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Global patterns and trends in deaths of influenza-associated lower respiratory infections from 1990 to 2019

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Abstract

This study examined global trends in influenza-associated lower respiratory infections (LRIs) deaths from 1990 to 2019 using data from the GBD 2019. The annual percentage change (APC) and average annual percentage change (AAPC) were used to analyze age-standardized death rates (ASDR). Globally, the ASDR of influenza-associated LRIs was 3.29/100,000 in 2019, which was higher in the African region (6.57/100,000) and among adults aged 70 years and older (29.88/100,000). The ASDR of influenza-associated LRIs decreased significantly from 1990 to 2019 (AAPC = −1.88%, $P < 0.05$). However, it was significantly increased among adults aged 70 years and older during 2017–2019 (APC = 2.31%, $P < 0.05$), especially in Western Pacific Region and South-East Asia Regions. The ratio of death rates between adults aged 70 years and older and children aged under 5 years increased globally from 1.63 in 1990 to 5.34 in 2019, and the Western Pacific Region experienced the most substantial increase, with the ratio soaring from 1.83 in 1990 to 12.98 in 2019. Despite a decline in the global ASDR of influenza-associated LRIs, it continues to impose a significant burden, particularly in the African, Western Pacific regions and among the elderly population.

Introduction

In 2019, lower respiratory infections (LRIs) accounted for approximately 2.6 million global fatalities, which ranked as the fourth leading cause of death and the second leading cause of disability-adjusted life-years [1,2]. Despite a decline in deaths in recent years, LRIs remain a substantial global health challenge, particularly affecting children and older adults [3]. Influenza was identified as a high-burden aetiology of LRIs. In 2019, there were 243,671 (95% uncertainty interval [UI]: 95,991–459,921) reported deaths attributed to influenza, accounting for 9.60% of global LRIs deaths [4,5].

Previous studies have revealed variations in the patterns and progress of reducing infections and deaths associated with LRIs across different etiologies, age groups, and genders [6,7]. Currently, many researches are being conducted to investigate the disease burden of influenza-associated LRIs deaths in specific populations and regions [8–10]. Nevertheless, there remains a dearth of comprehensive and systematic research on the dynamic changes, prevention, and control progress regarding influenza-associated LRIs deaths among the entire population and various age groups, which is crucial for assessing progress and adapting prevention and control strategies for influenza-associated LRIs deaths. Therefore, in this study, we utilized data from the Global Burden of Disease 2019 Study (GBD 2019) to examine the change patterns of influenza-associated LRI deaths on a global scale. The annual percentage change (APC) and average annual percentage change (AAPC) were computed as metrics to describe and quantify these changes.

Methods

Data sources

The data regarding influenza-associated LRIs deaths were obtained from the GBD 2019 database. The GBD 2019 was established three decades ago with the aim of delivering accurate, up-to-date, and pertinent evaluations of health outcomes. The most recent iteration encompasses the assessment of thousands of diseases, injury, and risk factor outcomes across 204 countries and territories [11]. We utilized the Global Health Data Exchange query tool (http://ghdx.healthdata.org/gbd-results-tool) provided by GBD 2019 to obtain data on the number and rate of deaths, as well as the age-standardized death rate (ASDR) of influenza-associated LRIs deaths, including their corresponding 95% uncertainty intervals (UIs). These data were further categorized by age, sex, and location. Specifically, within the Global Health Data Exchange query tool, there are eight sections: GBD Estimates, Measure, Metric, Cause, Location, Age, Sex, and Year. We began by selecting "Etiology" in the GBD Estimate section, followed by choosing "Influenza" in the Etiology section. Subsequently, we opted for "Deaths" in the Measure section and selected "Rate" in the Metric section, and "Lower Respiratory Infections" in the Cause section. Finally, we included five age groups (<5 years old, 5–14 years old, 15–49 years old, 50–60 years old, and 70+ years), and selected Global, 6 WHO regions, 21 GBD regions, and 204 countries and territories in the "Location" section.

Join-point regression model analysis

We employed a joint-point regression model to analyze the trends in ASDR of influenza-associated LRIs deaths globally and within the six WHO regions from 1990 to 2019 [12]. To describe the trends, we calculated the APC and AAPC along with their corresponding 95% confidence intervals (CIs). The trends in ASDR were assessed based on whether the APC or AAPC was greater or smaller than 0, indicating an upward or downward trend, respectively. The level of significance was set at $P < 0.05$ [13].

