneumoniae*). We estimated the expected incidence of ACS if each respiratory pathogen was not present during the study period by using the same equation and set each respiratory pathogen term equal to zero. The estimated fraction of ACS potentially attributable to each pathogen was calculated as the percentage change between the ACS incidence fitted by the model and the predicted ACS incidence with each pathogen set to zero for each time point of the study period.[10,28]

We performed seven sensitivity analyses: (1) a quasi-Poisson regression model involving a dummy variable estimating a progressive lifting of NPIs starting in April 2021 (2) a quasi-Poisson regression model with ACS defined as the combination of both ACS and

pneumonia episodes, (3) a quasi-Poisson regression model with the ICD-10 code for pneumonia (J189) excluded from the ACS definition to explore the potential overlap between ACS and pneumonia,[3,29,30] (4) a quasi-Poisson regression model with the ICD-10 code for pulmonary embolism (I269) excluded from the ACS definition, (5) a quasi-Poisson regression adjusted for the monthly incidence of VOC over the same period to assess the potential fraction of the change in ACS incidence associated with VOC, (6) a quasi-Poisson regression model including harmonic terms with 3-, 6-, and 12-month periods to explore potential non-yearly seasonal patterns, and (7) a quasi-Poisson regression model excluding highly correlated covariates that could adversely affect multiple regression results. We identified such multicollinearity using a correlation matrix and the generalized variance inflation factor (VIF).[31,32]

All statistical tests were two-sided, with $P < .05$ considered to be statistically significant. The validity of the models was assessed by visual inspection of correlograms and analysis of the residuals.[24] The data were extracted from the PMSI database using SAS version 9.4 (SAS Institute, Cary, North Carolina) and statistical analyses performed using R software version 4.2.1 (R Foundation for Statistical Computing).

Ethics

Access to the database was requested from and approved by the National Commission on Information and Liberty. As it is part of an ongoing continuous mission of public health and used anonymous aggregated data for public health purposes, this study did not require ethics committee approval or written informed consent based on the 2021 National Data Protection Act.[33]

Results

Characteristics of Hospitalized Children with Sickle-Cell Disease

Between January 2015 and May 2022, 55,941 hospitalizations of children with SCD were included (median [IQR] age, 9 [4-13] years; 28,191 [50.4%] boys). ACS accounted for 2306 (4.1%) cases (1690 in pre COVID-19 period, 237 during NPIs, and 379 during NPI lifting period), pneumonia 730 (1.3%), acute pyelonephritis 651 (1.2%), and VOC 52,254 (93.4%) (**Table 1**).

Changes in ACS Incidence Following the Implementation and Lifting of NPIs

We observed a significant decrease in ACS incidence after NPI implementation in March 2020 (immediate change, -29.5%; 95% CI, -46.8% to -12.2%; *P* = .001), followed by a significant increase after lifting of the NPIs in April 2021 (immediate change, 24.4%; 95% CI, 7.2% to 41.6%; *P* = .007; **Figure 1**). These changes were similar for all age groups. In addition, implementation and lifting of NPIs were associated with significant changes in the incidence of VOC **(Figure 2** and **Table 2)**. The sensitivity analysis hypothesizing a progressive lifting of NPIs showed similar results (eTable 4**).** Correlograms and residuals analysis indicated satisfactory quality of the final model (eFigure 3).

Estimated Fraction of ACS Attributable to Respiratory Pathogens

The evolution of the incidence of respiratory pathogen infections in the general population between January 2015 and May 2022, and the demographic characteristics of patients are presented in eFigure 4 and eTable 5. After a large decrease following NPIs implementation, there was a large rebound of these pathogens following the lifting of NPIs, with different timing and a different pattern of increase. The multivariate quasi-Poisson

regression model including the 12 respiratory pathogens as explanatory variables showed the fraction of ACS potentially attributable to *S. pneumoniae* to be 30.9% (95% CI, 4.9% to 56.9%; *P* = .02) and that to influenza 6.8% (95% CI, 2.3% to 11.3%; *P* = .004), whereas that to the other respiratory pathogens, including *M. pneumoniae*, was not significant (**Table 3**). The sensitivity analyses, in particular the model without hRV and *H. influenzae* to minimalize multicollinearity, and the model with combined ACS and pneumonia to explore the potential overlap between ACS and pneumonia, showed similar results. Of note, *S. pneumoniae* was correlated with RSV and influenza, without affecting the reliability of the regression model (eTables 6-8, eFigure 5). The quality assessment of the models was satisfactory (eFigures 6-7).

Control outcome

The incidence of acute pyelonephritis per 1000 children with SCD did not significantly change after NPI implementation or after the lifting of NPIs (**Table 2,** eFigure 8), reinforcing the link between these interventions and ACS incidence. In addition, the proportion of undocumented pneumonia among all hospitalized pneumonia cases in the general population remained stable during the study period, limiting the risk of bias due to changes in testing practices since the COVID-19 pandemic (eFigure 9).

Discussion

This study is the first to show a sharp decrease in ACS incidence after NPI implementation in March 2020 and a subsequent significant rebound after the lifting of NPIs in April 2021. These large changes were temporally associated with unprecedented changes in respiratory pathogen dynamics, with a potentially attributable fraction of 30% and 7% of pediatric ACS for *S. pneumoniae* and influenza, respectively.

Before the COVID-19 pandemic, epidemiological studies were unable to identify the differential role of respiratory pathogens in ACS because of the considerable temporal overlap between them. Therefore, the microorganisms found in individuals hospitalized for ACS were solely assessed in microbiological studies. In a prospective case-control analysis of children with SCD, Ploton et al. frequently detected respiratory viruses in children with ACS, with a predominance of hRV, followed by RSV and hAdV.[6] In addition, Vichinsky et al. suggested that atypical bacteria prevail in cases of ACS due to infection in a cohort study using microbiological samples of children presenting with ACS, whereas *S. pneumoniae* was found in only 4.5% of cases.[5] However, the main limitation of microbiological methods is their relative inability to accurately differentiate respiratory carriage from infection.[34,35,36] After their quasi-disappearance following the implementation of the COVID-19-related NPIs, respiratory pathogens reemerged with different timing and at a different magnitude following discontinuation of the NPIs in April 2021, thus making it possible to quantify their involvement in ACS. For example, we observed an RSV outbreak that was delayed by three months in 2020-2021, with a peak that was reduced by half, whereas an unusual surge occurred in December 2021. Concerning influenza, no outbreak was reported in 2021, whereas a large peak appeared in February 2022. Finally, pneumococcal infections have gradually increased since April 2021, without reaching the pre COVID-19 incidence. Thus, taking advantage of this

unique epidemiological scenario of the sequential re-emergence of pathogens after the lifting of NPIs and using the strength of a population-based methodology, we estimated that 30% of ACS incidence was independently associated with *S. pneumoniae* and almost 7% with influenza.

This study reinforces the important role of *S. pneumoniae* and influenza, namely a pneumococcal disease-associated virus,[37] in driving ACS epidemiology. Indeed, our results are in line with a recent time-series analysis that showed a 42% decrease in ACS incidence following implementation of the 13-valent pneumococcal conjugate vaccine (PCV13) in France, thus suggesting important pneumococcal involvement in childhood ACS.[3] Our results are also consistent with those of population-based studies, which suggested that certain viruses capable of increasing the virulence of *S. pneumoniae*, such as RSV and influenza, are epidemiologically associated with pneumococcal disease in young children.[10,28,38] This provides guidance for the prevention and management of ACS, suggesting that optimizing PCV and influenza vaccine coverage in children with SCD may be beneficial in this highly vulnerable population. Of note, ACS was not temporally associated with *M. pneumoniae* or *C. pneumoniae*. However, this methodological approach may be less sensitive to explore their role in ACS, as these pathogens do not have a strong seasonal pattern. Thus, further studies are needed to assess the role of atypical organisms in pediatric ACS to guide recommendations for antimicrobial therapy, in particular the systematic use of macrolides.[39,40]

The observed high pneumococcal involvement in ACS contrasts with the low proportion of pneumococcal-related ACS suggested by microbiological studies.[5] Several points merit discussion. First, various limitations in terms of the microbiological methods could explain their low capacity to accurately estimate the role of *S. pneumoniae* in ACS. Indeed, as in community-acquired pneumonia, blood cultures, pleural puncture, and pneumococcal

antigen detection tests in urine are often unsuccessful and microbiological documentation is rarely obtained.[11,34] Therefore, the population-based approach appears to represent a reliable alternative method to estimate the potentially attributable fraction of *S. pneumoniae* in ACS. Second, PCV13 implementation in France was associated with a 42% decrease in the incidence of pediatric ACS incidence between 2010 and 2019.[3] The role of *S. pneumoniae* in ACS in the remaining 30% of cases from 2015 onwards, despite high PCV13 coverage in children,[41] can be explained by serotype replacement reported in the nasopharyngeal carriage and in invasive pneumococcal disease in the general population[42,43] and among children with SCD.[44] Third, the efficacy of the 23-valent-pneumococcal polysaccharide vaccine (PPSV23) has been demonstrated for invasive pneumococcal disease (IPD), but no effect on non-IPD, such as pulmonary involvement, has been found.[45] This could explain the remaining pneumococcal involvement in ACS, despite high PPSV23 coverage in children with SCD, and highlights the importance of conjugate-vaccines in preventing ACS. Thus, the preferential use of the next-generation PCVs[46,47] currently being evaluated for approval in children with SCD may contribute to further reducing the burden of ACS in children.

Limitations

Our study had several limitations. First, in this study, we correlated the incidence of ACS in children with SCD to the population-level circulation of several respiratory pathogens. Thus, as in any observational study, a definitive causal relationship between respiratory pathogen epidemiology and ACS incidence could not be established. However, the strong decline, followed by a rapid increase, in respiratory pathogen circulation was concomitant with the decline and rebound in ACS incidence, strengthening this temporal association.

Second, our analysis may have been affected by simultaneous cointerventions targeting the same outcome. Thus, we cannot exclude changes in testing practices since the COVID-19 pandemic.[48] However, the proportion of undocumented pneumonia cases among all hospitalized children with pneumonia in the general population remained stable over the study period, limiting this risk of bias. Similarly, we cannot exclude a decreased healthcare utilization in patients with SCD during the NPI period, which could explain the decrease in hospitalized ACS and VOC. However, the incidence of a control outcome, acute pyelonephritis in children with SCD, did not significantly change over the study period. Finally, the indication of hydroxyurea and the PCV13 vaccine uptake were unchanged during the study period, limiting the risk of bias related to these potential cofounders.

Third, we used a hospital-based surveillance system to assess the circulation of respiratory pathogens in children over time, which may not be exhaustive. However, it has previously been shown that hospital admission rates for respiratory viral infections in children were correlated with data from ambulatory observatories and laboratory-based surveillance networks in France before and during the COVID-19 pandemic.[10,49]

Fourth, clinical overlap between ACS and pneumonia in children with SCD can occur.[3] To account for this potential misclassification, we conducted sensitivity analyses combining ACS and pneumonia and excluding the ICD-10 code for pneumonia (J189) from the ACS definition, leading to similar results.

