Emerging evidence for non-pharmacologic interventions in reducing the burden of respiratory illnesses

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Received: 19 November 2021 / Accepted: 15 January 2022 / Published online: 4 February 2022
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Abstract
The global pandemic caused by SARS-CoV-2 (COVID-19) has led to significant morbidity and mortality, and unprecedented economic and health system disruption. Non-pharmacologic interventions (NPIs) such as masking and physical distancing have formed the underpinnings of COVID-19 infection control strategies. Concomitantly, numerous jurisdictions have seen a decrease in hospitalizations for non-COVID-19 respiratory illnesses (NCRIs) such as asthma, community-acquired pneumonia, influenza, and chronic obstructive pulmonary disease relative to pre-pandemic levels. These associations give rise to a number of testable hypotheses regarding the efficacy of NPIs in reducing the substantial burden of NCRIs. Here, we review emerging perspectives on the role of NPIs in NCRI prevention with the ultimate goal of informing future research and public policy development as we move into what may be the endemic phase of the COVID-19 pandemic.

Keywords COVID-19 pandemic · Non-pharmacologic interventions (NPIs) · Masking · Physical distancing · Respiratory illness · Viral triggers · Chronic obstructive pulmonary disease (COPD) · Asthma · Influenza · Pneumonia · Hospitalizations

Introduction
The ongoing coronavirus disease 2019 (COVID-19) pandemic has been the source of significant global morbidity and mortality and placed an immense strain on financial and health care infrastructure. Non-pharmacologic interventions (NPIs), such as physical distancing and mask-wearing, implemented to reduce COVID-19 transmission rates have been shown to effectively control disease spread [1, 2]. Concomitantly, a near-eradication of symptomatic influenza has been observed in most global jurisdictions [3, 4]. Similarly, there has been a dramatic decrease in hospitalization rates for patients with acute exacerbations of chronic obstructive pulmonary disease (COPD) and asthma, and non-COVID-19 community-acquired pneumonia (CAP) relative to pre-pandemic levels [5, 6]. However, there have been no randomized studies to date investigating the efficacy of NPIs in preventing respiratory illnesses and it remains unknown as to which specific public health interventions may be most beneficial for prevention. The emerging literature from numerous regions worldwide raises a number of testable hypotheses regarding the effects of relatively simple infection control measures on high burden respiratory illnesses. In this article, we review the current literature on the association of NPIs with reductions in respiratory disease-related hospitalizations and explore potential explanations for this phenomenon. Based on these findings, we provide recommendations for future research and the development of public policy guidelines for the continued use of NPIs in high-risk populations for the purpose of controlling the perennial burden of respiratory diseases.
The natural experiment of the pandemic

Acute and chronic respiratory diseases are among the most significant causes of morbidity and mortality worldwide [7], and are associated with a significant hospitalization rate and extended inpatient stays that negatively impact quality of life in the long-term [6, 8].

Throughout the pandemic, NPIs including masking, physical distancing, and lockdowns have been effective at reducing the transmission of COVID-19 [9–11]. This was recently validated in a large-scale randomized controlled trial (RCT) of 342,000 individuals in Bangladesh which reported a significant reduction in symptomatic COVID-19 among the intervention arm that received community-level mask promotion [2].

A surprising revelation from the implementation of COVID-19-related NPIs has been a concomitant decrease in the number of hospitalizations for other respiratory illnesses [5, 12–16]. Early in the pandemic, the decrease in healthcare utilization was likely contributed to by fears related to nosocomial acquisition of COVID-19, and the perception that hospital were overwhelmed and unable to accommodate nonemergent cases. This was evidenced by a global decrease in hospitalizations for many non-respiratory conditions, including congestive heart failure and diabetes [5, 15, 17]. Concomitantly, there was a decline in elective surgical admissions and procedures as operating rooms closed and surgeons re-deployed to support other clinical services [5, 6, 18].

However, while there was a rapid rebound in the number of surgical admissions and hospitalizations for non-respiratory illnesses a few months into the pandemic [5, 17], healthcare utilization for non-COVID-19 respiratory illnesses has consistently remained low (Fig. 1). In fact, data from the Canadian Institute of Health Information (CIHI) suggests that even accounting for hospitalizations due to COVID-19, there was still a net reduction in the number of total hospitalizations related to respiratory diseases (Table 1) [6, 19]. This is unsurprising, given that NPIs are effective at stemming the spread of viral agents [9–11], which are the most commonly identified triggers of both acute respiratory illnesses and exacerbations of chronic airway diseases including COPD and asthma [20, 21]. In many ways, the institution of public health measures in response to the pandemic has served as a natural experiment into the efficacy of NPIs in preventing the spread of common respiratory viruses.