Spatial and temporal aggregation analysis

We utilized SaTScan software to identify spatial and temporal clusters of influenza-associated LRIs deaths [14]. The SaTScan software utilized a dynamic spatiotemporal two-dimensional cylindrical scanning window, based on the Poisson distribution model, to perform a comprehensive scan of 204 countries and territories across different time periods on a global scale. For each scanning window, the expected number of deaths was calculated, taking into account the actual number of deaths and population size. The log-likelihood ratio and relative risk (RR) were calculated to detect spatial and temporal clustering. In spatiotemporal scan analysis, the RR value is calculated by comparing the observed number of events in a specific area and time to the expected number of events. This involves estimating the expected number of events. When RR is greater than 1, it indicates that the observed event rate is higher than expected, while an RR less than 1 indicates that the observed event rate is lower than expected. Significance testing of the RR value can help determine the degree of unusual event occurrence in a specific area and time, aiding in the identification of potential disease outbreaks or clusters [15].

Software

We utilized Microsoft Excel 2016 to extract, sort, and clean the data. For statistical analysis, we employed Join-point (version 4.8.0.1), SaTScan (version 9.5), and R (version 3.2.3).

Results

Global influenza-associated LRI deaths in 2019

The global ASDR of influenza-associated LRIs was 3.29/100,000 (95% UI: 1.31/100,000–6.25/100,000). It was higher in males (4.00/100,000, 95% UI: 1.6/100,000–7.52/100,000) than in females (2.78/100,000, 95% UI: 1.09/100,000–5.33/100,000) (Table 1). Death rate was significantly higher in the adults aged 70 years and older (29.88/100,000, 95% UI: 10.99/100,000–59.56/100,000) and children aged 5 years and under (5.59/100,000, 95% UI: 1.83/100,000–12.74/100,000). The ASDR was higher in the African region (6.57/100,000, 95% UI: 2.43/100,000–13.16/100,000) (Table 1 and Figure 1A). The Western Pacific region had the highest proportion of LRIs deaths attributable to influenza among the six WHO regions (Supplementary Figure 1).

Spatial and temporal aggregation of influenza-associated LRIs deaths

Three main spatial and temporal aggregation events were observed from 1990 to 2019. The first-level spatial and temporal aggregation event were mainly occurred in the Western Pacific region, with a gathering time from 1 January 2005 to 31 December 2019 (RR = 3.55, $P < 0.01$). The second spatial and temporal aggregation event occurred in Africa from 1 January 1990 to 31 December 2004, with an RR of 3.24. Respectively, the third spatial and temporal aggregation region mainly occurred in Central Asia from 1 January 1990 to 31 December 2003 (RR = 1.81, $P < 0.01$) (Figure 2).

Global trends of influenza-associated LRIs deaths from 1990 to 2019

Between 1990 and 2019, there was a significant decrease in the ASDR of influenza-associated LRIs (AAPC = −1.88%, 95% CI: −2.11% to −1.65%, $P < 0.05$) (Table 1 and Supplementary Figure 2). However, it is noteworthy that the ASDR experienced a significant increase in the Western Pacific Region from 2017 to 2019 (APC = 5.01%, 95% CI: 2.87% - 7.89%, $P < 0.05$) (Supplementary Figure 2).

Age-specific influenza-associated LRIs deaths and its trends from 1990 to 2019

Death rates of children aged 5 years and under (11.06/100,000, 95% UI:3.39/100,000–25.50/100,000) and adults aged 70 years and older (50.61/100,000, 95% UI: 17.08/100,000–106.05/100,000) was both highest in Africa Region (Figure 3A–B). In the region of the Americas (34.39/100,000, 95% UI: 12.60/100,000–67.64/100,000) and Western Pacific region (33.71/100,000, 95% UI: 12.27/100,000–65.82/100,000), they also have a higher death rate of adults aged 70 years and older (Figure 3B). The death rate among children aged 5 years and under exhibited a significant decrease (−4.49%, 95% CI: −4.61% to −4.38%, $P < 0.05$) (Table 1 and Figure 3C). However, in many countries and territories, the death rate in adults aged 70 years and older remained stable or showed an increasing trend (Figure 3D).