Fifth, a substantial proportion of ACS cases remains unexplained in this analysis. Other factors not included in our model as explanatory variables, such as environmental parameters, may have also played a role in ACS epidemiology, especially other factors that could affect the incidence of VOC (i.e., less exposure to cold, stopping physical activity, increasing rest). Further studies are therefore needed to assess other potential causes of ACS. Moreover, the

respective share of vaso-occlusion and infection in the onset of ACS is difficult to determine, in particular, as these phenomena are closely interrelated.[5] We cannot exclude that the decrease in ACS incidence could be partially related to the decrease in VOC frequency, which was also affected by the changes in respiratory pathogen dynamics. However, the sensitivity analysis adjusted for VOC gave similar results.

Finally, pneumococcal infections can be induced by respiratory viruses, namely RSV infection.[28] This interaction could have biased the association between RSV and ACS incidence in our study, thus masking RSV involvement in ACS. Further studies are needed to explore the specific role of RSV in triggering ACS.

Interpretation

During the COVID-19 pandemic, the incidence of ACS significantly decreased after NPI implementation in March 2020 and rebounded after the lifting of NPIs in April 2021, concomitantly with unprecedented changes in respiratory pathogen dynamics. We took advantage of this unique epidemiological scenario to untangle the contribution of numerous respiratory pathogens, highlighting the key role of *S. pneumoniae* and influenza in childhood ACS. These results could guide further public health interventions targeting these pathogens, such as next generation PCVs and influenza vaccines, to further reduce the burden of ACS in children with SCD.

Acknowledgements:

Author guarantor statement: NO and ZA take responsibility for the content of the manuscript, including the integrity of the data and the accuracy of the data analysis.

Author Contributions: ZA, NO, FA, BK, and AF made substantial contributions to the conception or design of the work. ZA and NO drafted the manuscript. ZA, FK, ZV, AL, FG, AV, BK, AF, FA, and NO were involved in the acquisition, analysis, or interpretation of data. All authors provided critical revision of the manuscript for important intellectual content.

Funding/Support: NO was supported by an ESPID (European Society of Pediatric Infectious Diseases) 2021–2023 Fellowship Award and the 2022 ISPPD (International Symposium on Pneumococci and Pneumococcal Diseases) Robert Austrian Research award. This study received support from the 2023 ATIP-Avenir partnership between the National Institute for Health and Medical Research (Inserm) and the French National Center for Scientific Research (CNRS), and La Foundation de France as part of the alliance Tous unis contre le virus.

Role of the Funder/Sponsor: The study sponsors had no role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

Conflicts of Interest Disclosures: NO reports travel grants from GSK, Pfizer, and Sanofi. AR reports travel grants from Pfizer and AstraZeneca and personal fees from MSD outside the submitted work. AV reports personal fees from Sanofi, Moderna, GSK, and MSD. AR reports travel grants from Pfizer and personal fees from MSD. EV reports grants from Santé Publique France, Pfizer, and MSD. FA reports honoraria from Pfizer, GSK, MSD, and Sanofi outside the submitted work. All other authors have no potential conflicts of interest to disclose.

Other contributions: We are grateful to the medico-university department of pediatrics, Robert Debré Hospital, APHP, Paris, France, for its support.

Prior abstract presentation: European Society for Pediatric Infectious Diseases (ESPID) 2023, 8-12 June 2023, Lisbon, Portugal.

Take Home Points

STUDY QUESTION. What are the respective contributions of the main respiratory pathogens in pediatric acute chest syndrome (ACS) epidemiology?

RESULTS. This time-series analysis of a prospective national surveillance from 2015 to 2022 shows that *Streptococcus pneumoniae* accounted for 30.9% of ACS incidence, and influenza 6.8%, while other respiratory pathogens had a minor role.

INTERPRETATION. We showed the high contribution of *S. pneumoniae* and influenza to the burden of childhood ACS, highlighting the potential benefit of vaccine prevention in this vulnerable population.

References

1. Piel FB, Hay SI, Gupta S, Weatherall DJ, Williams TN. Global burden of sickle cell anaemia in children under five, 2010-2050: modelling based on demographics, excess mortality, and interventions. PLoS Med. 2013;10(7):e1001484.
2. Brousse V, Allaf B, Benkerrou M. [Newborn screening for sickle cell disease in France]. Med Sci MS. 2021 May;37(5):482–90.
3. Assad Z, Michel M, Valtuille Z, Lazzati A, Boizeau P, Madhi F, et al. Incidence of Acute Chest Syndrome in Children With Sickle Cell Disease Following Implementation of the 13-Valent Pneumococcal Conjugate Vaccine in France. JAMA Netw Open. 2022 Aug 2;5(8):e2225141.
4. Jain S, Bakshi N, Krishnamurti L. Acute Chest Syndrome in Children with Sickle Cell Disease. Pediatr Allergy Immunol Pulmonol. 2017 Dec;30(4):191–201.
5. Vichinsky EP, Neumayr LD, Earles AN, Williams R, Lennette ET, Dean D, et al. Causes and outcomes of the acute chest syndrome in sickle cell disease. National Acute Chest Syndrome Study Group. N Engl J Med. 2000 Jun 22;342(25):1855–65.
6. Ploton MC, Sommet J, Koehl B, Gaschignard J, Holvoet L, Mariani-Kurkdjian P, et al. Respiratory pathogens and acute chest syndrome in children with sickle cell disease. Arch Dis Child. 2020 Sep;105(9):891–5.
7. Srinivasan A, Wang WC, Gaur A, Smith T, Gu Z, Kang G, et al. Prospective evaluation for respiratory pathogens in children with sickle cell disease and acute respiratory illness. Pediatr Blood Cancer. 2014 Mar;61(3):507–11.
8. Ben-Shimol S, Ramilo O, Leber AL, van der Beek BA, Everhart K, Mertz S, et al. A Hypothesis-Generating Prospective Longitudinal Study to Assess the Relative Contribution of Common Respiratory Viruses to Severe Lower Respiratory Infections in Young Children. Pediatr Infect Dis J. 2023 Mar 8;
9. Gonzales J, Chakraborty T, Romero M, Mraheil MA, Kutlar A, Pace B, et al. Streptococcus pneumoniae and Its Virulence Factors H2O2 and Pneumolysin Are Potent Mediators of the Acute Chest Syndrome in Sickle Cell Disease. Toxins. 2021 Feb 17;13(2).
10. Rybak A, Levy C, Angoulvant F, Auvrignon A, Gembara P, Danis K, et al. Association of Nonpharmaceutical Interventions During the COVID-19 Pandemic With Invasive Pneumococcal Disease, Pneumococcal Carriage, and Respiratory Viral Infections Among Children in France. JAMA Netw Open. 2022 Jun 1;5(6):e2218959.
11. Levy C, Biscardi S, Dommergues MA, Dubos F, Hees L, Levieux K, et al. Impact of PCV13 on community-acquired pneumonia by C-reactive protein and procalcitonin levels in children. Vaccine. 2017 Sep 5;35(37):5058–64.
12. Kadambari S, Goldacre R, Morris E, Goldacre MJ, Pollard AJ. Indirect effects of the covid-19 pandemic on childhood infection in England: population based observational study. BMJ. 2022 Jan 12;376:e067519.
13. Maison N, Peck A, Illi S, Meyer-Buehn M, von Mutius E, Hübner J, et al. The rising of old foes: impact of lockdown periods on “non-SARS-CoV-2” viral respiratory and gastrointestinal infections. Infection. 2022 Apr;50(2):519–24.
14. Perniciaro S, van der Linden M, Weinberger DM. Reemergence of Invasive Pneumococcal Disease in Germany During the Spring and Summer of 2021. Clin Infect Dis Off Publ Infect Dis Soc Am. 2022 Sep 30;75(7):1149–53.
15. Bertran M, Amin-Chowdhury Z, Sheppard CL, Eletu S, Zamarreño DV, Ramsay ME, et al. Increased Incidence of Invasive Pneumococcal Disease among Children after COVID-19

Pandemic, England. Emerg Infect Dis. 2022 Aug;28(8):1669–72.
16. Ouldali N, Deceuninck G, Lefebvre B, Gilca R, Quach C, Brousseau N, et al. Increase of invasive pneumococcal disease in children temporally associated with RSV outbreak in Quebec: a time-series analysis. Lancet Reg Health Am. 2023 Mar;19:100448.
17. Agence Technique de l'Information sur l'Hospitalisation. ATIH website. Accessed April 1, 2023. https://www.atih.sante.fr
18. Haute Autorité de Santé HAS. ALD n° 10 - Syndromes drépanocytaires majeurs de l'enfant et de l'adolescent. Haute Autorité de Santé website. Published April 2, 2010. Accessed April 1, 2023. https://www.has-sante.fr/jcms/c_938890/fr/ald-n-10-syndromes-drepanocytaires-majeurs-de-l-enfant-et-de-l-adolescent
19. Institut National de la Statistique et des Etudes Economiques. INSEE website. Accessed December 15, 2022. https://www.insee.fr/fr/statistiques/series/103088458
20. Mills MC, Rüttenauer T. The effect of mandatory COVID-19 certificates on vaccine uptake: synthetic-control modelling of six countries. Lancet Public Health. 2022 Jan;7(1):e15–22.
21. European Centre for Disease Prevention and Control. Data on country response measures to COVID-19. ECDC Europe website. Accessed April 1, 2023. https://www.ecdc.europa.eu/en/publications-data/download-data-response-measures-covid-19
22. Hale T, Angrist N, Goldszmidt R, Kira B, Petherick A, Phillips T, et al. A global panel database of pandemic policies (Oxford COVID-19 Government Response Tracker). Nat Hum Behav. 2021 Apr;5(4):529–38.
23. Covid-19 Stringency Index. Our World in Data website. Accessed April 1, 2023. https://ourworldindata.org/covid-stringency-index
24. Bernal JL, Cummins S, Gasparrini A. Interrupted time series regression for the evaluation of public health interventions: a tutorial. Int J Epidemiol. 2017 Feb 1;46(1):348–55.
25. Angoulvant F, Ouldali N, Yang DD, Filser M, Gajdos V, Rybak A, et al. Coronavirus Disease 2019 Pandemic: Impact Caused by School Closure and National Lockdown on Pediatric Visits and Admissions for Viral and Nonviral Infections-a Time Series Analysis. Clin Infect Dis Off Publ Infect Dis Soc Am. 2021 Jan 27;72(2):319–22.
26. Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. J Clin Pharm Ther. 2002 Aug;27(4):299–309.
27. Hawley S, Ali MS, Berencsi K, Judge A, Prieto-Alhambra D. Sample size and power considerations for ordinary least squares interrupted time series analysis: a simulation study. Clin Epidemiol. 2019;11:197–205.
28. Weinberger DM, Klugman KP, Steiner CA, Simonsen L, Viboud C. Association between respiratory syncytial virus activity and pneumococcal disease in infants: a time series analysis of US hospitalization data. PLoS Med. 2015 Jan;12(1):e1001776.
29. Bundy DG, Richardson TE, Hall M, Raphael JL, Brousseau DC, Arnold SD, et al. Association of Guideline-Adherent Antibiotic Treatment With Readmission of Children With Sickle Cell Disease Hospitalized With Acute Chest Syndrome. JAMA Pediatr. 2017 Nov 1;171(11):1090–9.
30. Badaki-Makun O, Casella JF, Tackett S, Tao X, Chamberlain JM. Association of Antibiotic Choice With Hospital Length of Stay and Risk Factors for Readmission in Patients With Sickle Cell Disease and Acute Chest Syndrome: An Observational Cohort Study. Ann Emerg Med. 2020 Sep;76(3S):S37–45.

