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COMMENTARY

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Circulating multiple respiratory viruses alongside SARS-CoV-2 variants: An open call for vaccine vendors

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Introduction

A small cluster of novel viral pneumonia cases from Wuhan, China in 2019 evolved into a great pandemic ever [1,2]. COVID-19, caused by SARS-CoV-2 virus, impacted countless population worldwide and its long-term consequences are yet unclear. On March 11, 2020, the World Health Organisation (WHO) declared COVID-19 as a global pandemic with most of the research diverting its attention to understanding the etiology, pathology and immunology of the fairly unknown pathogen and developing measures to counter it [2]. The ongoing scenario depicts a modest increase in COVID-19 cases and hospitalisation, and dramatic rise in cases in the monthof January 2023 worldwide (https://covid19.who.int/) [3].

Numerous restrictions at local, regional and global levels were imposed to curb the spread of COVID-19 and acquire time to develop effective medical interventions since its insurgence. Nations imposed multiple stringent lockdowns and shutdowns, and encouraged social distancing to limit human-to-human contact. The measures included masking in public places, regular hand washing and sanitising, quarantine, etc. [4]. 'Work-from-home' trended and Global travelling was stalled [5]. While these helped curb transmission, there were many medical side-benefits too. The instances of the spread of other respiratory pathogens like RSV, influenza virus, parainfluenza viruses (including measles) notably decreased particularly in the early 2020 [5,6]. Another startling result was a decrease in food-borne infections and sexually transmitted infections in Spain [7]. Epidemiological studies in numerous countries have shed light on the serious impact of viral coinfections. Research conducted in the UK revealed that influenza and SARS-CoV-2 coinfections increased the mortality risk. Similar concerns were in Iran, Egypt and Saudi Arabia too, where hospitalisation and mortality rates increased due to coinfections with influenza or other respiratory viruses. On the contrary, data also hinted at 'viral interference' wherein one viral infection might actually reduce infection risk by another. That healthcare facilities were predominantly occupied in managing COVID-19 during the pandemic is another plausible reason that potentially resulted in underreporting and consequently underestimation of the actual number of cases [6,8].

RSV accounted for a considerable annual morbidity and mortality especially among the pediatric in the pre-COVID normal situations. RSV infection caused an average 3.2 million hospitalisation and over 110000 deaths annually [9]. An average of about 3.6 million (2.9-4.6 million) hospital admissions RSV-infected children between 0 and 60 months in 2019 were reported, especially in the low and middle income countries [10]. The cases declined in March-April 2020, as schools closed and children were home-contained. Even giving the benefit of doubt to the diagnosis bias, pediatric hospitalisation for severe respiratory infections reduced, supporting this [8].

There was a sudden surge of RSV infection in children in 2021, setting in early before season instead of the usual winter peak, possibly attributed to a reduced immunity against RSV [4,9]. As RSV doesn't have a recommended vaccine nor did the children inherit passive immunity, the 'disease lag' of earlier year might have been compensated in 2021. Countries like New Zealand, Australia and the US reported an upward trend of RSV cases [4]. International travelling was opened up by New Zealand to Australia in April 2021 resulting in a remarkable increase in RSV cases [11]. A New Zealand study pointed to a possible RSV-transmission by adults [8]. Instances of carriage and transmission of RSV disease by the adults need to be critically analysed [8].

Influenza is a respiratory ailment with an infection pattern similar to RSV. As it spreads by direct touch, airborne or droplet infection, non-medical (appropriate behaviour) interventions like hand-washing, sanitising and face-masking seemed effective in limiting transmission. However, routine influenza vaccination is available unlike RSV [4]. The CDC noted early influenza season and increased instances in 2021-2022, hypothesising that respiratory infection might increase severity of infection further [3]. For example, Influenza A increases COVID-19 susceptibility. This is worrisome as it may lead to novel dreaded strains with increased severity of disease [12].

Infections and management

Triple endemic of respiratory (influenza, COVID-19 and RSV) viruses is reported. Reported early onset of influenza and RSV

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cases seem to have doubled, occurring earlier than usual season [3]. Such trends point to a complex transmission interplay of respiratory aetiological agents. Though non-medical interventions seemed to protect and counter infections, a rapidly increasing trend followed later. Long-term implications of COVID-19 pandemic and the effect on other viruses are still hazy and need proper vigilance. It is to note that, seasonal patterns of respiratory viruses have blurred with cunning overlapping that needs differential inclusion. It will guide the clinician in general and pediatricians in particular to prescribe effective treatments and reduce criticalities due to late diagnosis or, more importantly, misdiagnosis [4-6, 8].

