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Review Article

Changing epidemic patterns of infectious diseases during and after COVID-19 pandemic in Taiwan

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Abstract Mitigation measures aimed at curbing the transmission of the severe acute respiratory syndrome coronavirus 2 effectively suppressed the occurrence of many respiratory infections other than coronavirus disease 2019. Several infections experienced a resurgence following the relaxation of non-pharmaceutical interventions, surpassing pre-pandemic levels in Taiwan. This phenomenon, known as immune debt, primarily affected respiratory infections in young children, including respiratory syncytial virus (RSV) infection. Infections transmitted by means other than droplets or contact did not exhibit significant changes in their epidemic patterns, such as varicella and Japanese encephalitis. Alterations in seasonality were noted for RSV infection and influenza, and these changes are also linked to immune debt. The recent emergence of severe pediatric pneumonia in northern China may be associated with immune debt and the rise of macrolide-resistant *Mycoplasma pneumoniae* associated with severe illness.

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic strikes the whole world since the beginning of 2020. Resulting in devastating medical and economic impacts.[1–4] Many interventions are strictly applied to limit the spread of COVID-19, including mask wearing, reinforced hand hygiene, physical distancing, school closure, and contact tracing and isolation of patients.[2,5–10]

These mitigation measures not only curtailed the transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) but also affected the spread of other respiratory pathogens.[11–14] Pathogens that exhibited a notable decline in incidence following the onset of the COVID-19 pandemic include respiratory syncytial virus (RSV), influenza virus, human coronavirus, parainfluenza virus, human metapneumovirus, adenovirus, enterovirus, and pneumococcus.[11–16] However, there were variations in the epidemic changes of respiratory infections during the early pandemic phase across different countries. In Taiwan, for example, RSV, rhinovirus, and adenovirus continued to be prevalent,[11,13,14] potentially attributed to the highly successful control of SARS-CoV-2 spread in the early phase,[2,9] coupled with relatively lax restrictions compared to other countries. The non-pharmaceutical interventions adopted during the COVID-19 pandemic exhibited varied impacts on the epidemic patterns of different infectious diseases.

Epidemic changes of notifiable infectious disease in Taiwan

Taiwan effectively controlled the spread of COVID-19 during the early phase of the pandemic.[2,9] Non-pharmaceutical interventions to mitigate SARS-CoV-2 transmission were gradually eased starting in April 2023.[17] Extracting data from the notifiable infectious disease reporting system database in Taiwan[18] and defining the COVID-19 pandemic period as 2020 to 2022, we observed a significant decrease in the incidence of several notifiable infectious diseases during the pandemic, including influenza with complications, invasive pneumococcal disease (IPD), pertussis, and severe enterovirus infection (Fig. 1, Fig. 2).[18] All differences between the pre-pandemic and pandemic periods were statistically significant, as determined by the Mann-Whitney U test.

The definition of severe enterovirus infection is as follows: The case must meet at least one of the following three criteria: 1. Presence of typical hand, foot, and mouth disease or herpangina, along with severe complications; 2. Respiratory infection symptoms accompanied by brainstem encephalitis or acute flaccid myelitis, suspected to be caused by enterovirus infection; 3. Infants within three months of age presenting with signs of sepsis, such as myocarditis, hepatitis, encephalitis, thrombocytopenia, or multiple organ failure. Contrary to the common belief that enterovirus is mainly transmitted through the fecal-oral route,[19] the significant decrease in severe enterovirus infection during the pandemic suggests that the major transmission route for enterovirus is likely similar to that for COVID-19 and influenza, i.e., through droplet and contact transmission.