31. Fox J, Monette G. Generalized Collinearity Diagnostics. J Am Stat Assoc. 1992 Mar;87(417):178–83.
32. Lenglart L, Ouldali N, Honeyford K, Bognar Z, Bressan S, Buonsenso D, et al. Respective roles of non-pharmaceutical interventions in bronchiolitis outbreaks: an interrupted time-series analysis based on a multinational surveillance system. Eur Respir J. 2023 Feb;61(2):2201172.
33. Commission nationale de l'informatique et des libertés. 2021 Data Protection Act. Published March 14, 2021. CNIL website. Accessed December 1, 2022. https://www.cnil.fr/fr/la-loi-informatique-et-libertes
34. Murdoch DR, O'Brien KL, Driscoll AJ, Karron RA, Bhat N, Pneumonia Methods Working Group, et al. Laboratory methods for determining pneumonia etiology in children. Clin Infect Dis Off Publ Infect Dis Soc Am. 2012 Apr;54 Suppl 2:S146-152.
35. Pneumonia Etiology Research for Child Health (PERCH) Study Group. Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study. Lancet Lond Engl. 2019 Aug 31;394(10200):757–79.
36. Spuesens EBM, Fraaij PLA, Visser EG, Hoogenboezem T, Hop WCJ, van Adrichem LNA, et al. Carriage of Mycoplasma pneumoniae in the upper respiratory tract of symptomatic and asymptomatic children: an observational study. PLoS Med. 2013;10(5):e1001444.
37. Dagan R, van der Beek BA, Ben-Shimol S, Greenberg D, Shemer-Avni Y, Weinberger DM, et al. The COVID-19 pandemic as an opportunity for unravelling the causative association between respiratory viruses and pneumococcus-associated disease in young children: a prospective study. EBioMedicine. 2023 Apr;90:104493.
38. Hernández S, Muñoz-Almagro C, Ciruela P, Soldevila N, Izquierdo C, Codina MG, et al. Invasive Pneumococcal Disease and Influenza Activity in a Pediatric Population: Impact of PCV13 Vaccination in Pandemic and Nonpandemic Influenza Periods. J Clin Microbiol. 2019 Aug;57(8):e00363-19.
39. Howard J, Hart N, Roberts-Harewood M, Cummins M, Awogbade M, Davis B, et al. Guideline on the management of acute chest syndrome in sickle cell disease. Br J Haematol. 2015 May;169(4):492–505.
40. Hemenway CS. Re-examining a strong recommendation based on low-quality evidence in acute chest syndrome. Pediatr Blood Cancer. 2023 Mar 1;e30266.
41. Cohen R, Biscardi S, Levy C. The multifaceted impact of pneumococcal conjugate vaccine implementation in children in France between 2001 to 2014. Hum Vaccines Immunother. 2016;12(2):277–84.
42. Ladhani SN, Collins S, Djennad A, Sheppard CL, Borrow R, Fry NK, et al. Rapid increase in non-vaccine serotypes causing invasive pneumococcal disease in England and Wales, 2000-17: a prospective national observational cohort study. Lancet Infect Dis. 2018 Apr;18(4):441–51.
43. Ouldali N, Varon E, Levy C, Angoulvant F, Georges S, Ploy MC, et al. Invasive pneumococcal disease incidence in children and adults in France during the pneumococcal conjugate vaccine era: an interrupted time-series analysis of data from a 17-year national prospective surveillance study. Lancet Infect Dis. 2021 Jan;21(1):137–47.
44. Oligbu G, Collins S, Sheppard C, Fry N, Dick M, Streetly A, et al. Risk of Invasive Pneumococcal Disease in Children with Sickle Cell Disease in England: A National Observational Cohort Study, 2010-2015. Arch Dis Child. 2018 Jul;103(7):643–7.
45. Jackson LA, Janoff EN. Pneumococcal vaccination of elderly adults: new paradigms for

protection. Clin Infect Dis Off Publ Infect Dis Soc Am. 2008 Nov 15;47(10):1328–38.
46. Greenberg D, Hoover PA, Vesikari T, Peltier C, Hurley DC, McFetridge RD, et al. Safety and immunogenicity of 15-valent pneumococcal conjugate vaccine (PCV15) in healthy infants. Vaccine. 2018 Oct 29;36(45):6883–91.
47. Senders S, Klein NP, Lamberth E, Thompson A, Drozd J, Trammel J, et al. Safety and Immunogenicity of a 20-valent Pneumococcal Conjugate Vaccine in Healthy Infants in the United States. Pediatr Infect Dis J. 2021 Oct 1;40(10):944–51.
48. Huang HS, Tsai CL, Chang J, Hsu TC, Lin S, Lee CC. Multiplex PCR system for the rapid diagnosis of respiratory virus infection: systematic review and meta-analysis. Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis. 2018 Oct;24(10):1055–63.
49. Santé Publique France. SPF website. Accessed April 1, 2023. https://www.santepubliquefrance.fr

Table 1. Baseline Characteristics of Hospitalizations of Children with Sickle-Cell Disease by Discharge Diagnosis, January 2015 to May 2022.

	Children, No. (%)				
Characteristics	**ACS**	**Pneumonia**	**Acute pyelonephritis**	**VOC**	**Total cases**
No. of cases	2306 (4.1)	730 (1.3)	651 (1.2)	52 254 (93.4)	55 941
Age, median (IQR), years	9 (5-13)	4 (2-7)	1 (0.9-7)	9 (4-13)	9 (4-13)
Sex					
Boys	1289 (55.9)	387 (53.0)	305 (46.9)	26 210 (50.2)	28 191 (50.4)
Girls	1017 (44.1)	343 (47.0)	346 (53.1)	26 044 (49.8)	27 750 (49.6)
Duration of stay, median (IQR), days	7 (4-10)	4 (3-7)	4 (3-6)	3 (1-5)	3 (1-5)
Recurrence[a]	47 (2.0)	14 (1.9)	21 (3.2)	1930 (3.7)	2012 (3.6)
Hospital death	10 (0.4)	1 (0.1)	0	43 (0.1)	54 (0.1)

The median age and duration of stay are presented as medians (IQR), and categorical data (number of cases, sex, recurrence, hospital death) as numbers (%).

[a] defined by >1 hospitalization in a child. Recurrent ACS episodes occurred in 29 (1.7%), 2 (0.8%), and 16 (4.2%) children during the pre COVID-19, the NPI, and the NPI lifting periods, respectively.

Abbreviations: ACS, acute chest syndrome; VOC, vaso-occlusive crisis.

Figure 1. Association of NPI Implementation and Lifting with the Monthly Incidence of ACS per 1000 Children with SCD

The black line shows the observed data. The blue line shows the model estimates based on observed data using the quasi-Poisson regression model. The red and orange dotted lines show the expected values without NPI implementation and NPI lifting, respectively, using the same quasi-Poisson model. The dotted vertical lines indicate the NPI implementation in March 2020 and the lifting of NPIs in April 2021.
Abbreviations: NPIs, non-pharmaceutical interventions; ACS, acute chest syndrome; SCD, sickle-cell disease.

Figure 2. Association of NPI Implementation and Lifting with the Monthly Incidence of
a) pneumonia per 1000 Children with SCD
b) VOC per 1000 Children with SCD

The black line shows the observed data. The blue line shows the model estimates based on observed data using the quasi-Poisson regression model. The red and orange dotted lines show the expected values without NPI implementation and NPI lifting, respectively, using the same quasi-Poisson model. The dotted vertical lines indicate the NPI implementation in March 2020 and the NPI lifting in April 2021.
Abbreviations: NPIs, non-pharmaceutical interventions; VOC, vaso-occlusive crisis; SCD, sickle-cell disease.

Table 2. Association of the Implementation and Lifting of NPIs with the Monthly Incidence of ACS per 1000 Children with Sickle-Cell Disease

Outcome	NPI implementation[a]		NPI lifting[b]	
	Immediate change, % (95% CI)	*P* value for immediate change	Immediate change, % (95% CI)	*P* value for immediate change
Monthly incidence of ACS per 1000 children with SCD[c,d]	-29.5 (-46.8 to -12.2)	.001	24.4 (7.2 to 41.6)	.007
Monthly incidence of ACS by age group, years[c,d]				
0-5	-21.3 (-58.7 to 16.0)	.27	32.9 (-8.2 to 73.9)	.12
6-10	-33.9 (-61.4 to -6.5)	.02	25.7 (-1.7 to 53.1)	.07
11-14	-40.9 (-71.9 to -9.8)	.01	18.5 (-8.6 to 45.7)	.18
15-17	-26.1 (-56.1 to 12.8)	.22	15.0 (-18.4 to 48.5)	.38
Secondary outcomes[c,d]				
Monthly incidence of pneumonia per 1000 children with SCD	-55.7 (-84.2 to -27.3)	< .001	18.2 (-22.9 to 59.3)	.39
Monthly incidence of VOC per 1000 children with SCD	-33.7 (-40.3 to -27.0)	< .001	11.0 (3.0 to 19.0)	.01
Control outcome[c,d]				
Monthly incidence of acute pyelonephritis per 1000 children with SCD	-14.1 (-62.9 to 34.8)	.57	1.6 (-4.7 to 8.0)	.62

[a] NPI implementation was in March 2020

[b] Lifting of NPIs was in April 2021

[c] Monthly incidence expressed as the number of cases per 1000 children with SCD.

[d] Analysis by quasi-Poisson regression.

Abbreviations: ACS, acute chest syndrome; NPIs, non-pharmaceutical interventions; VOC, vaso-occlusive crisis.

