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Title: Resurgence of Death from Respiratory Infections after COVID-19 Pandemic

Running Title: Resurgence of Respiratory Infection Deaths

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Clinical Question Box

How did the COVID-19 pandemic affect deaths from respiratory infections such as Influenza and invasive pneumococcal diseases, and did mortality rates change after the pandemic?

Due to strict control measures, the COVID-19 pandemic led to a significant decrease in deaths in Japan. However, after these measures were relaxed after the pandemic, mortality rates from both diseases increased. This highlights the importance of monitoring and maintaining infection prevention strategies to manage future outbreaks.

Abstract

Introduction: Numerous studies have reported a global decline in respiratory infection-related deaths during the COVID-19 pandemic. This decrease was primarily attributed to implementing precautionary measures and changes in public behavior. However, respiratory infections have increased since the pandemic ended, and normal social activities have resumed.

Methods: Data from e-Stat, Japan's official database, covered influenza (2011–2024) and invasive pneumococcal diseases (2013–2024). The study period was divided into pre-pandemic, pandemic (April 2020–September 2021), and post-pandemic eras. The Mann-Whitney U test was used for comparisons.

Results: Influenza-related deaths declined sharply during the pandemic era compared to the pre-pandemic period ($P < 0.001$), dropping from 3,353 in 2019 to 19 in 2022. However, mortality increased in the post-pandemic era, reaching 1,220 by mid-2024 ($P = 0.005$). Similarly, deaths from invasive pneumococcal diseases decreased significantly during the pandemic ($P < 0.001$) but rose again in the post-pandemic era.

Conclusion: The COVID-19 pandemic significantly reduced deaths from influenza and invasive pneumococcal diseases due to public health measures. However, there has been a noticeable resurgence in these deaths after the lifting of most restrictions. Ongoing

monitoring and the maintenance of basic infection prevention measures are crucial to prevent future outbreaks.

Keywords: COVID-19, Influenza, Mortality, Pneumococcus, Surveillance study, Epidemiology

Introduction

The pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in December 2019 and rapidly escalated into one of the most severe global health crises in modern history. Policymakers worldwide have implemented stringent mitigation strategies such as national lockdowns and mandatory quarantine measures. In Japan, the first confirmed case was reported in January 2020, and the government declared a state of emergency in April 2020. This enforcement had few legally binding measures and relied on voluntary public cooperation, encouraging people to minimize social contacts by emphasizing the importance of non-pharmaceutical interventions, such as wearing masks, hand hygiene, and social distancing.[1] As the pandemic spread and overwhelmed public healthcare systems across the world, there were concerns that the seasonal outbreaks of traditional respiratory infections would overlap with the ongoing pandemic and further strain these systems. Nonetheless, various researchers have reported that these respiratory deaths notably decreased during the pandemic.[2,3] According to Chang et al.(2020), in Hong Kong, the number of deaths from laboratory-confirmed influenza in adults was 113, which is significantly lower than the average of 299.8 deaths per year during the period from 2015 to 2019.[4] Moreover, in Japan, death cases of invasive pneumococcal diseases declined by 98.5% during the

pandemic.[5] This decrease is largely attributed to the high level of health awareness, as well as the basic infection prevention measures.

However, respiratory infections are increasing again as the COVID-19 pandemic ends.[6] This issue extends beyond Japan and represents a global issue that demands immediate action. Despite this concern, there are no nation-wide reports clearly indicating a resurgence in deaths from respiratory infections. The objective of this study is to analyze changes in the number of deaths from Influenza and invasive pneumococcal diseases using a nationwide mortality database in Japan before, during, and after the pandemic.

Methods

The observational period was categorized into the 'pre-pandemic era', 'pandemic era', and 'post-pandemic era'. The 'pandemic era' was defined as April 2020 to September 2021 since the state of emergency declared by the government lasted until then. The period prior to this was classified as the 'pre-pandemic era,' while the period following it was the 'post-pandemic era.' We also defined the winter season as the most prevalent season for both influenza and invasive pneumococcal diseases, from September of the previous year to August of the current year.

The explanatory variable was the number of death cases recorded since January 2009. Data from all available periods were utilized, covering January 2011 to July 2024 for influenza and April 2013 to July 2024 for invasive pneumococcal diseases. The 'pandemic era' was compared with both the 'pre-pandemic era' and the 'post-pandemic era' using the Mann-Whitney U test, a non-parametric test suitable for comparing two independent samples, with statistical significance set at $P < 0.05$. Informed consent was not required for this study. The data analyzed were obtained from e-Stat, Japan's official statistical database.[7]

A multivariable linear regression analysis was conducted to evaluate monthly variation in influenza and invasive pneumococcal disease cases (Table 1). The dependent

variable was the log-transformed, continuity-corrected monthly case count, calculated as $\log_{10}$(monthly cases + 0.5) to account for zero values. Explanatory variables included nominal indicators for each calendar month (February through December), with January as the reference; calendar year as a continuous variable; and a binary variable representing the pandemic period.