Various respiratory virus infections, including minor infections other than influenza and COVID-19, can predispose to pneumococcal infections. Studies showed that the pneumococcal carriage in young children did not change significantly during the pandemic, even though the incidence of pneumococcal infection had decreased remarkably.[15,16] The reduced pneumococcal infections were apparently due to the suppression of respiratory virus

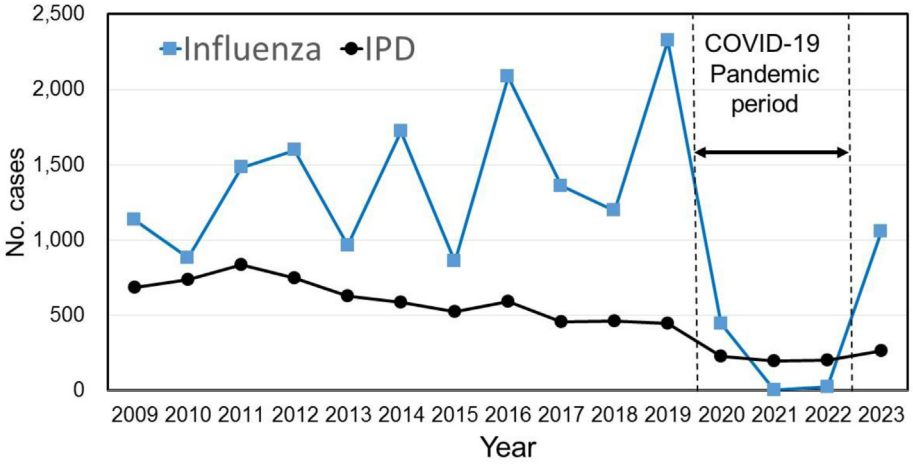

Figure 1. Annual reported cases of invasive pneumococcal disease and severe influenza in the database of notifiable infectious disease reporting system in Taiwan.[18] IPD, invasive pneumococcal disease.

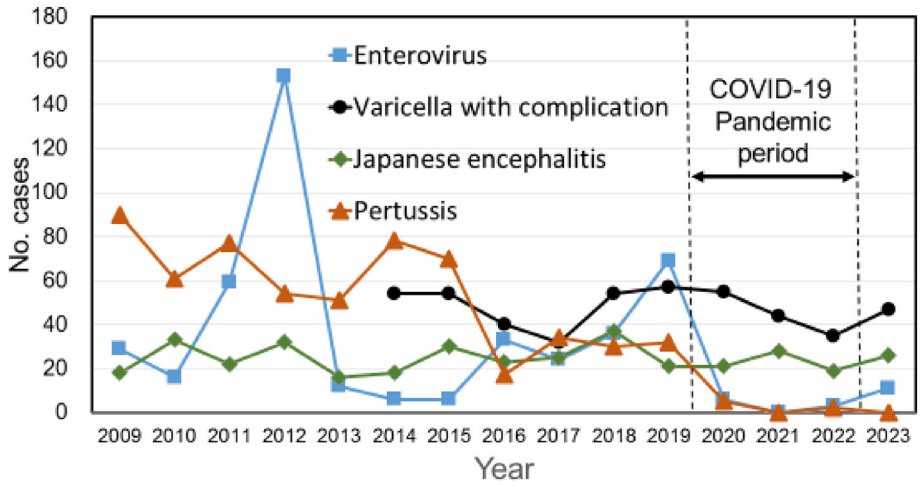

Figure 2. Annual reported cases of severe enterovirus infection, varicella with complication, pertussis, and Japanese encephalitis in the database of notifiable infectious disease reporting system in Taiwan.[18] Data of varicella with complication were not available before 2014 because the reporting requirement started in 2014.

infections that may be complicated by pneumococcal infections.[15,16] On the other hand, rhinovirus infection and other minor viral respiratory infections still prevail during the pandemic,[11,14] resulting in a comparatively modest reduction in reported IPD in Taiwan.

Reported number of cases with Japanese encephalitis and varicella with complication did not fluctuate before, during, and after the implementation of non-pharmaceutical interventions (Fig. 2). Japanese encephalitis is a mosquito-transmitted infection inherently unaffected by non-pharmaceutical interventions.[20] The finding of a relatively stable epidemic curve for varicella with complications contrasts with observations in other reports.[21,22] We have had relatively good control over COVID-19 transmission in Taiwan, especially during the early phase of the pandemic.[2,9] As a result, the non-pharmaceutical interventions adopted in Taiwan were less stringent than those in other countries, and person-to-person contact was not strictly prohibited. This may explain the different impact of COVID-19 on varicella epidemiology in Taiwan.

Varicella is believed to be efficiently transmitted via the airborne route.[23,24] Although the varicella-zoster virus can survive in the environment for a few hours,[25] our data suggest that transmission through direct or indirect contact may be more efficient.