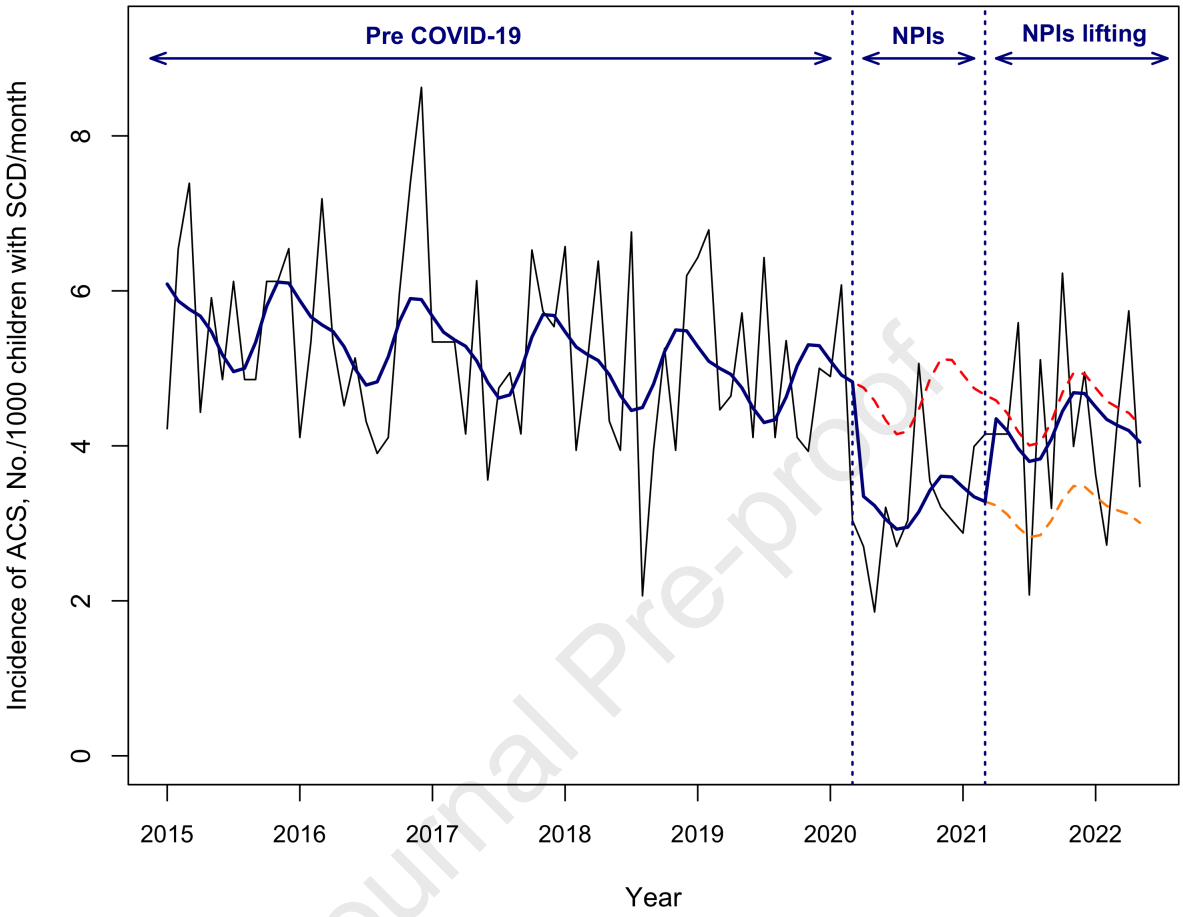
Table 3. Estimated Fraction of ACS in Children with Sickle-Cell Disease Attributable to Respiratory Pathogens

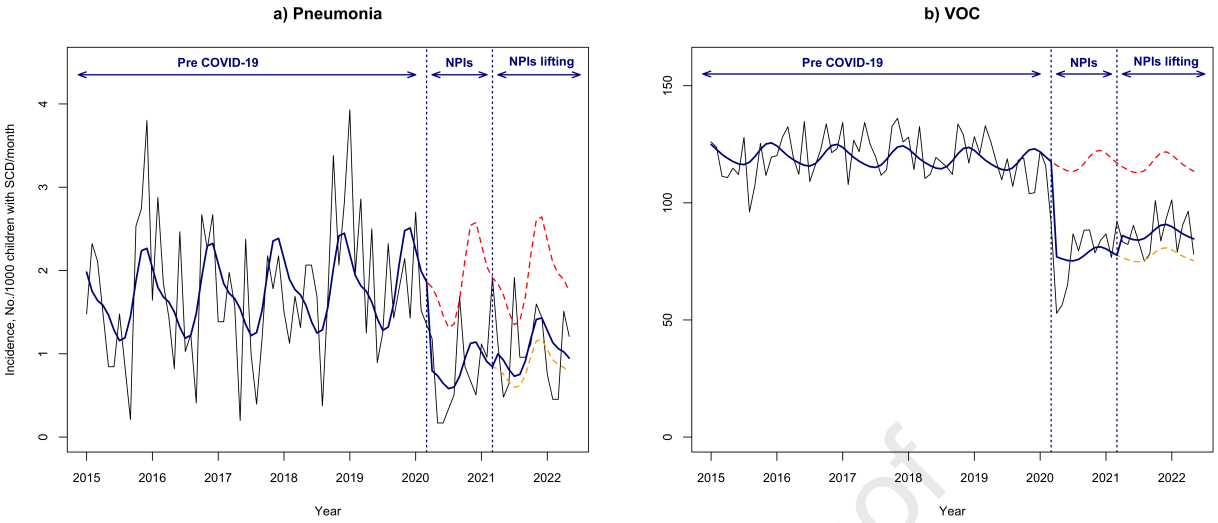
	Estimated fraction of ACS[a]	
Respiratory pathogen	**% (95% CI)**	***P* value**
RSV	6.0 (-1.7 to 13.5)	.13
Influenza	6.8 (2.3 to 11.3)	.004
hPIV	10.9 (-0.15 to 22.0)	.06
hMPV	-5.9 (-14.1 to 2.3)	.16
hAdV	-9.9 (-34.9 to 15.1)	.44
hRV	5.0 (-11.9 to 21.9)	.57
hEV	6.3 (-7.7 to 20.4)	.38
SARS-CoV-2[b]	2.9 (-7.1 to 13.0)	.57
Streptococcus pneumoniae	30.9 (4.9 to 56.9)	.02
Haemophilus influenzae	3.5 (-22.1 to 29.2)	.79
Mycoplasma pneumoniae	-6.5 (-20.7 to 7.8)	.38
Chlamydia pneumoniae	-3.3 (-11.6 to 5.0)	.44

[a] Analysis by seasonally-adjusted quasi-Poisson regression model

[b] Analysis including the COVID-19 period only (April 2020 to May 2022)

Abbreviations: ACS, acute chest syndrome; RSV, respiratory syncytial virus; hPIV, human parainfluenza virus; hMPV, human metapneumovirus; hAdV, human adenovirus; hRV, human rhinovirus; hEV, human enterovirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.





Declaration of interests

☐ 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.

☒ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Naim Ouldali reports a relationship with GSK, Pfizer, and Sanofi that includes: travel reimbursement. Alexis Rybak reports a relationship with Pfizer and AstraZeneca that includes: travel reimbursement, and a relationship with MSD that includes: speaking and lecture fees. Astrid Vabret reports a relationship with Sanofi, Moderna, and GSK that includes: speaking and lecture fees, and a relationship with MSD that includes: travel reimbursement. Robert Cohen reports a relationship with Sanofi, GSK, and MSD that includes: speaking and lecture fees, and with Pfizer that includes: consulting or advisory, funding grants, speaking and lecture fees, and travel reimbursement. Francois Angoulvant reports a relationship with Pfizer, Sanofi, GSK and MSD that includes: consulting or advisory. Emmanuelle Varon reports a relationship with Santé Publique France, Pfizer, and MSD that includes: funding grants.

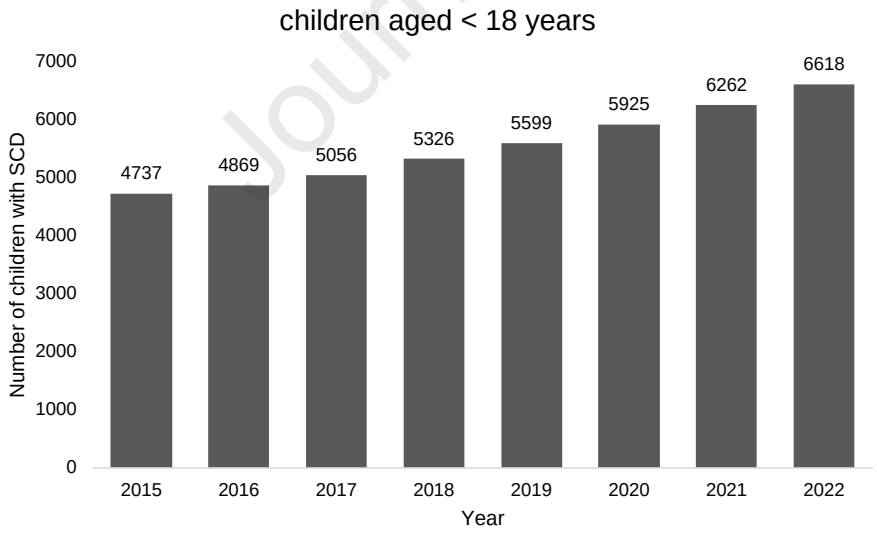
Supplementary Materials

eTable 1. Clinical Diagnoses for Acute Diseases in Children with SCD, Defined by ICD-10 Code Combinations

Diagnosis	ICD-10 code combinations		
Acute chest syndrome	D570 (Hb-SS disease with crisis) or D572 (Sickle-cell/Hb-C disease)	and	J960 (acute respiratory failure) or J189 (pneumonia, unspecified organism) or I269 (pulmonary embolism without acute pulmonary heart disease)
Pneumonia with SCD	D571 or D578	and	J13 (pneumonia due to Streptococcus pneumoniae) or J159 (unspecified bacterial pneumonia) or J18 (pneumonia, unspecified organism) or J180 (bronchopneumonia, unspecified organism) or J181(lobar pneumonia, unspecified organism) or J189 (pneumonia, unspecified organism) or J851 (abscess of lung with pneumonia) or J90 (pleural effusion, not elsewhere classified)
Acute pyelonephritis with SCD	D570 or D571 or D572 or D578	and	N10 (acute pyelonephritis) or N136 (pyonephrosis)
Vaso-occlusive crisis	D570 or D572	and	no diagnosis for other acute SCD

Hb, hemoglobin, ICD, International Classification of Diseases, SCD, sickle-cell disease.

eFigure 1. Number of Children < 18 Years of Age with SCD Living in France Over Time



