Accepted author's manuscript of an editorial published in final edited form as:
European Respiratory Journal 2023; 61(2): 2202214. Publisher DOI: 10.1183/13993003.02214-2022

Preventing bronchiolitis among infants with non-pharmaceutical interventions outside pandemics - is it realistic?

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Take home message (248 of 256 characters)

Non-pharmaceutical interventions, such as wearing facemasks and teleworking, may help prevent bronchiolitis among infants; however, we need more knowledge about the feasibility and impact of such interventions outside the COVID-19 pandemic context.

Manuscript (1386 of 1500 words)

Bronchiolitis is the leading cause of hospitalization for lower respiratory tract illness (LRTI) among infants.[1] It is usually caused by respiratory syncytial virus (RSV) but also results from human metapneumovirus, rhinovirus, adenovirus, or other viruses.[2] By age 3, virtually all children have had an RSV infection. RSV-caused disease is most severe for young infants in their first 6 months of life and among high-risk infants, such as those suffering from bronchopulmonary dysplasia, congenital cyanotic heart disease, or born very preterm.[3, 4] Although vaccines are in development, pharmaceutical prophylaxis is currently limited to palivizumab, a monoclonal antibody against the RSV fusion protein, which needs to be administered intramuscularly monthly during the 5–6 months of peak RSV season (November to April in the northern hemisphere).[5] Administering palivizumab is expensive and cumbersome. In high-income countries, about 3% of infants younger than 12 months are hospitalised with bronchiolitis yearly [6] and 0.1% need intermediate or intensive care, while fortunately very few die.[7, 8] With annual hospitalization rates up to 0.2% among adults older than age 65, the burden of RSV disease among older people is more recently recognised.[9, 10] Among community-dwelling healthy older adults, studies suggest the disease is usually mild.[11]

In parallel with other viral and some bacterial infections during the COVID-19 pandemic, hospitalizations for bronchiolitis decreased in spectacular ways in many countries.[2, 12, 13] The decrease was a consequence of health behaviour changes and non-pharmaceutical interventions (NPIs), including social distancing, handwashing, travelling restrictions, closing schools, and teleworking.[14, 15] Understanding the impact of distinct NPIs on hospitalisations and deaths from RSV infections could reveal opportunities for reducing the burden of disease in the future.

A multicentre study analysing routine data from an international surveillance system

In this month's *European Respiratory Journal*, Lenglart et al.[16] studied the impact of NPIs implemented to prevent SARS-CoV-2 transmission on bronchiolitis cases among infants. They included data from 42,916 children younger than 1 year who presented with bronchiolitis at 27 paediatric emergency care units in 14 European countries from January 2018 to March 2021. The study compared numbers of bronchiolitis cases observed before and after NPIs were introduced in March 2020. On average, bronchiolitis cases declined by 78% with large variations between countries. Full lockdown was most strongly associated with the decline (incidence rate ratio (IRR) 0.21); closing secondary schools (IRR 0.33), wearing facemasks indoors (IRR 0.49), and teleworking (IRR 0.55) were also independently associated with reduction.

Methodological aspects

Their carefully conducted and transparently reported study is an excellent example of combining routine data from clinical information systems with public data—in this case, time periods of NPI implementation from different countries—to answer emerging health care questions quickly with a quasi-experiment. As part of the Research in Paediatric Emergency Medicine (REPEM) network, hospitals extracted anonymized and aggregated data monthly from clinic information systems. They recorded total number of infants with bronchiolitis presenting to the emergency department broken down by age, sex, virology testing, and outcomes (admission to the ward, paediatric intensive care, or death). Their use of fully anonymized, aggregated data eliminated confidentiality issues. Data were not reviewed manually, which reduced data collection costs. Questionnaires supplemented hospital data by assessing participating centres' diagnostic guidelines and management strategies for bronchiolitis. Despite minimal costs for data collection, the analysis elegantly investigated independent effects from different NPIs on bronchiolitis trends with results backed up by diverse sensitivity analyses. On the whole, Lenglart et al.'s study is a great example of thoughtfully using routine data in an international context—an approach worthy of leveraging in the future.

Yet, their study has limitations. Although they attempted to do so, it was impossible to fully disentangle different NPI effects because they were combined when introduced, so their individual impact if singularly implemented is unknown. Other untestable interventions, such as avoiding handshakes and kissing and improving hand hygiene, could also play a role resulting in residual confounding. Because information on exposures (NPIs) were only available at the country level, we don't know if they were also implemented in study participants, families with young infants, but the analyses assumed so—this limitation could result in a bias called ecological fallacy. Individual risk factors, such as number of siblings, parental professions, and periods of quarantine could not be considered in this study design. Thus, we can only guess what impact the same NPIs would have if applied alone and outside the context of the COVID-19 pandemic. Furthermore, using individual patient data from standardized electronic health records, with federated analysis to preserve confidentiality, could further enhance analytical options and statistical power.[17]

Would such interventions be feasible and worthwhile? Three scenarios

Although Lenglart et al. suggest that some interventions might be adopted to reduce the future burden of bronchiolitis, they did not expand on the design of these interventions, who would be targeted, or how many people would need to follow measures to avoid one case.