Immune debt

During the pandemic, numerous individuals might not have had the opportunity to develop immunity against certain respiratory tract infections, rendering them susceptible to various respiratory pathogens. This phenomenon is referred to as "immune debt," and it is expected to be associated with a resurgence of infectious diseases with a larger epidemic in the post-pandemic era.[12,26,27]

Following the relaxation of COVID-19 mitigation measures, several infectious diseases experienced a resurgence, including RSV infection, influenza, enterovirus infection, and various other viral infections.[12,26,28] Influenza activity did rebound after the easing of restrictions but did not surpass baseline levels in most reports.[12,28] This trend is also observable in Taiwan (Fig. 1). Unlike other respiratory tract infections that are more prevalent in young children, influenza can affect individuals across all age groups, explaining why influenza is not associated with the concept of "immune debt." The phenomenon of "immune debt" is primarily observed in young children. A similar pattern was observed for enterovirus infection, where affected children increased but remained at approximately pre-pandemic levels after the loosening of restrictions (Fig. 2).[29,30] Enterovirus infection may affect older children,[19] which could be a reason why a higher-than-expected epidemic did not occur after COVID-19 pandemic.

A true "immune debt," that is a larger post-pandemic epidemic than the pre-pandemic epidemic, is observed only in young children. In Japan, the largest annual increase in RSV cases since monitoring began in 2003 was reported for 2021.[31] After partial relaxation of New Zealand's strict border closure policy in April, 2021, the incidence of RSV hospitalization in 2021 was three times higher than the average of peaks in 2015–19.[32] The surge in RSV cases in Australia occurred in late 2020, surpassing the seasonal peak median observed from 2012 to 2019. The median age of RSV hospitalized patients increased significantly in 2020 than the median age of patients observed between 2012 and 2019.[33] A study in Italy showed a larger than expected epidemic of respiratory infections in children from June to October 2021, including infections caused by RSV, parainfluenza virus, rhinovirus/enterovirus, metapneumovirus, human coronavirus, and adenovirus.[34]

In England and Germany, the incidence of IPD in children was observed to be higher in 2021 compared to the pre-pandemic years of 2017–2019. Both reports noted that the incidence of IPD surpassed pre-pandemic levels primarily in young children rather than the older population.[35,36] In Taiwan, the overall incidence of IPD increased after the relaxation of non-pharmaceutical interventions but did not exceed the pre-pandemic level (Fig. 1). This observation emphasizes again that immune debt is particularly evident in young children.

The altered epidemic pattern of infectious diseases after the pandemic represents not only a shift in disease burden but also a change in seasonality. Typically, RSV peaks during cold seasons in temperate areas and is more prevalent during rainy seasons in subtropical and tropical areas.[37,38] Reports of out-of-season RSV resurgences emerged from both the southern and northern hemispheres after a subdued winter during the COVID-19 pandemic.[26,28,39,40] The post-COVID-19 pandemic seasonal patterns of influenza were unusually late and protracted.[27,41,42] The shift in seasonality of RSV and influenza may also be explained by immune debt. An increase in population susceptibility coupled with the relaxation of non-pharmaceutical interventions may override the mitigating effects of higher temperatures, enabling viruses that were once prevalent in the cold season to persist in warmer seasons as well.[43] A comparable phenomenon was observed during the 2009 H1N1 influenza pandemic, which began in the summer months due to the lack of effective immunity among the population.[44] A delayed onset of the RSV epidemic also occurred in the aftermath of the 2009 H1N1 influenza pandemic.[45]

Epidemic change of *Mycoplasma pneumoniae* infection

In early 2020, the introduction of non-pharmaceutical interventions also resulted in an abrupt ending of *Mycoplasma pneumoniae* epidemic worldwide. A further reduction in the incidence of *M. pneumoniae* infection was observed in 2021—2022 when other respiratory infections had resurged. After 2023, a prospective surveillance data showed a delayed re-emergence of *M. pneumoniae* globally more than 3 years after the introduction of COVID-19 pandemic restrictions. The incidence of *M. pneumoniae* infection did not exceed the pre-pandemic level.[46] The absence of a true immune debt for *M. pneumoniae* infection may be due to the fact that the infection prevails in older age groups than that of other respiratory infections.[47,48]