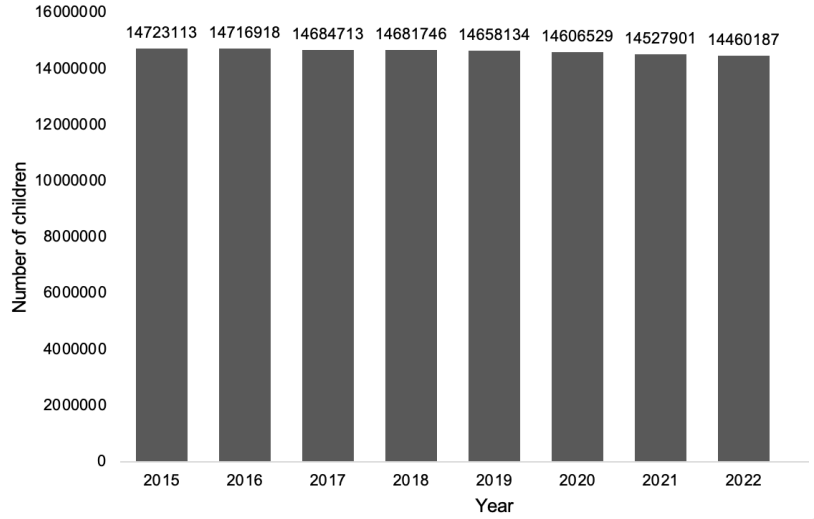
Data provided by the National Health Insurance Scheme database (*https://assurance-maladie.ameli.fr/etudes-et-donnees/prevalence-beneficiaires-ald-2019*).
SCD, sickle-cell disease

eTable 2. ICD-10 Codes for Respiratory Pathogens in the General Population

Diagnosis	ICD-10 code	Label
RSV	J121	Respiratory syncytial virus pneumonia
	J205	Acute bronchitis due to respiratory syncytial virus
	J210	Acute bronchiolitis due to respiratory syncytial virus
Influenza	J10	Influenza due to other identified influenza virus
	J100	Influenza due to other identified influenza virus with pneumonia
	J101	Influenza due to other identified influenza virus with other respiratory manifestations
	J108	Influenza due to other identified influenza virus with other manifestations
hPIV	J122	Parainfluenza virus pneumonia
	J204	Acute bronchitis due to parainfluenza virus
hMPV	J123	Human metapneumovirus pneumonia
hAdV	J120	Adenoviral pneumonia
	A082	Adenoviral enteritis
	A851	Adenoviral encephalitis
	B340	Adenovirus infection, unspecified
hRV	J206	Acute bronchitis due to rhinovirus
hEV	A850	Enteroviral encephalitis
	A870	Enteroviral meningitis
	A880	Enteroviral exanthematous fever
	B085	Enteroviral vesicular pharyngitis
	B341	Enterovirus infection, unspecified
	B971	Unspecified enterovirus as the cause of diseases classified elsewhere
SARS-CoV-2	U0714	COVID-19, other clinical forms, virus identified
	U0710	COVID-19, respiratory form, virus identified
S. pneumoniae	A403	Sepsis due to *Streptococcus pneumoniae*
	G001	Pneumococcal meningitis
	J13	Pneumonia due to *Streptococcus pneumoniae*
H. influenzae	J14	Pneumonia due to *Hemophilus influenzae*
M. pneumoniae	J157	Pneumonia due to *Mycoplasma pneumoniae*
	A493	Mycoplasma infection, unspecified site
C. pneumoniae	J160	Chlamydial pneumonia
Undocumented pneumonia	J18	Pneumonia, unspecified organism
	J180	Bronchopneumonia, unspecified organism
	J181	Lobar pneumonia, unspecified organism
	J188	Other pneumonia, unspecified organism
	J189	Pneumonia, unspecified organism
	J159	Unspecified bacterial pneumonia

RSV, respiratory syncytial virus; hPIV, human parainfluenza virus; hMPV, human metapneumovirus; hAdV, human adenovirus; hRV, human rhinovirus; hEV, human enterovirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; *S. pneumoniae*, *Streptococcus pneumoniae*; *H. influenzae*, *Haemophilus influenzae*; *M. pneumoniae*, *Mycoplasma pneumoniae*; *C. pneumoniae*, *Chlamydia pneumoniae*.

eFigure 2. Number of Children < 18 years Living in France Over Time



Data provided by National Institute for Statistics and Economic Studies (*https://www.insee.fr/fr/statistiques/series/103088458*).

eTable 3: Main Non-Pharmaceutical Interventions Implemented in France Against the Spread of SARS-CoV-2 During the Study Period

Non-Pharmaceutical Interventions	Start and end dates
Stay at home orders	
General order (lockdown)	03/17/2020 to 05/11/2020 10/29/2020 to 12/14/2020
Partial order (curfew)	05/12/2020 to 06/02/2020 10/17/2020 to 10/28/2020 12/15/2020 to 06/20/2021
Physical distancing	
Public gathering restrictions	03/17/2020 to 06/15/2020 10/19/2020 to 05/18/2021
Closure of public spaces	03/16/2020 to 06/01/2020 10/28/2020 to 05/18/2021
Closure of educational institutions	
Total closure of higher education	10/27/2020 to 01/24/2021
Partial closure of higher education	03/16/2020 to 06/22/2020 01/25/2021 to 09/03/2021
Total closure of secondary schools	03/16/2020 to 05/10/2020 04/06/2021 to 05/02/2021
Partial closure of secondary schools	05/11/2020 to 06/22/2020
Total closure of primary schools	04/06/2021 to 04/26/2021
Partial closure of primary schools	06/16/2020 to 06/22/2020
Total closure of daycare or nursery	03/16/2020 to 06/01/2020 04/06/2021 to 04/26/2021
Partial closure of daycare or nursery	06/02/2020 to 06/22/2020
Workplace measures	03/17/2020 to 05/11/2020 10/28/2020 to 06/08/2021
Mandatory wear of protective mask	
In all spaces	10/28/2020 to 06/16/2021
In closed spaces	07/20/2020 to 10/28/2020 06/17/2021 to 03/14/2022
Indoor transports	05/11/2020 to 07/19/2020 03/15/2022 to 05/15/2022
In health care facilities	05/16/2022 ongoing

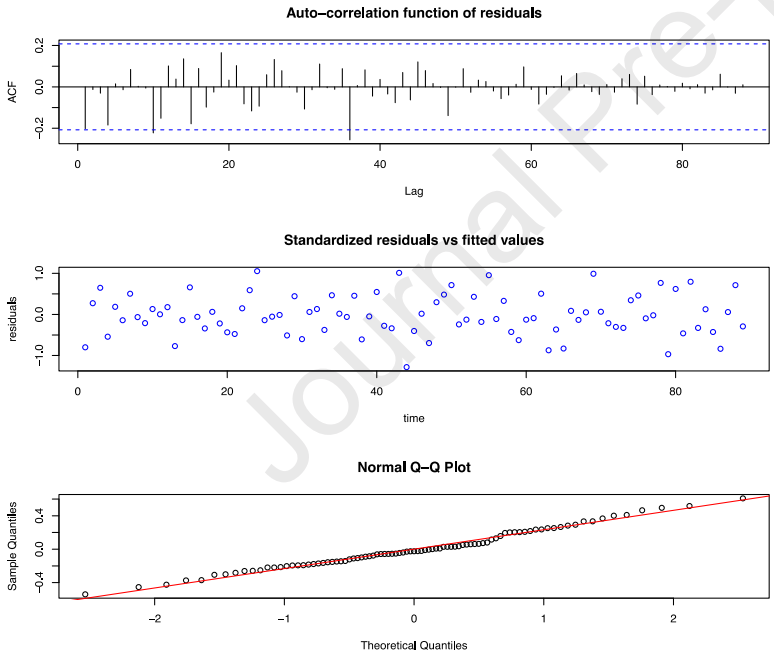
Data provided by the European Centre for Disease Prevention and Control. Data on country response measures to COVID-19 (https://www.ecdc.europa.eu/en/publications-data/download-data-response-measures-covid-19).

eTable 4. Sensitivity Analysis for the Association of the Implementation and Progressive Lifting of NPIs with the Monthly Incidence of ACS per 1000 Children with Sickle-Cell Disease

Outcome	NPI implementation[a]		NPI lifting[b]	
	Immediate change, % (95% CI)	*P* value for immediate change	Progressive change, % (95% CI)	*P* value for progressive change
Monthly incidence of ACS per 1000 children with SCD[c,d]	-29.6 (-47.1 to -12.2)	.001	27.9 (1.1 to 54.7)	.04

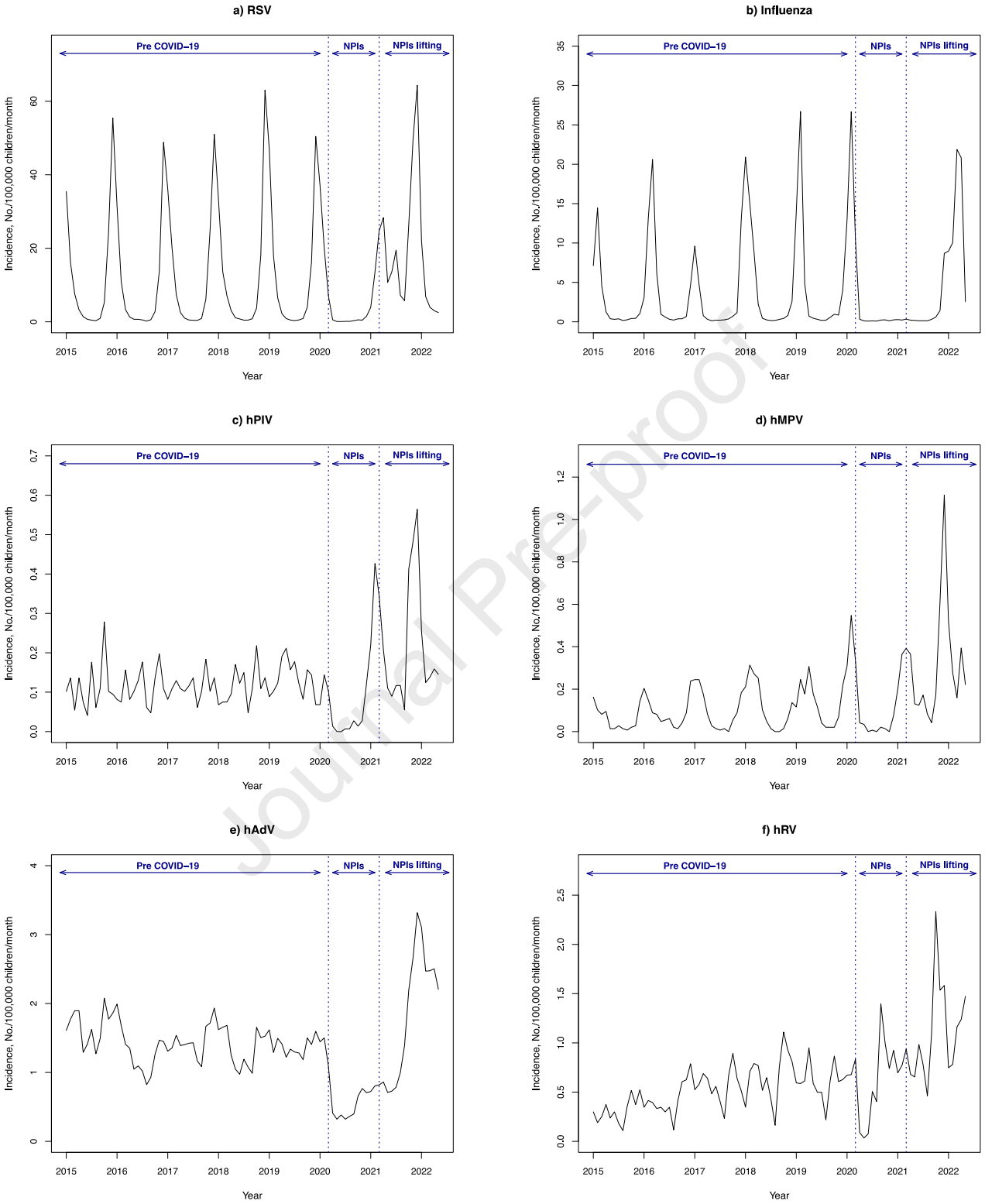
[a] NPI implementation was in March 2020
[b] Lifting of NPIs was starting progressively from April 2021
[c] Monthly incidence expressed as the number of cases per 1000 children with SCD.
[d] Analysis by quasi-Poisson regression.
Abbreviations: NPIs, non-pharmaceutical interventions