Between 2017 and 2019, we observed an increasing trend in the death rate among adults aged 70 years and older (AAPC = 2.31%, 95% CI: 1.05–3.59, $P < 0.05$) (Figure 4 and Supplementary Table 1). We identified this upward trend specifically in the Western Pacific Region (AAPC = 6.48%, 95% CI: 3.09 to 9.97, $P < 0.05$) and the South-East Asia Region (AAPC = 0.79%, 95% CI: 0.34 to 1.25, $P < 0.05$) (Figure 4D and Figure 4F). The ratio of death rates between adults aged 70 years and older and children aged 5 years and under witnessed a significant increase, rising from 1.63 in 1990 to 5.34 in 2019 (Figure 5). Notably, the Western Pacific region experienced the most substantial increase, with the ratio soaring from 1.83 in 1990 to 12.98 in 2019 (Figure 5).

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Table 1. The age-standardized deaths rate of influenza-associated lower respiratory infections in 1990 and 2019 with AAPC over the 30 years

	ASDR (/100,000, 95% UI)		
	1990	2019	AAPC (%)
Global	5.68 (2.29–10.71)	3.29 (1.31–6.25)	−1.88 (−2.11 to −1.65)*
Male	6.6 (2.61–12.21)	4.00 (1.6–7.52)	−1.73 (−1.96 to −1.51)*
Female	5.07 (2–9.66)	2.78 (1.09–5.33)	−2.06 (−2.18 to −1.94)*
WHO regions			
Region of the Americas	5.06 (2.16–8.84)	3.19 (1.28–5.87)	−1.55 (−1.78 to −1.32)*
European Region	3.42 (1.36–6.25)	2.23 (0.91–4.07)	−1.37 (−1.69 to −1.05)*
Western Pacific Region	7.26 (2.94–13.6)	3.12 (1.24–5.82)	−2.95 (−3.27 to −2.62)*
Eastern Mediterranean Region	4.76 (1.87–9.16)	3.16 (1.22–6.15)	−1.39 (−1.56 to −1.21)*
South-East Asia Region	5.58 (2.09–10.88)	2.98 (1.06–5.99)	−2.17 (−2.63 to −1.7)*
African Region	10.01 (3.79–19.97)	6.57 (2.43–13.16)	−1.43 (−1.55 to −1.3)*
Age group			
Under 5 year	21.19 (6.61–47.08)	5.59 (1.83–12.74)	−4.49 (−4.61 to −4.38)*
5–14 year	0.71 (0.23–1.56)	0.32 (0.1–0.69)	−2.7 (−3.03 to −2.38)*
15–49 year	0.56 (0.19–1.1)	0.47 (0.16–0.94)	−0.62 (−0.89 to −0.35)*
50–69 year	4.43 (1.54–8.61)	3.29 (1.14–6.45)	−1.04 (−1.21 to −0.87)*
≥ 70 year	34.64 (12.61–68.4)	29.88 (10.99–59.56)	−0.53 (−0.71 to −0.35)*