We invented three simple scenarios to compare efforts and effects of specific interventions and considered their feasibility, while assuming effects were causal and effect sizes applicable outside pandemic contexts (**Table 1**). We varied target groups from entire population to high-risk groups. We assumed full lockdowns and business and school closures are unacceptable outside pandemics for a rarely lethal disease. We focused on interventions we think are realistic such as wearing facemasks indoors and while on public transport and teleworking, during the months with highest RSV infection rates (November to April). We calculated scenarios with rounded population data from Switzerland—a country with 8 million documented inhabitants, including 80,000 (1%) infants younger than 12 months and 1.5 million (19%) people age 65 and older.[18] We assumed 3% of infants[6, 19] and 0.2% of people age 65 and older are normally hospitalised with an RSV-induced LTRI;[9, 20] 0.1% of infants would need intensive or intermediate care;[7, 21] and hardly any people died (1/year among the whole population).[1] Finally, we assumed 50% of cases could be avoided by the NPI [16]).

In scenario 1, the NPI targets only families with infants, requiring parents to wear facemasks when meeting other people and teleworking from November through April. Scenario 1 prevents 1200 hospitalisations overall with a number needed to treat (NNT) of 67. Thus, 67 couples (134 adults) need to adhere to the NPI to prevent one infant's hospitalisation **(Table 1)**. **In scenario 2**, the intervention targets the entire population of 8 million. With scenario 2, we avoid 3012 hospitalisations (combining infants and older adults) with an NNT of 2657. **Scenario 3** is intermediate and targets families with infants and older adults. Although lower than scenario 2, the NNT is 647, which is still high.

Would people comply with these measures?

Trust in science and governments, perceptions of individual risk, and social acceptability drove compliance with COVID-19 protective regulations.[22-24] During the COVID-19 pandemic, risk perceptions were influenced by death rates, intensive care stays, and perceptions of high vulnerability among individuals or family members. People with chronic diseases [22, 25-27] and parents of high-risk children were shown to comply well with protective regulations.[23] Social norms, with poor compliance when only a few people abide measures, influenced the social acceptability of measures. For instance in Spain, perceptions about family and friends complying with COVID-19 protective regulations led to higher self-compliance.[23] It suggests if we want people to wear facemasks or work from home with managerial approval, measures must be perceived as social norms and followed by most people. In addition, measures during the pandemic were compulsory; however, in the scenarios we describe, measures are voluntary since outcomes are less fatal. Thus, it might be possible that parents of infants at very high risk of bronchiolitis follow seasonally implemented NPIs, yet it is unlikely that the rest of the population complies. An RSV vaccine for pregnant women or infants, which would at least decrease severity of infections, would clearly be easier to administer and thus preferable.

Aside from feasibility, we need to know more about long-term effects from reduced exposure to common viruses and bacteria during the first year of life before thinking about introducing preventive measures on large scales. For example, avoiding contact with common viruses in early life could lead to delayed and more pronounced peaks of infectious diseases such as we observe at the moment. It could also lead to impaired training of the developing immune system and increased incidence of allergic diseases, autoimmune diseases, and other disorders associated with immune dysregulation.[28, 29] This might be less of a problem if protective measures are applied during certain periods, such as winter months, and among subgroups, such as high-risk infants. In summary, future use of non-pharmaceutical interventions against common air-borne viruses at the population-level are clearly worth-while considering, but this needs further research based on well-thought through, collaborative observational and interventional studies.

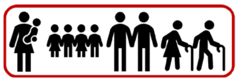
Conflict of interest

Both authors declare no conflict of interest

Financial support

Our research was supported by the Swiss National Science Foundation (SNSF 320030B_192804/1), Switzerland and the Swiss Lung Association, Switzerland (2021-08_Pedersen).

Table 1: Three hypothesized scenarios of non-pharmaceutical interventions (wearing facemasks indoor and teleworking) to prevent hospitalization for RSV.

			
Prevention scenario (target group for intervention)	Scenario 1: Targets infants and their parents	Scenario 2: Targets whole population	Scenario 3: Targets infants, their parents, plus adults aged 65+ years
Intervention	Wearing facemasks and teleworking by parents with infants aged <1yr from Nov. 1st to May 1st	Entire population wearing facemasks and teleworking from Nov. 1st to May 1st	Wearing facemasks and teleworking by parents of infants aged <1yr, and wearing facemasks by adults aged 65+ years from Nov. 1st to May 1st
People targeted by NPI (number and % of population)	240,000 (3%), including 80,000 infants and 160,000 parents	8,000,000 (100%), entire population)	1,760,000 (22%), families with infants and older people
Expected RSV hospitalisations (% of population at risk)	2400 (3% of infants)	6024 (0.08% of total population)	5440 (0.3% of older people)
Prevented RSV hospitalisations (assuming 50% effectiveness)	1200	3012	2720
Absolute risk reduction (ARR)	0.015 (1200/ 80,000)	0.00038 (3012/ 8,000,000)	0.0015 (2720/ 1,760,000)
Number needed to treat (1/NNT)	67	2657	647

Estimations based on the following assumptions: European country similar to Switzerland with 8,000,000 documented inhabitants, 1% aged <1 year, 18% aged 1–17 years, 62% aged 18–64, 19% aged 65 years and older (Demographic information from Switzerland for year 2020[18]); *Effectiveness of NPI = 50%, seasonality cut-offs based on data from Switzerland[30]. Incidence rate of RSV hospitalization per 100,000 person-years: 3000 for infants aged<1 years,[6] 600 for children aged 1–2 years,[6] 130 for children aged 2–3 years,[6] 100 for adults aged 65 years and older,[20] and 0 for rest of population; Abbreviations: ARR Absolute risk reduction (calculated as event rate without NPI minus event rate with NPI), NNT number needed to treat (calculated as 1/ARR).

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