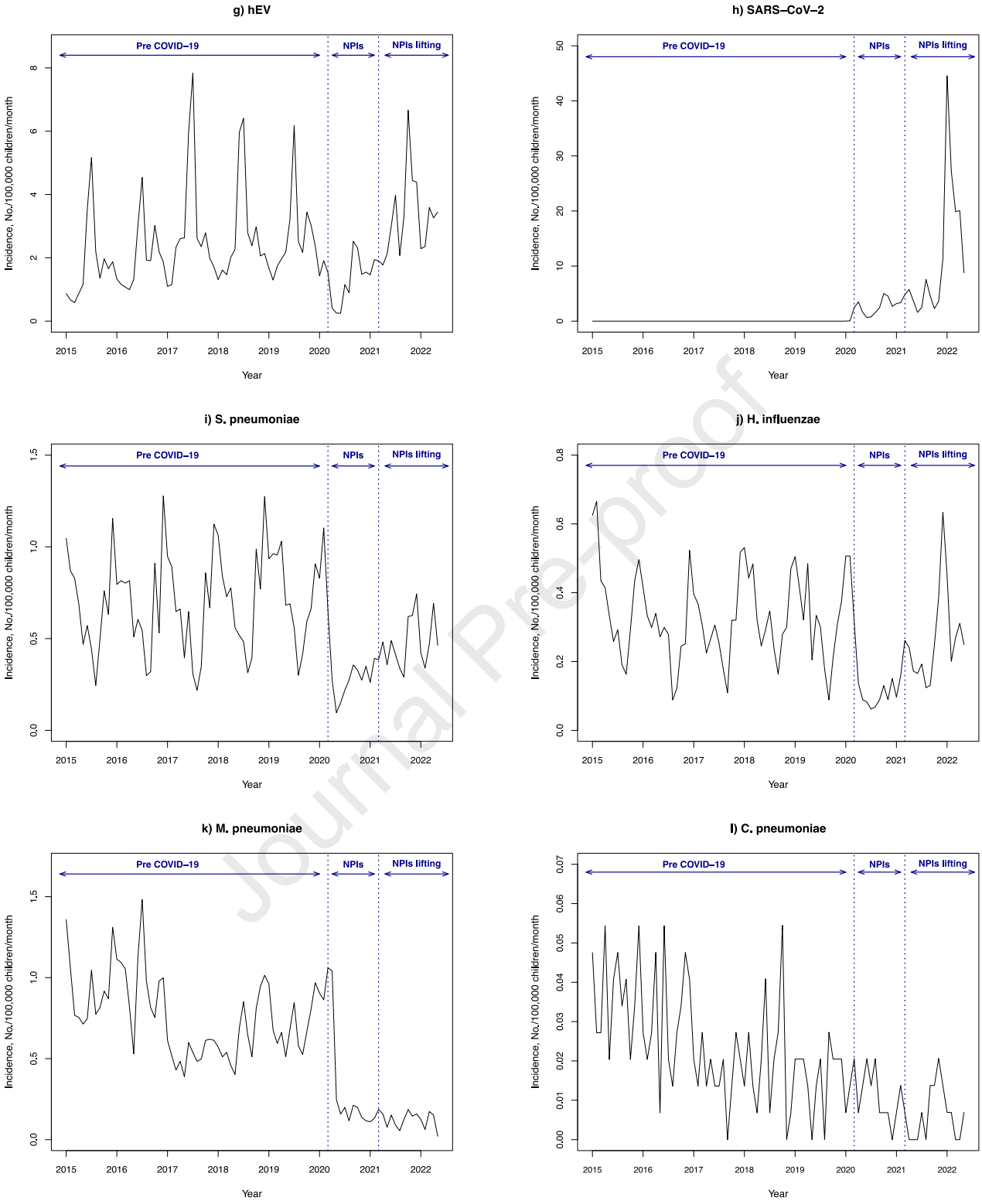
eFigure 3. Correlograms and Residuals Analysis of the Final Quasi-Poisson Regression Model for the Monthly Incidence of ACS per 1,000 Children with SCD



To assess the quality of the Quasi-Poisson model, we used correlograms (autocorrelation and partial autocorrelation functions which measure the linear relationship between lagged values of a time series) and residuals analysis. Inspection of the correlograms relies on identifying remaining autocorrelation or seasonal pattern of the residuals. The significance of any remaining autocorrelation or seasonality is defined by a correlation higher than +1.96 standard error or lower than -1.96 standard error for each lag of the time series. We checked whether the residuals of the models were normally distributed and had a constant variance over time. The correlograms were satisfactory (no remaining autocorrelation nor seasonal pattern of the residuals)"
ACF, autocorrelation function.

eFigure 4. Monthly Incidence of Hospitalizations for Respiratory Infections in the General French Pediatric Population (< 18 years) Over Time, by Pathogen, January 2015 to May 2022





The black line shows the observed data. The dotted vertical lines indicate the NPIs implementation in March 2020 and the NPIs lifting in March 2021. RSV, respiratory syncytial virus; hPIV, human parainfluenza virus; hMPV, human metapneumovirus; hAdV, human adenovirus; hRV, human rhinovirus; hEV, human enterovirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; *S. pneumoniae*, *Streptococcus pneumoniae*; *H. influenzae*, *Haemophilus influenzae*; *M. pneumoniae*, *Mycoplasma pneumoniae*; *C. pneumoniae*, *Chlamydia pneumoniae*.

eTable 5. Baseline Characteristics of Hospitalizations for Respiratory Infections in the General French Pediatric Population (age < 18 years), January 2015 to May 2022

Respiratory pathogens	No. of cases	Age, median (IQR), y	Duration of stay, median (IQR), d	Hospital death (%)
RSV	158,660	0.24 (0.12-0.54)	4 (2-6)	122 (0.001)
Influenza	50,901	2 (0.85-5)	2 (1-3)	154 (0.003)
hPIV	1695	1 (0.42-3)	4 (2-9)	24 (0.01)
hMPV	1841	2 (0.88-3)	5 (3-8)	20 (0.01)
hAdV	17,983	1 (0.44-2)	2 (2-4)	85 (0.005)
hRV	8194	0.98 (0.22-3)	4 (2-8)	73 (0.009)
hEV	31,357	1 (0.13-4)	3 (2-4)	67 (0.002)
SARS-CoV-2	28,975	1 (0.18-7)	2 (1-3)	78 (0.003)
S. pneumoniae	7946	2 (0.88-5)	4 (2-9)	130 (0.02)
H. influenzae	3807	2 (0.62-8)	7 (3-14)	87 (0.02)
C. pneumoniae	251	4 (1-10)	4 (2-7)	2 (0.008)
M. pneumoniae	7788	5 (3-9)	3 (2-5)	10 (0.001)
Undocumented pneumonia	124,195	2 (1-5)	3 (2-5)	572 (0.46)

RSV, respiratory syncytial virus; hPIV, human parainfluenza virus; hMPV, human metapneumovirus; hAdV, human adenovirus; hRV, human rhinovirus; hEV, human enterovirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; *S. pneumoniae*, *Streptococcus pneumoniae*; *H. influenzae*, *Haemophilus influenzae*; *M. pneumoniae*, *Mycoplasma pneumoniae*; *C. pneumoniae*, *Chlamydia pneumoniae*.

eTable 6. Sensitivity Analyses for the Estimated Fraction of ACS Potentially Attributable to Respiratory Pathogens

	Estimated fraction of ACS											
	Model with combined ACS and pneumonia[a]		Model with J189 excluded from ACS definition[a]		Model with I269 excluded from ACS definition[a]		Model adjusted for the monthly incidence of VOC[a]		Model without highly correlated covariates[a,b]		Model with 3- 6- and 12-month periods seasonality[a]	
Respiratory pathogen	% (95% CI)	*P* value	% (95% CI)	*P* value	% (95% CI)	*P* value	% (95% CI)	*P* value	% (95% CI)	*P* value	% (95% CI)	*P* value
RSV	5.7 (-1.7 to 13.2)	.13	4.4 (-5.8 to 14.7)	.40	5.8 (-1.9 to 13.6)	.15	7.2 (-0.66 to 15.0)	.08	6.2 (-1.2 to 13.6)	.11	6.0 (-2.0 to 14.0)	.15
Influenza	4.5 (0.2 to 8.9)	.04†	8.0 (1.8 to 14.1)	.01†	6.5 (2.1 to 11.0)	.007†	6.5 (2.0 to 11.1)	.006†	6.8 (2.4 to 11.2)	.004†	6.5 (1.9 to 11.1)	.007†
hPIV	12.3 (1.8 to 22.8)	.02†	18.8 (3.5 to 34.1)	.02†	10.4 (-0.78 to 21.5)	.07	10.8 (-0.24 to 21.9)	.06	11.1 (0.18 to 21.9)	.05	10.9 (-0.37 to 22.3)	.06
hMPV	-7.9 (-15.7 to -0.10)	.05†	-12.3 (-23.4 to -1.1)	.03†	-5.9 (-14.2 to 2.3)	.16	-5.7 (-13.9 to 2.5)	.18	-5.5 (-13.3 to 2.4)	.18	-6.2 (-14.5 to 2.1)	.15
hAdV	-5.3 (-29.6 to 18.9)	.67	-7.5 (-41.6 to 26.5)	.67	-9.5 (-34.8 to 15.8)	.47	-10.8 (-35.7 to 14.1)	.40	-8.3 (-31.4 to 14.9)	.49	-11.7 (-37.0 to 13.6)	.37
hRV	0.67 (-15.2 to 16.5)	.93	13.1 (-10.2 to 36.4)	.27	5.3 (-11.8 to 22.3)	.55	5.6 (-11.4 to 22.6)	.52	.		5.2 (-12.1 to 22.4)	.56
hEV	8.6 (-4.9 to 22.1)	.22	-0.40 (-19.1 to 18.3)	.97	6.2 (-7.9 to 20.4)	.39	4.0 (-10.4 to 18.4)	.58	8.4 (-3.9 to 20.7)	.19	7.8 (-6.8 to 22.5)	.30
SARS-CoV-2[c]	0.10 (-9.4 to 9.6)	.98	4.4 (-9.1 to 18.0)	.52	1.1 (-8.9 to 11.1)	.83	3.6 (-6.4 to 13.7)	.48	2.6 (-7.3 to 12.4)	.57	4.2 (-6.3 to 14.6)	.44
S. pneumoniae	43.7 (18.0 to 69.5)	.001†	41.6 (5.1 to 78.1)	.03†	31.2 (4.9 to 57.5)	.02†	22.3 (-5.6 to 50.1)	.12	34.4 (11.3 to 57.5)	.005†	34.1 (6.8 to 61.4)	.02†
H. influenzae	3.3 (-21.1 to 27.7)	.79	7.1 (-27.8 to 42.1)	.69	5.2 (-20.9 to 31.4)	.69	3.1 (-22.5 to 28.6)	.81	.		4.3 (-22.0 to 30.5)	.75
M. pneumoniae	1.3 (-12.7 to 15.2)	.89	-0.98 (-20.2 to 18.2)	.92	-8.4 (-22.7 to 6.0)	.26	-6.1 (-20.4 to 8.2)	.41	-7.4 (-20.8 to 6.1)	.29	-6.2 (-20.6 to 8.3)	.41
C. pneumoniae	-2.0 (-9.9 to 5.9)	.62	-12.6 (-23.2 to -2.1)	.02†	-3.0 (-11.4 to 5.5)	.49	-2.7 (-11.0 to 5.6)	.53	-3.1 (-11.3 to 5.1)	.46	-3.1 (-11.5 to 5.4)	.48