SDI rank			
High SDI	3.2 (1.21–6.06)	2.28 (0.88–4.3)	−1.2 (−1.53 to −0.88)*
High-middle SDI	3.57 (1.46–6.55)	2.15 (0.85–4)	−1.72 (−2.12 to −1.33)*
Middle SDI	6.01 (2.43–11.17)	3.07 (1.19–5.72)	−2.29 (−2.45 to −2.13)*
Low-middle SDI	7.33 (2.87–13.97)	4.11 (1.54–8.01)	−1.97 (−2.12 to −1.81)*
Low SDI	9.59 (3.64–18.77)	5.73 (2.16–11.5)	−1.75 (−1.93 to −1.58)*
GBD regions			
Western Sub-Saharan Africa	12.95 (4.93–25.5)	8.74 (3.16–17.7)	−1.34 (−1.51 to −1.16)*
Oceania	11.07 (4.51–20.68)	8 (3.09–16.15)	−1.16 (−1.48 to −0.83)*
Central Sub-Saharan Africa	12.31 (4.36–25.97)	7.45 (2.48–16.21)	−1.69 (−1.82 to −1.56)*
Southern Sub-Saharan Africa	8.6 (3.17–16.7)	7.29 (2.78–14.44)	−0.55 (−1.02 to −0.07)*
Caribbean	10.05 (4.3–17.24)	6.91 (2.73–12.51)	−1.28 (−1.43 to −1.12)*
Tropical Latin America	10.21 (4.3–17.92)	6.42 (2.54–11.55)	−1.57 (−1.76 to −1.38)*
Southern Latin America	6.3 (2.6–11.18)	5.91 (2.24–11.4)	−0.21 (−0.68 to 0.27)*
South-East Asia	8.71 (3.57–15.75)	5.86 (2.27–10.86)	−1.38 (−1.5 to −1.26)*
Eastern Sub-Saharan Africa	7.23 (2.6–14.93)	4.3 (1.45–9)	−1.76 (−1.85 to −1.66)*
High-income Asia Pacific	7.89 (3.05–14.5)	4.24 (1.61–7.8)	−2.22 (−3.01 to −1.42)*
Central Latin America	8.82 (3.87–14.83)	4.23 (1.77–7.57)	−2.49 (−2.71 to −2.28)*
Eastern Europe	3.12 (1.4–5.08)	3.75 (1.63–6.25)	0.71 (−0.21 to 1.63)*
Andean Latin America	5.97 (2.1–12.45)	3.28 (1.07–7.13)	−1.99 (−2.4 to −1.57)*
South Asia	5.19 (1.94–10.18)	2.96 (1.04–5.95)	−1.93 (−2.47 to −1.38)*
Central Asia	5.39 (1.93–10.72)	2.71 (1.05–5.31)	−2.3 (−2.53 to −2.06)*
North Africa and Middle East	3.91 (1.48–7.81)	2.35 (0.85–4.73)	−1.72 (−1.94 to −1.51)*
Central Europe	3.51 (1.38–6.4)	1.78 (0.68–3.45)	−2.27 (−2.58 to −1.96)*
East Asia	5.85 (2.18–11.26)	1.78 (0.65–3.44)	−4.12 (−4.5 to −3.74)*
Western Europe	2.3 (0.83–4.53)	1.35 (0.48–2.69)	−1.79 (−2.11 to −1.48)*
Australasia	1.42 (0.51–2.81)	0.88 (0.31–1.81)	−1.44 (−1.78 to −1.09)*
High-income North America	1.44 (0.5–2.96)	0.87 (0.3–1.81)	−1.71 (−2.17 to −1.25)*