Worldwide decrease in non-COVID-19 respiratory illnesses

The decreased burden of non-COVID-19 respiratory illness has also been reported in numerous regions internationally. A recently published systematic review and meta-analysis by Alqahtani et al. examined the relationship between COPD exacerbations and NPI’s during the COVID-19 pandemic [12]. Thirteen studies were included, consisting of 15,677 patients from 9 countries [12], and pooled results showed a rate ratio of 0.50 [95% confidence interval (CI): 0.44–0.57] for COPD exacerbation-related hospital admissions.

Three of the studies included in the meta-analysis specifically evaluated reduction in respiratory viral infections (RVIs) [13, 14, 22]. In a study from Singapore, the incidence rate ratio (IRR) was 0.35, with an absolute decrease of 60% in admissions for acute exacerbations of COPD when comparing the pre-pandemic and pandemic periods [13]. Similarly, a study from Korea reported that influenza-related hospitalizations in patients with pre-existing COPD and asthma were reduced by 73% and 83%, respectively [14]. Finally, a study from Hong Kong found that there was a 52% decrease in the detection of influenza A/B and that this corresponded with a concomitant 55% decrease in admissions for COPD exacerbations [22]. Together, the findings of these studies suggest that reducing viral infections may be linked to a reduction in COPD exacerbations [12], and that NPIs used during the pandemic period may be used to effectively reduce COPD exacerbations.

Future directions

As we look towards the possibility of a post-pandemic future, applying these preliminary findings on NPIs and the burden of respiratory illnesses will become increasingly important. At present, there is a paucity of literature evaluating the effects and acceptability of NPIs on disease-specific mortality with most studies from the pre-pandemic period
having focused on interventions such as pulmonary rehabilitation, supplemental oxygen, and surgery [23]. Therefore, we provide the following recommendations on how focused studies may address current gaps in the literature.

Firstly, the substantial worldwide decrease in hospital admissions for acute respiratory illnesses [6] must be confirmed and linked to robust disease-specific mortality data. Research can be directed towards evaluating NPIs, looking at timelines for mandated measures, changes in intensity, and subsequent effects on the hospital burden of respiratory illness via a time-series analysis. A limitation of current epidemiological data is that NPIs are often considered as a whole due to the overlap in the timeline for implementation of different interventions. The use of time-series analyses will help determine whether specific NPIs have different effects and which interventions are most effective at preventing viral transmission. Since the common viral triggers can differ based on disease type and patient demographics, this would also allow for the implementation of more targeted NPIs for different subsets of the population. Additionally, RCTs involving individuals at high risk for developing CAP or those who suffer from lung disease are needed to evaluate the efficacy of interventions such as masking on patient mortality, rates of hospitalization, and quality of life outcomes. Current evidence suggests that the efficacy of NPIs may be based more on their ability to work as a source control strategy than as personal protective equipment [24]. Therefore, randomized studies will also be required to answer the question of whether the recently demonstrated benefits of NPIs can still be attained when implemented in a selected group of patients, rather than at a population level.

Second, if there is a true effect of NPIs on the burden of non-COVID-19 respiratory illnesses, it is worthwhile considering how policies should be framed in response to this. While high quality research will help guide future evidence-based public health policies and decision making, this will take time. For example, a well-designed RCT may take several years to complete. Furthermore, as variable definitions exist for terms such as “personal protective equipment” and “medical/surgical apparatus,” production standards can vary between various regions. This may pose a challenge in replicating the findings of RCTs across diverse regional and global demographics [25].

In the interim, policy-makers can evaluate current observational data and consider whether the implementation of masking measures is appropriate for patients with chronic lung diseases, those at high-risk of developing CAP, or for individuals in direct contact with them. These recommendations may be revisited and revised in the future, but voluntary measures, even on an interim basis, may help protect at-risk populations.