[a] Analysis by seasonally-adjusted quasi-Poisson regression model

[b] Model excluding the following highly correlated covariates: rhinovirus and *Haemophilus influenzae*

[c] *Analysis including the COVID-19 period only (April 2020 to May 2022)*

† Statistically significant

Abbreviations: ACS, acute chest syndrome; SCD, sickle-cell disease; VOC, vaso-occlusive crisis; RSV, respiratory syncytial virus; hPIV, human parainfluenza virus; hMPV, human metapneumovirus; hAdV, human adenovirus; hRV, human rhinovirus; hEV, human enterovirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; *S. pneumoniae*, *Streptococcus pneumoniae*; *H. influenzae*, *Haemophilus influenzae*; *M. pneumoniae*, *Mycoplasma pneumoniae*; *C. pneumoniae*, *Chlamydia pneumoniae*.

eTable 7. Variance Inflation Factors (VIF) of the Final Quasi-Poisson Regression Model

Respiratory pathogen	GVIF	Df	GVIF^(1/(2*Df))
RSV	5.361531	1	2.315498
Influenza	2.952271	1	1.718217
hPIV	3.113611	1	1.764543
hMPV	4.820405	1	2.195542
hAdV	5.012884	1	2.238947
hRV	5.290792	1	2.300172
hEV	3.868910	1	1.966954
SARS-CoV-2	3.072347	1	1.752811
S. pneumoniae	5.114230	1	2.261466
H. influenzae	6.956956	1	2.637604
C. pneumoniae	1.915031	1	1.383846
M. pneumoniae	3.361602	1	1.833467

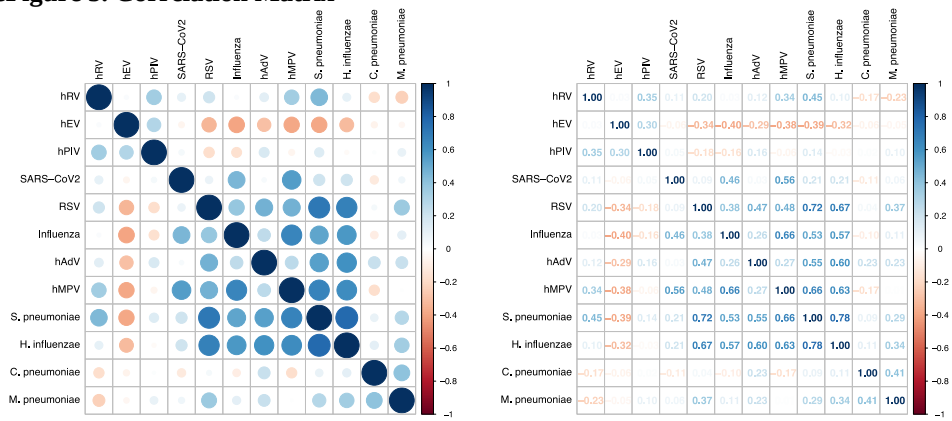
GVIF, generalized variance inflation factor; Df, degree of freedom; RSV, respiratory syncytial virus; hPIV, human parainfluenza virus; hMPV, human metapneumovirus; hAdV, human adenovirus; hRV, human rhinovirus; hEV, human enterovirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; *S. pneumoniae*, *Streptococcus pneumoniae*; *H. influenzae*, *Haemophilus influenzae*; *M. pneumoniae*, *Mycoplasma pneumoniae*; *C. pneumoniae*, *Chlamydia pneumoniae*.

eTable 8. Variance Inflation Factors of the Quasi-Poisson Regression Model Without Highly Correlated Covariates (*H. influenzae* and hRV)

Respiratory pathogen	GVIF	Df	GVIF^(1/(2*Df))
RSV	5.206312	1	2.281735
Influenza	2.917739	1	1.708139
hPIV	3.064941	1	1.750697
hMPV	4.540092	1	2.130749
hAdV	4.338515	1	2.082910
hEV	2.993342	1	1.730128
SARS-CoV-2	3.010997	1	1.735223
S. pneumoniae	4.025046	1	2.006252
C. pneumoniae	1.898446	1	1.377841
M. pneumoniae	3.044670	1	1.744898

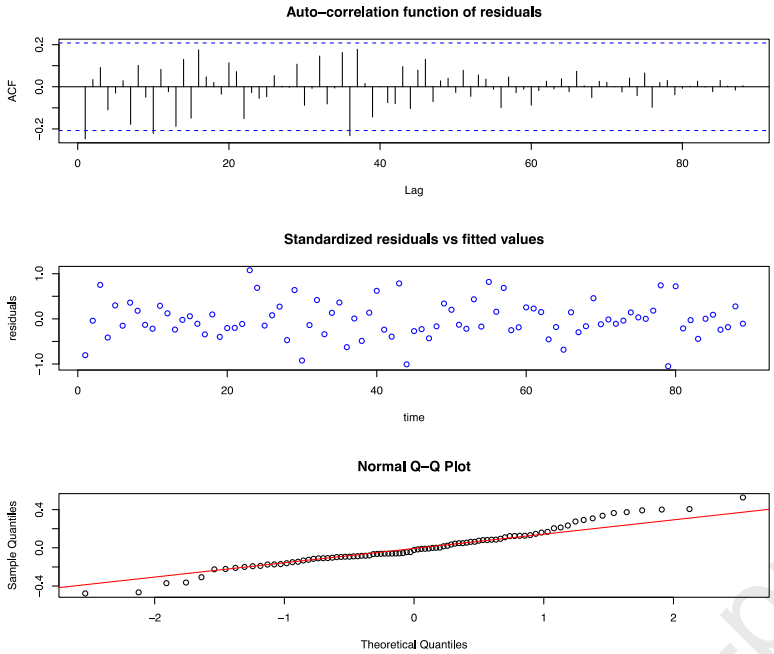
GVIF, generalized variance inflation factor; Df, degree of freedom; RSV, respiratory syncytial virus; hPIV, human parainfluenza virus; hMPV, human metapneumovirus; hAdV, human adenovirus; hRV, human rhinovirus; hEV, human enterovirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; *S. pneumoniae*, *Streptococcus pneumoniae*; *H. influenzae*, *Haemophilus influenzae*; *M. pneumoniae*, *Mycoplasma pneumoniae*; *C. pneumoniae*, *Chlamydia pneumoniae*.

eFigure 5. Correlation Matrix



RSV, respiratory syncytial virus; hPIV, human parainfluenza virus; hMPV, human metapneumovirus; hAdV, human adenovirus; hRV, human rhinovirus; hEV, human enterovirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; *S. pneumoniae*, *Streptococcus pneumoniae*; *H. influenzae*, *Haemophilus influenzae*; *M. pneumoniae*, *Mycoplasma pneumoniae*; *C. pneumoniae*, *Chlamydia pneumoniae*.

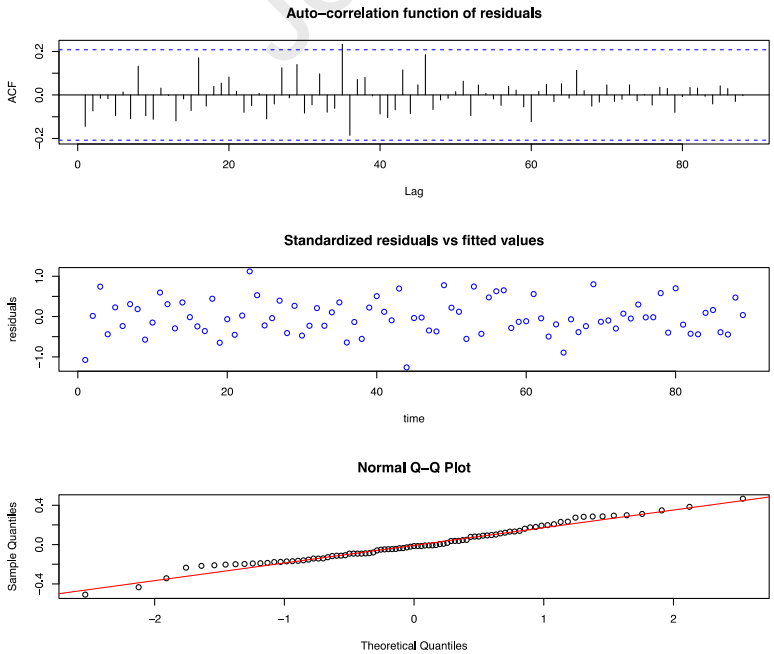
eFigure 6. Correlograms and Residuals Analysis of the Quasi-Poisson Model for the Estimated Fraction of ACS Attributable to Respiratory Pathogens.



To assess the quality of the Quasi-Poisson model, we used correlograms (autocorrelation and partial autocorrelation functions which measure the linear relationship between lagged values of a time series) and residuals analysis. Inspection of the correlograms relies on identifying remaining autocorrelation or seasonal pattern of the residuals. The significance of any remaining autocorrelation or seasonality is defined by a correlation higher than +1.96 standard error or lower than -1.96 standard error for each lag of the time series. We checked whether the residuals of the models were normally distributed and had a constant variance over time. The correlograms were satisfactory (no remaining autocorrelation nor seasonal pattern of the residuals)"
ACF, autocorrelation function.