Results

Influenza

We obtained the data from January 2011 to July 2024: a total of 187 months, during which 22,048 deaths due to Influenza were reported nationwide. The number of deaths due to Influenza in the winter season of 2019 was 3,353. The pandemic occurred during the winter season of 2020, and it decreased to 1,275. It further dropped to 78 in 2021 and 19 in 2022. In 2023, classified as the 'post-pandemic era', it increased to 386. Although the data is limited to July, it reached 1,220 in 2024.

The monthly death count significantly decreased during the 'pandemic era' compared to the 'pre-pandemic period era' ($P < 0.001$) (Figure 1). However, it increased dramatically in the 'post-pandemic era' compared to the 'pandemic era' ($P = 0.005$).

Invasive pneumococcal diseases

We collected data for the same period as for Influenza, during which a total of 562 deaths from invasive pneumococcal diseases were reported nationwide. In the winter season of 2019, there were 69 deaths, which decreased to 60 in 2020, and further fell to 19 in 2021 and 14 in 2022. The number rose to 62 in 2023, during the 'post-pandemic era', and reached 54 in 2024.

The monthly death count saw a notable decline during the 'pandemic era'

compared to the ‘pre-pandemic period era’ (P<0.001) (Figure 2). Additionally, there was a notable increase in deaths during the ‘post-pandemic era’ compared to the ‘pandemic era’ (P<0.001).

Discussion

The COVID-19 pandemic had a massive impact on the economy and public health worldwide. In Japan, the government successfully managed to curb the pandemic early on.[8] This success was largely due to early actions taken by the government to prevent the spread of the virus with various infection control practices. These interventions coincided with a reduction of both COVID-19 and traditional respiratory tract infections. However, the worldwide resurgence of influenza and invasive pneumococcal disease in the post-pandemic period requires urgent attention. To the best of our knowledge, we are the first to report the death toll based on nationwide surveillance.

There are several factors that may have contributed to this phenomenon. Firstly, The removal of precautionary measures may have contributed to this shift. The relaxation of these measures, notably basic infection prevention maneuvers, allowed for an increase in human mobility and interactions, including social gatherings, resumed commuting and engaging in social events. This return to pre-pandemic behaviors combined with fewer public health restrictions in place was likely associated with increased exposure to common pathogens.

Moreover, residual immunity in the population may have decreased during the pandemic, primarily due to the reduced exposure to viruses resulting from unprecedented

levels of social isolation.[9] For instance, a recent study reported a significant resurgence in the positivity rate of influenza in the USA and England following the removal of non-pharmaceutical interventions, which may reflect the presence of immunity debt accumulated during the pandemic.[10] Now that the restrictions have been lifted, the viruses are able to circulate among individuals with weakened immunity, potentially causing local outbreaks.

However, the main limitation of this study is that casual relationships cannot be inferred due to the use of an observational design. For instance, the rebound in healthcare access after the pandemic might have led to increased detection. It is possible that widespread avoidance of healthcare facilities during the pandemic led to underdiagnosis, which was offset as access improved.[11] Further individual-level analyses are required to validate these observations.

Measures like international lockdowns and stay-at-home orders have had significant impacts on the economy and have limited individual freedoms. However, these findings highlight the importance of maintaining basic infection prevention measures even after the pandemic subsides. It is essential that we continue to monitor the prevalence of respiratory infections to ensure prompt interventions and minimize the risk of future outbreaks.

Conclusion

In conclusion, the COVID-19 pandemic had a significant impact worldwide on the incidence of respiratory infections, including influenza and invasive pneumococcal diseases due to stringent public health measures. However, we observed a noticeable resurgence in the number of deaths in the post-pandemic era as most restrictions are eased and pre-pandemic behaviors have returned. This highlights the importance of monitoring respiratory infections and maintaining basic infection prevention measures even after the pandemic.

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Data availability: The datasets generated during and/or analyzed during the current study are available in the e-Stat repository, https://www.e-stat.go.jp/."

Ethical Statement: Not applicable.

Conflict of Interest: The authors report no conflicts of interest in this work.