Circulating multiple viruses during COVID-19 pandemic era could increase the respiratory tract infection risks. The impact of SARS-CoV-2 coexisting with the circulating respiratory viruses on the human health remains to decipher. Depending on geographical regions, interactions between the viruses may influence infection dynamics. Human bronchial epithelial cell was infected with SARS-CoV-2 alone and co-infected with IAV and RSV in vitro to determine the interactions between SARS-CoV-2, Influenza a Virus (IAV) and RSV [13]. It was observed that replication of SARS-CoV-2 inhibited IAV and RSV. Both SARS-CoV-2 and IAV are zoonotic pathogens primarily infecting the respiratory tract, exhibiting mild to severe to fatal clinical symptoms. Clinical outcomes of coinfections involving these viruses are concerning. Studies suggest that while SARS-CoV-2 did not hinder IAV replication, it was not true in reverse scenario [14,15]. SARS-CoV-2-IAV coinfection resulted in prolonged, severe pneumonia in hamsters [16].

Prevailing seasonal viral respiratory tract infections appear to reduce the SARS-CoV-2 infection rate. Hospitalisation and intensive care may be needed in SARS-CoV-2-IAV co-infected patients with severe complications. An earlier study found a 58% decrease in SARS-CoV-2 infections among IAV-positive patients but an increased fatality risk (5.92, CI: 3.21–10.91) among co-infected individuals as against those infected with either [17]. An in vitro study involving RSV-SARS-CoV-2 co-infected nasal human airway epithelial cells revealed that RSV did not interfere with SARS-CoV-2 replication unlike IAV, as reported earlier [18,19]. The in vitro study using human cervical carcinoma (HEp2) cells and an in vivo study on mice demonstrated that IAV-RSV co-infection inhibited RSV replication [20]. Such findings emphasise the complexity of SARS-CoV-2 co-infections and mandate further insights.

Factors like age, sex, comorbidity, frailty, lifestyle, genetic make-up, virus variant, co-infection and individual immunological status influence the clinical course and outcome of SARS-COV-2 infection [21]. Thus, an understanding of the effect of respiratory co-infection or super-infection involving bacteria, viruses, parasites and fungi seems low. In a clinical course and outcome study of SARS-CoV-2 co-infection with rhinovirus and adenovirus, a high 30-day mortality among SARS-CoV-2 patients co-infected with rhinovirus was observed as compared to SARS-CoV-2 infection alone (8/23 (34.8%) vs 8/69 (11.6%); p≤0.02) [22]. Co-infected cases were low on biochemical and inflammatory indicators like C-reactive protein, alanine transaminase and aspartate transaminase without a correlation between SARS-CoV-2 patients or co-infected with adenovirus (Figure 1).

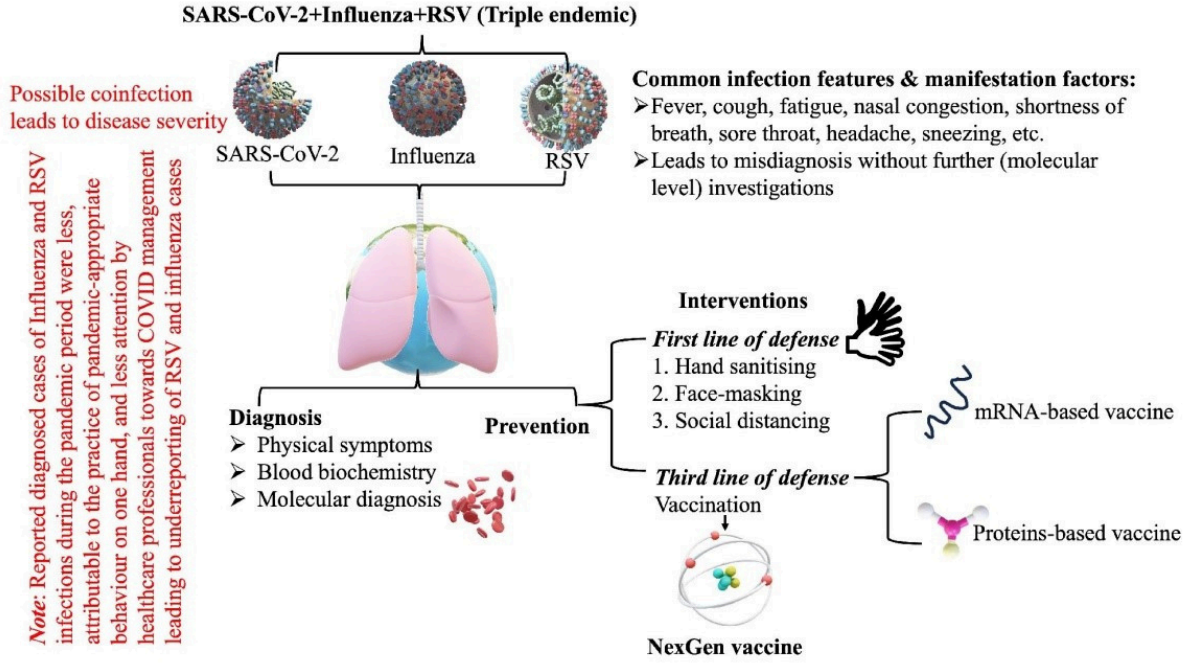

Figure 1. Graphical presentation of triple endemic respiratory infection, its diagnosis and the suggested preventive measures.