Surge of pediatric pneumonia in northern China

In the late 2023, a surge of pediatric pneumonia that overwhelmed pediatric emergency services was reported by several hospitals in Northern China, including Beijing and Liaoning. Medical authorities and news media began to speculate on the cause of these outbreaks, including the possibility of a new emerging new pathogen or a new virulent mutant of SARS-CoV-2.[49] Chinese health authorities claimed that this was a seasonal peak in a trend of rising respiratory infections in children, including *Mycoplasma pneumoniae*, influenza, RSV, adenovirus, and SARS-CoV-2.[26,50,51]

The predominant cause of pediatric pneumonia requiring hospitalization in China appears to be mycoplasma pneumonia.[51] *M. pneumoniae* commonly underlies "walking pneumonia" in children, a typically mild condition.[51] The estimated basic reproduction number of *M. pneumoniae* is 1.7, indicating low transmissibility and a low likelihood of causing a large epidemic.[52] It is unusual that during the epidemic in Northern China, a considerable number of children with *M. pneumoniae* infection required hospitalization, placing a strain on pediatric emergency services in the country.

Macrolide resistance and severe mycoplasma infection

Surveillance of *M. pneumoniae* infection in China revealed a decrease in incidence during the COVID-19 pandemic.[53] A resurgence of mycoplasma infection is anticipated in the post-COVID-19 era. Notably, a distinguishing feature of *M. pneumoniae* in China is a remarkably high macrolide resistance rate ranging from 50% to 90% in hospitalized patients, with some reports even indicating a 100% resistance rate.[54,55] In contrast, the macrolide resistance rate of *M. pneumoniae* is relatively low in Western countries.[54]

While controversial, the emergence of macrolide-resistant *M. pneumoniae* is linked to more severe mycoplasma infections. In recent years, the prevalence of macrolide resistance in *M. pneumoniae* in Taiwan has increased, reaching around 70%—80% in strains isolated from hospitalized children.[56—59] While most mycoplasma infections are mild and do not necessitate hospitalization, some individuals experience significant respiratory distress requiring oxygen therapy and intensive care, especially among younger children.[47,60,61]

Two fulminant children requiring extracorporeal membrane oxygenation were reported in Taiwan.[57] A report from China showed that severe clinical and radiological features, and extra-pulmonary complications were more frequently associated with macrolide-resistant *M. pneumoniae*.[62,63] An outbreak of macrolide-resistant *M. pneumoniae* infection in a Nebraska long-term care facility resulted in 12 admissions and 7 deaths.[64] Mycoplasma pneumonia is no longer necessarily synonymous with "walking pneumonia."

Given the evolving resistance patterns and clinical characteristics, *M. pneumoniae* in children is poised to become increasingly significant and challenging to treat in the future. In addition to the resurgence of respiratory tract infections in the post-COVID-19 era, the recent atypical surge in pediatric pneumonia cases in China may also be attributed to the emergence of macrolide-resistant *M. pneumoniae* and the ensuing severe illness it causes. This presents a cause for concern in the medical field, warranting vigilant surveillance.

Conclusion

Mitigation measures implemented to control the transmission of SARS-CoV-2 effectively suppressed the occurrence of various respiratory infections, distinct from COVID-19. Epidemics of several respiratory virus infections experienced a resurgence on a larger scale than that observed in the pre-COVID-19 era. This phenomenon of immune debt primarily affected young children. The emergence of severe pediatric pneumonia in China may be attributed to immune debt and the concurrent rise in severe illness, accompanied by an increasing incidence of macrolide-resistant *M. pneumoniae*.

CRediT authorship contribution statement

Ping-Ing Lee: Conceptualization, Data curation, Validation, Writing — original draft, Writing — review & editing. **Po-Ren Hsueh:** Conceptualization, Writing — review & editing. **Jen-Hsiang Chuang:** Data curation, Validation, Writing — review & editing. **Ming-Tsan Liu:** Data curation, Validation, Writing — review & editing.

Declaration of competing interest

The authors declare that they have no conflicts of interest.

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