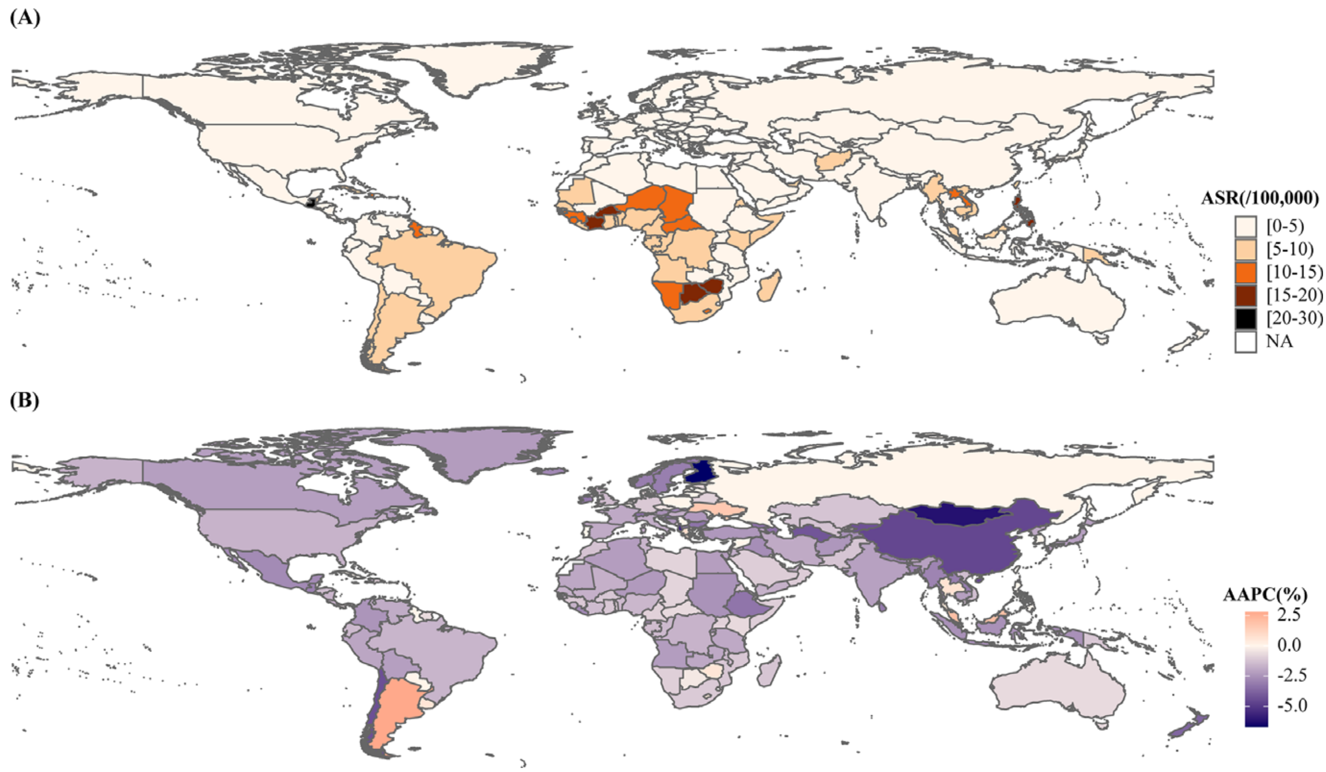
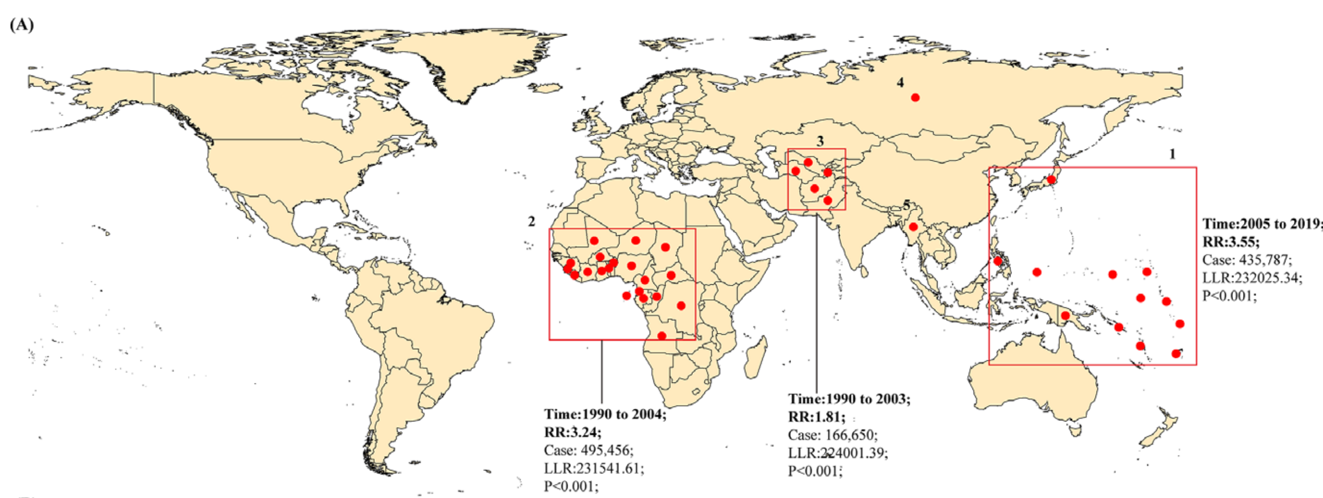


