Streptococcus pneumoniae is a leading cause of acute respiratory infection and invasive disease in all ages. Nasopharyngeal carriage is a necessary step preceding any pneumococcal disease. However, S pneumoniae is also a normal part of the microbiome of the upper respiratory tract in early childhood, and children constantly acquire and clear carriage, mostly without incident. This apparent paradox suggests that other factors beyond nasopharyngeal carriage play an important role in the pathogenesis of pneumococcal disease. Epidemiological, clinical, and experimental evidence suggests that certain respiratory viruses may have a substantial role in the burden of pneumococcal disease. However, most of the evidence for either coinfections or virus-induced pneumococcal secondary infections in children has been derived from observational epidemiological studies reporting association, which does not demonstrate a causative relationship.

Interventions such as vaccination can unveil interactions between pathogens. A randomized clinical trial of a pneumococcal conjugate vaccine demonstrated reductions in pneumonia hospitalizations that were believed to be caused by viruses. Likewise, the widespread implementation of pneumococcal conjugate vaccines had considerable consequences for the rates of viral lower respiratory tract infections in infants and toddlers. Although these interventions against pneumococcus have revealed a role for the bacteria in viral pneumonia, there has not been an opportunity to observe the reverse consequences of an intervention against viruses with regard to the burden of pneumococcal disease. The respiratory viruses most commonly implicated in the burden of pneumococcal disease (namely respiratory syncytial virus [RSV], influenza, human metapneumovirus, and parainfluenza) typically share seasonality with pneumococcal disease, and vaccines that could substantially reduce the circulation of these viruses have not yet been introduced or widely administered. The COVID-19 pandemic that emerged in early 2020 disrupted the transmission of many respiratory pathogens and provided an opportunity to probe interactions. For several months, RSV, influenza, and human metapneumovirus largely disappeared around the world. At the same time, reduced rates of pneumococcal disease were reported in many countries, with patterns resembling those of the respiratory viruses. The unusual patterns of both viral and pneumococcal diseases were mostly associated with nonpharmaceutical interventions that were intended to limit the spread of SARS-CoV-2.

Elsewhere in JAMA Network Open, Rybak and colleagues shed new light on the potential role of 2 respiratory viruses, RSV and influenza, in the pathogenesis of invasive pneumococcal disease (IPD) in children. The authors conducted an impressive multicenter study using several nationwide prospective surveillance programs in France, including a multiple-hospital IPD surveillance system, a national continuous surveillance program involving children in 70 metropolitan areas, a national continuous surveillance system of influenza-like illness (as a proxy for influenza cases, which can also capture the activity of other respiratory viruses), and a national laboratory surveillance program for RSV cases. The authors applied a quasi-experimental interrupted time series analysis to assess the changes in these outcomes after the implementation of nonpharmaceutical interventions. They then estimated the fraction of the change in IPD that was associated with RSV and influenza-like illness vs the fraction of change associated with pneumococcal carriage alone by fitting a quasi-Poisson regressive model. They observed a decrease of 63% (95% CI, −82% to −43%; P < .001) in IPD incidence but, notably, pneumococcal carriage rates were not significantly reduced (−12%; 95% CI,
−37% to 12%; \( P = .32 \)). This result held true regardless of whether the pneumococcal strains belonged to serotypes with high or low disease potential. In contrast, the changes in influenza and RSV rates were significantly associated with IPD changes. They estimated that 53% (95% CI, 28%-78%; \( P < .001 \)) of the decrease in IPD incidence observed during the pandemic was associated with the change in influenza (or, more accurately, with influenza-like illness) cases and 40% (95% CI, 15%-65%; \( P < .001 \)) was associated with the change in RSV cases. In contrast, an association with nasopharyngeal carriage was not found, with carriage accounting for only 4% (95% CI, −7% to 15%; \( P = .49 \)) of the decrease in IPD incidence.

The findings by Rybak et al\(^3\) complement recent findings from a prospective study in Israel.\(^1\) Similar to France, the COVID-19 pandemic in Israel was first detected by the end of February 2020 and, during the following year, no activity of RSV, influenza, or human metapneumovirus was observed, including during the expected seasonal peak activity in the fall of 2020 and the winter of 2021. Compared with the 4 years before the COVID-19 pandemic, significant reductions were reported in rates of community-acquired alveolar pneumonia (93%, considered mostly bacterial), pneumococcal bacteremic pneumonia (81%), IPD without concomitant pneumonia (42%), and non-community-acquired alveolar pneumonia lower respiratory tract infections (46%). Similar to France, the overall rate of pneumococcal carriage was not significantly altered. Furthermore, the density of carriage in the positive samples and the serotype distribution were similar to those observed during the 4 years before the COVID-19 pandemic. A third study from Belgium\(^9\) reported that rates of nasopharyngeal pneumococcal carriage in children from November 2020 to March 2021 were similar to those observed during the same months in 2017 to 2019, despite a significant reduction in IPD rates among children younger than 3 years. Reemergence of IPD among children in the United Kingdom and Germany since mid-2021 occurred in parallel with the reemergence of RSV and influenza-like disease rates.\(^6,9\)

What new insights can we acquire from the thought-provoking study by Rybak and colleagues?\(^3\) First, the COVID-19 pandemic has temporarily but strikingly modified the global epidemiological patterns of multiple infectious diseases. Understanding the epidemiological changes and their consequences essentially depends on the availability and quality of baseline pre–COVID-19 data and the ability to proceed with surveillance programs during the pandemic. For this type of evaluation, it is important to examine multiple outcomes in the same population and have the ability to conduct a composite analysis of these multiple ongoing processes. This approach is beautifully exemplified by the current study.\(^3\)

Second, IPD rates were reduced during the first year of the COVID-19 pandemic. This decrease was initially believed to be associated with the ability of nonpharmaceutical interventions to reduce transmission of \( S \) pneumoniae, among other pathogens.\(^6\) However, the fact that pneumococcal nasopharyngeal carriage remained essentially unchanged, including in rates and density, strongly suggests no significant reduction in pneumococcal transmission in the community. Furthermore, across the studies reported to date, the distribution of serotypes did not significantly change compared with the pre–COVID-19 period. An important aspect of the analysis performed by Rybak and colleagues\(^3\) was the distinction between carriage among children who had serotypes with high vs low disease potential. The fact that even the carriage of serotypes with high disease potential did not change, including carriage of the most common invasive serotype, 24F, strengthens the point that although nasopharyngeal carriage is necessary for progression of disease, it is certainly not sufficient in most cases.

Third, and most important, the current study\(^3\) clearly highlights the role of RSV and influenza as cofactors in the pathogenesis of IPD, strengthening previous assumptions\(^1\) and emphasizing that certain respiratory viruses are crucial in the process. Unfortunately, other viruses beyond RSV and influenza were not examined individually or might have been captured in the category of influenza-like illness.\(^3\) For example, human metapneumovirus is also implicated in pneumococcal disease.\(^1\) As implicated viruses reemerged sequentially since mid-2021, with apparently parallel trends for IPD,
further analysis of the period starting in mid-2021 will, without doubt, provide additional insight into the individual roles of the different viruses.