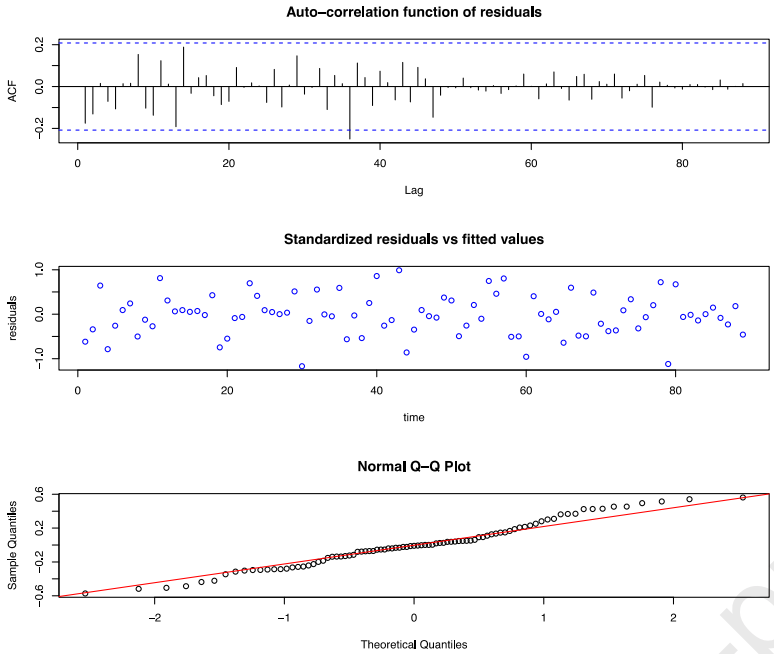
eFigure 7. Correlograms and Residuals Analysis of the Sensitivity Analyses

a) Quasi-Poisson regression model with combined ACS and pneumonia



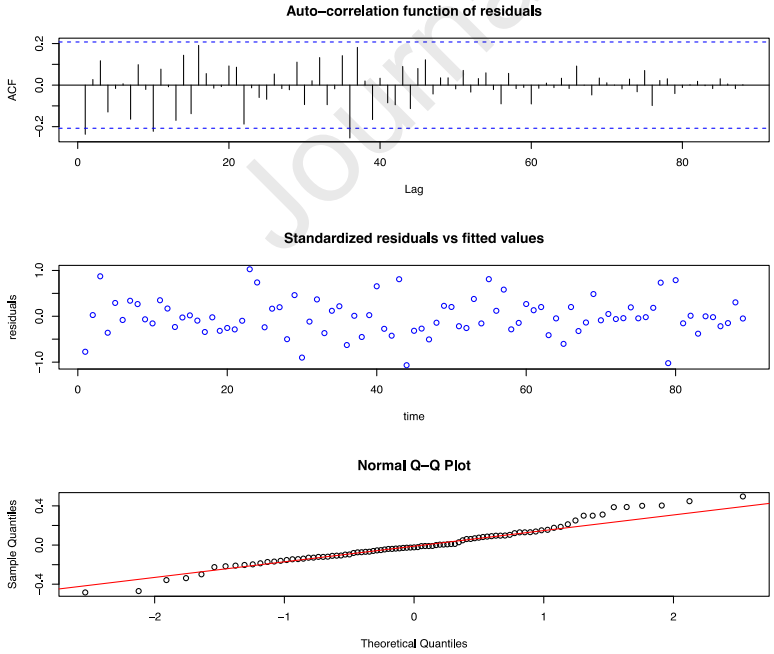
ACF, autocorrelation function.

b) Quasi-Poisson model with the ICD-10 code J189 (i.e. “pneumonia, unspecified organism”) excluded from ACS definition



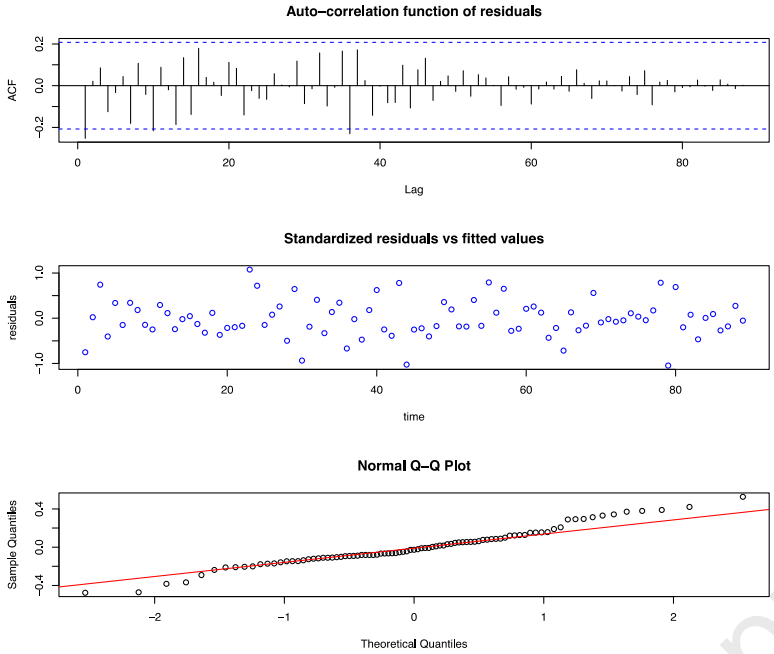
ACF, autocorrelation function.

c) Quasi-Poisson regression model adjusted for the monthly incidence of VOC



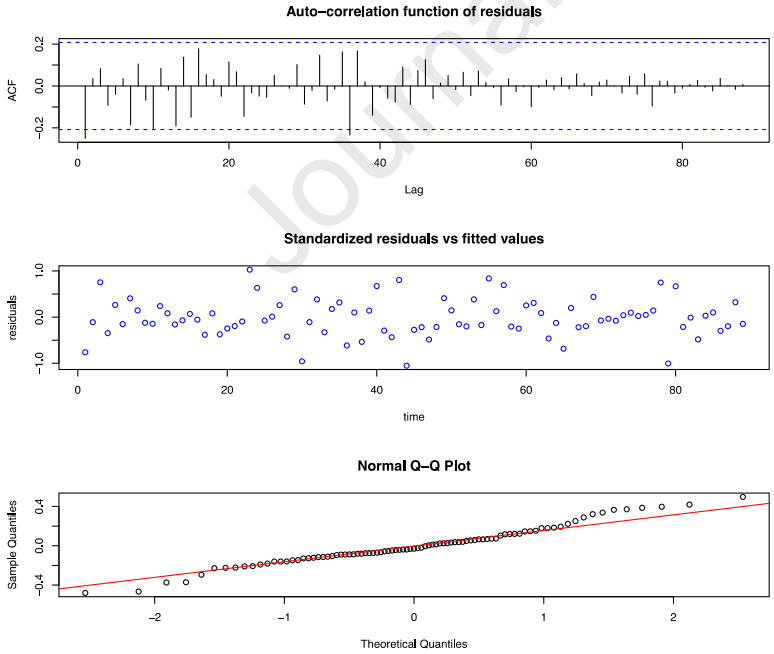
VOC, vaso-occlusive crisis; ACF, autocorrelation function.

d) Model without highly correlated covariates (*H. influenzae* and hRV)



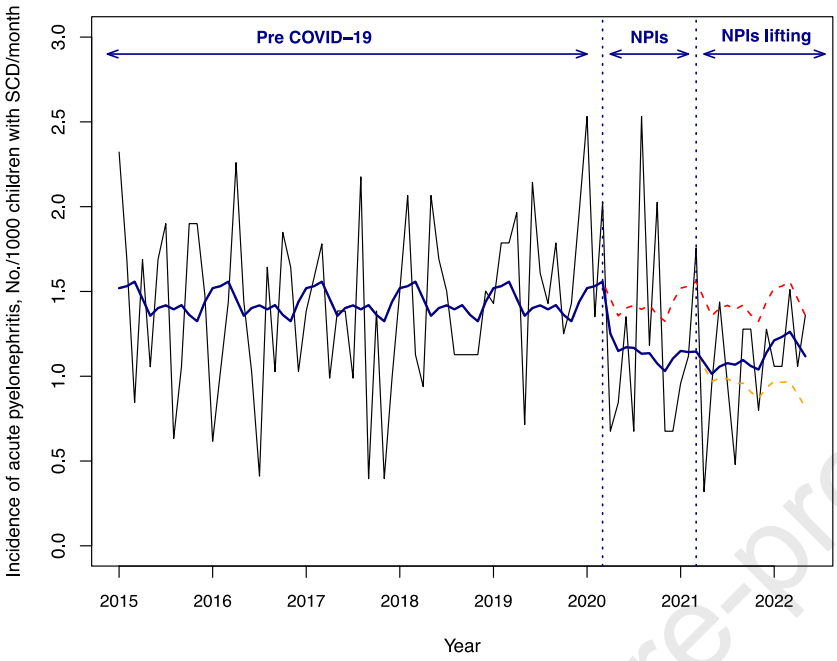
H. influenzae, *Haemophilus influenzae*; hRV, human rhinovirus; ACF, autocorrelation function.

e) Quasi-Poisson regression model with 3- 6- and 12-month periods seasonality



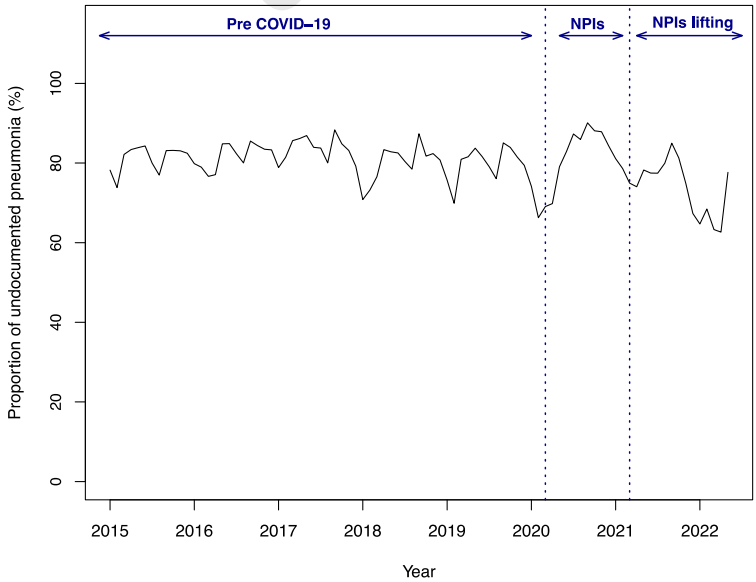
To assess the quality of the Quasi-Poisson model, we used correlograms (autocorrelation and partial autocorrelation functions which measure the linear relationship between lagged values of a time series) and residuals analysis. Inspection of the correlograms relies on identifying remaining autocorrelation or seasonal pattern of the residuals. The significance of any remaining autocorrelation or seasonality is defined by a correlation higher than +1.96 standard error or lower than -1.96 standard error for each lag of the time series. We checked whether the residuals of the models were normally distributed and had a constant variance over time. The correlograms were satisfactory (no remaining autocorrelation nor seasonal pattern of the residuals)"
ACF, autocorrelation function.

eFigure 8. Association of NPIs Implementation and Lifting with the Monthly Incidence of acute pyelonephritis per 1000 Children with SCD, January 2015 to May 2022



The black line shows the observed data. The blue line shows the model estimates based on observed data using the quasi-Poisson regression model. The red and orange dotted lines show the expected values without NPIs implementation and NPIs lifting, respectively, using the same quasi-Poisson model. The dotted vertical lines indicate the NPIs implementation in March 2020 and the NPIs lifting in April 2021.
Abbreviations: NPIs, non-pharmaceutical interventions; SCD, sickle-cell disease.

eFigure 9. Proportion of Undocumented Pneumonia Among All Pneumonia in the General Population Over Time, January 2015 to May 2022



The black line shows the observed data. The dotted vertical lines indicate the NPIs implementation in March 2020 and the NPIs lifting in April 2021.