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Table 1: Multivariable linear regression of log-transformed monthly case counts by calendar month, year, and pandemic period

Variables	Influenza		Invasive pneumococcal diseases	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
Februrary	-0.05 (-0.45 to 0.35)	0.806	-0.16 (-0.38 to 0.06)	0.148
March	-0.35 (-0.75 to 0.06)	0.091	-0.15 (-0.36 to 0.07)	0.177
April	-0.68 (-1.08 to -0.27)	0.001	-0.17 (-0.38 to 0.05)	0.122
May	-1.00 (-1.40 to -0.60)	<0.001	-0.10 (-0.31 to 0.11)	0.356
June	-1.31 (-1.71 to -0.90)	<0.001	-0.22 (-0.43 to -0.01)	0.044
July	-1.56 (-2.00 to -1.16)	<0.001	-0.45 (-0.66 to -0.24)	<0.001
August	-1.50 (-1.91 to -1.10)	<0.001	-0.48 (-0.70 to -0.26)	<0.001
September	-1.49 (-1.90 to -1.09)	<0.001	-0.57 (-0.78 to -0.35)	<0.001
October	-1.56 (-1.97 to -1.15)	<0.001	-0.49 (-0.71 to -0.27)	<0.001
November	-1.20 (-1.61 to -0.79)	<0.001	-0.20 (-0.41 to 0.02)	0.074
December	-0.66 (-1.06 to -0.24)	0.002	-0.01 (-0.22 to 0.21)	0.939
Year	0.01 (-0.02 to 0.03)	0.552	0.04 (0.03 to 0.06)	<0.001
Pandemic	-0.85 (-1.15 to -0.55)	<0.001	-0.44 (-0.57 to -0.32)	<0.001

Multivariable linear regression was performed using the log-transformed continuity corrected monthly case count as the dependent variable. Explanatory variables included nominal variables for each calendar month (February to December, with January as the reference), calendar year as a quantitative variable, and a binary variable for the pandemic period.

Figure 1: Impact of COVID-19 on Influenza Mortality

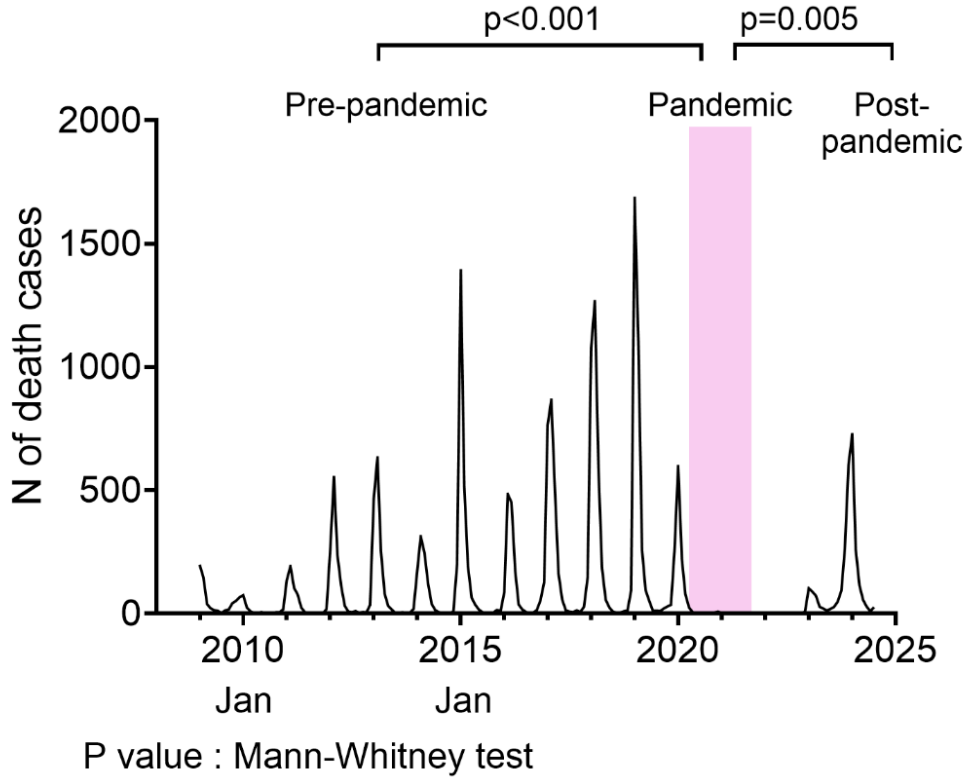

Figure 2: Impact of COVID-19 on Invasive Pneumococcal Disease Mortality