Finally, as with any medical intervention, it is necessary to balance the purported benefits with due consideration of any collateral risks and harms. This includes the potential dangers of masking as a mechanism for selecting out increasingly virulent viral illnesses such as those caused by respiratory syncytial virus (RSV) or influenza, as has been observed in numerous global jurisdictions following the relaxation of NPIs [26–30]. By preventing exposure, NPIs have increased the proportion of RSV-susceptible children in the population, who may be vulnerable to more serious infection if exposed at an older age when protection from maternal antibodies is no longer present. Similarly, in the case of influenza, the annual refresh of immunologic memory may serve as a barrier to the emergence of highly virulent strains from the zoonotic reservoir. Therefore, the use of

| Cause of hospitalization | Pre-pandemic period (# cases)a | Pandemic period (# cases)b | Differencec |
|--------------------------|-------------------------------|---------------------------|-------------|
| Controls                 | Major cardiac cause           | 71,455                    | 62,249      |
|                          | Gastrointestinal cause        | 70,675                    | 62,712      |
| Non-COVID-19 respiratory illnesses | COPD                             | 47,130                    | 29,111      |
|                          | Non-COVID-19 pneumonia (NCP)  | 51,310                    | 32,664      |
| COVID-19                 | COVID-19                      | 0                         | 21,912      |
| Total hospitalizations due to COPD, NCP & COVID-19 | –                                    | 97,440                    | 83,687      |

aMarch 2019–December 2019
bMarch 2020–December 2020 for non-COVID-19 respiratory illnesses and controls. January 2020–December 2020 for COVID-19

cP value calculated by comparing the incidence rate ratios using a non-parametric paired t test (Wilcoxon matched-pairs test). Analysis conducted with GraphPAD Prism software (version 5.02 for Windows, San Diego, California, USA)
NPIs beyond the pandemic period may have the potential to exacerbate future viral epidemics and protect some individuals while harming others. Widespread masking also has the potential to overwhelm medical waste disposal infrastructure, leading to the accumulation of masks in our landfills and oceans [31]. Additionally, if future studies reveal that more stringent NPI measures such as lockdowns are required to achieve desired efficacy, the benefit of preventing disease spread will have to be carefully weighted against the adverse impacts these measures may have on mental health and social inequity [32, 33].

Conclusion

In this article, we have presented evidence that the measures instituted globally to control the spread of COVID-19 have unexpectedly contributed to marked and sustained reductions in hospitalizations for non-COVID-19 respiratory illnesses. Additionally, we have laid out next steps that could help us better understand which NPIs have played the most significant roles in the observed reduction of non-COVID-19 respiratory diseases. It remains unclear whether these benefits were achieved with masking interventions alone or are also reliant on more stringent physical distancing measures related to the closure of establishments and restrictions on social gatherings and travel. Evaluation of which specific measures carry the highest yield, under what conditions they are most effective, and their potential for collateral adverse effects, will be crucial in guiding policy development. Due to the limitations of the current evidence base, including the lack of studies evaluating the effect of NPIs on mortality-related outcomes, the consideration of patient preferences will also be important in implementation.

Given reasonable evidence from the COVID-19 pandemic, policy-makers should consider empiric public health measures for individuals at high-risk of contracting viral respiratory illnesses or suffering from adverse outcomes as a result. Such policies will likely face barriers to widespread adoption including hesitancy to embracing masking and other NPIs on a voluntary basis, the association of these measures with repressive lockdown policies, and skepticism regarding their efficacy [34]. While the use of NPIs is now variable and may only transiently persist in the early post-pandemic period, it is also possible that people may continue to use them on a more routine basis as has been observed in many Asian countries.

Nonetheless, the recommendations highlighted in this analysis provide a basis for a research agenda which will aid in more conclusively determining the relative risk and benefits of selective NPI implementation on the burden of respiratory illnesses and their sequelae. We hope that relevant stakeholders will engage in elucidating the veracity and relevance of what may be the key learnings of the global COVID-19 pandemic.

Acknowledgements

We thank the Canadian Institute for Health Information (CIHI) for the use of primary data on respiratory disease hospitalizations. We would like to acknowledge Satchel Krawchuk (Emergency Strategic Clinical Network) for assisting in performing the literature review for this article.

Authors contribution

RAK performed the primary data analysis and constructed the figures. RAK, AT, and ESL drafted the manuscript. AA and MAP critically reviewed the manuscript for important scientific content. All authors approved the final version for publication.

Declarations

Conflict of interest

The authors declare no conflicts of interest.

Human and animal rights

No human and animal studies were conducted, as this article reports on a literature review and summary of previously published primary data only.

Informed consent

Not applicable to this literature review article, as no human participants were involved.

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