The rise of the triple epidemic highlighted the need for more cohesive vaccination and monitoring. Combinatorial (multivalent) vaccines to tackle both SARS-CoV-2 and influenza are under investigation, a smarter way to reduce the disease burden and load on healthcare facilities. Enhanced diagnostic tools to diagnose respiratory pathogens and facilitate the timely and accurate medical care were essential. Focusing on high-risk groups like the elderly, those with weakened immunity, children, etc. in vaccination efforts was especially important [22]. Respiratory virus co-infection especially during the monsoon may be imminent, and this could increase disease severity, complications and high mortality .

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Trend assessment of Influenza virus through COVID-19 pandemic in over 20 countries including India since 2019 through an elaborate population-based study demonstrated alternating viral predominance [23]. The infection was significantly regulated through viral interference wherein SARS-CoV-2 prevailed that lowered the risk of Influenza and vice versa. 1000 patients screened for SARS-CoV-2 co-infected with other respiratory viruses returned 2% co-infection prevalence, and that co-infection and disease severity were not correlated [24]. An Iranian study among SARS-CoV-2 co-infected patients revealed percent mortalities at 22.3% with IAV, 2.9% with IBV and human metapneumovirus, 9.7% with bocavirus, 1.9% with adenovirus, 9.7% with RSV and 3.9% with parainfluenza virus [25]. An Egyptian study on the severity and clinical course of SARS-CoV-2 in co-infected patients noted an increased severity with an incremental 70% hospitalisation and 20% fatal outcome cases, at 69.2% with IAV and 17.3% with IBV [26]. A Saudi Arabian study showed a 71% higher microbial co-infection rate with IAV, Chlamydia pneumoniae and human adenovirus among the SARS-CoV-2 infected [27]. It revealed that virus infection had higher mortality (OR 1.78, CI: 0.38–8.28) than bacterial infection (OR 0.44, CI: 0.08–2.45) in the co-infected.

Studies on the novel anti-SARS-CoV-2 agents highlight significant progress in developing broad-spectrum antiviral therapeutics. Ensitrelvir (S-217622) is a potent Uridine analogue that not only targets the main protease (Mpro) of SARS-CoV-2 but also exhibits strong inhibitory effects on conserved replication enzymes like RdRp and ExoN, at nanomolar EC_{50} values and with favourable pharmacokinetics. Similarly, Doramapimod (a p38 MAPK inhibitor) showing stronger binding affinity than Molnupiravir's active metabolite and offering dual antiviral and anti-inflammatory effects was repurposed to target RdRp, making it ideal to address both viral replication and cytokine storms in COVID-19. These collectively provided promising arsenals of broad-spectrum agents to inhibit multiple conserved SARS-CoV-2 enzymes, with a potential to protect against future Coronavirus attacks, across variants [28-33]. Seasonal viral infections continue to pose significant healthcare challenges as the aftermath of SARS-CoV-2 pandemic. Studies in mammals indicated that dual vaccination alleviated SARS-CoV-2 and IAV/H1N1 coinfections associated complications. Thus, developing a combined SARS-CoV-2 and influenza A virus (IAV) vaccine was particularly advisable for geriatric, immunocompromised and debilitated populations to mitigate the infection-related complications and minimise the risk of heightened disease severity [34].

Conclusion

Converging SARS-CoV-2, influenza and RSV infections underscore the complexity of viral interactions and their collective impact on public health. Evidence suggests that dual or combined vaccination strategies, particularly against SARS-CoV-2 and influenza A, not only mitigated complications but might also reduce the severity of coinfection outcomes. The in vitro, in vivo and clinical studies observations highlight the potential of viral interference, where one modulated the replication dynamics of the other. However, unpredictability of such interactions necessitates fail-safe surveillance and deeper mechanistic insights. From preventives perspective, prioritising vulnerable groups like the elderly, the immunocompromised and with comorbidities remains crucial. Development of multivalent vaccines and broad-spectrum antivirals , alongside enhanced diagnostic capabilities, could serve as pivotal strategies to curb the burden of seasonal and respiratory viruses. Integrating these measures into global healthcare preparedness was essential to minimise morbidity, mortality and the burden on healthcare systems.

Disclosure Statement

No potential conflict of interest was reported by the author.

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