Figure 1. Global deaths and trends of influenza-associated lower respiratory infections among 204 countries and territories. (A) ASDR in 2019; (B) AAPC of ASDR from 1990 to 2019.



(B)

No	Cluster region	Time frame	Number of cases	Expected cases	RR	LLR	P-value
1	Solomon Islands, Palau, Philippines, Nauru, Marshall Islands, Micronesia (Federated States of), Papua New Guinea Vanuatu, Kiribati, Tuvalu, Japan, Fiji	2005/1/1 to 2019/12/31	435787	128421.07	3.55	232025.34	< 0.01
2	Burkina Faso, Cote d'Ivoire, Guinea, Chad, Niger, Sierra Leone, Benin, Central African Republic, Togo, Cameroon, Liberia, Sao Tome and Principe, Democratic Republic of the Congo, Nigeria, Angola, Ghana, Equatorial Guinea, Congo, Gabon, Mali	1990/1/1 to 2004/12/31	495456	160618.36	3.24	231541.61	< 0.01
3	Afghanistan, Pakistan, Tajikistan, Turkmenistan, Uzbekistan	1990/1/1 to 2003/12/31	166650	92933.10	1.81	24001.38	< 0.01
4	Russian Federation	2000/1/1 to 2014/12/31	160208	78865.69	2.06	32677.92	< 0.01
5	Myanmar	1990/1/1 to 2004/12/31	64480	24687.90	2.63	22224.33	< 0.01

Figure 2. Spatial and temporal aggregation from 1990 to 2019.

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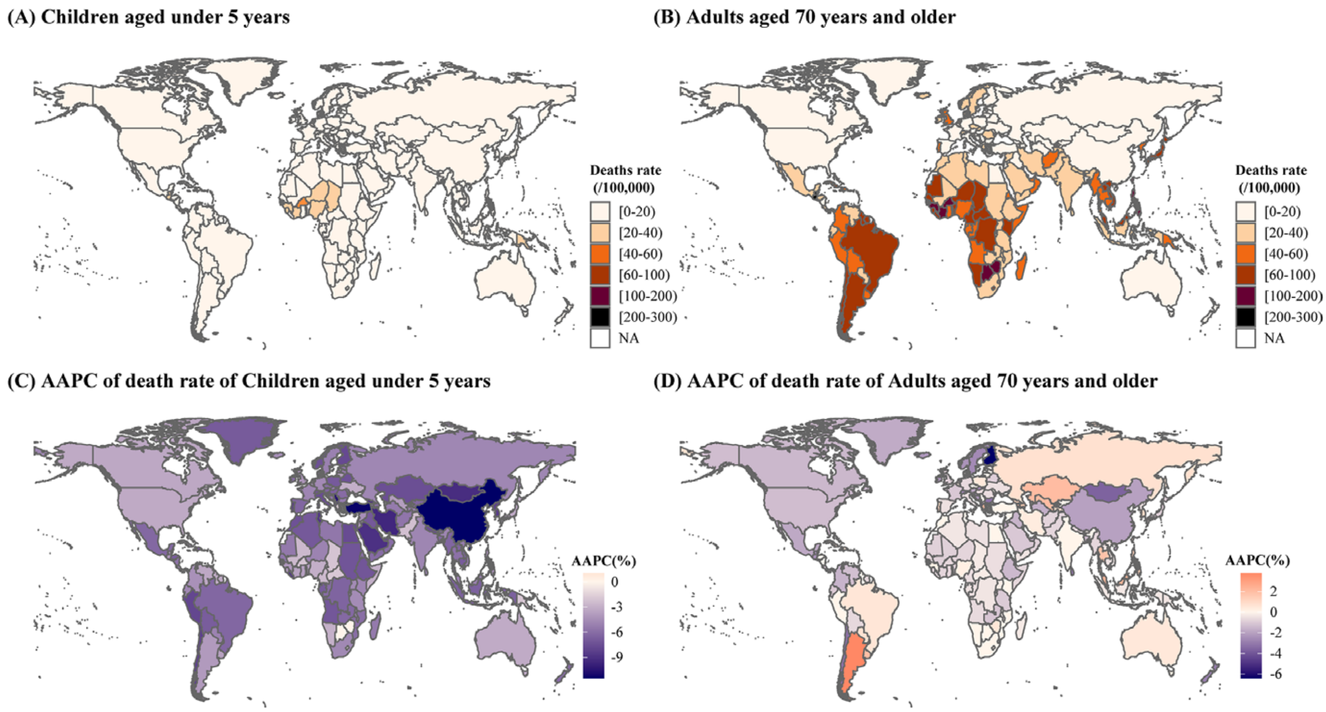

Figure 3. Global deaths and trends of influenza-associated lower respiratory infections in children aged 5 years and under and adults aged 70 years and older among 204 countries and territories. (A) Deaths rate of children aged 5 years and under in 2019; (B) AAPC of deaths rate of children aged 5 years and under from 1990 to 2019; (C) Deaths rate of adults aged 70 years and older in 2019; (D) AAPC of deaths rate of adults aged 70 years and older from 1990 to 2019.

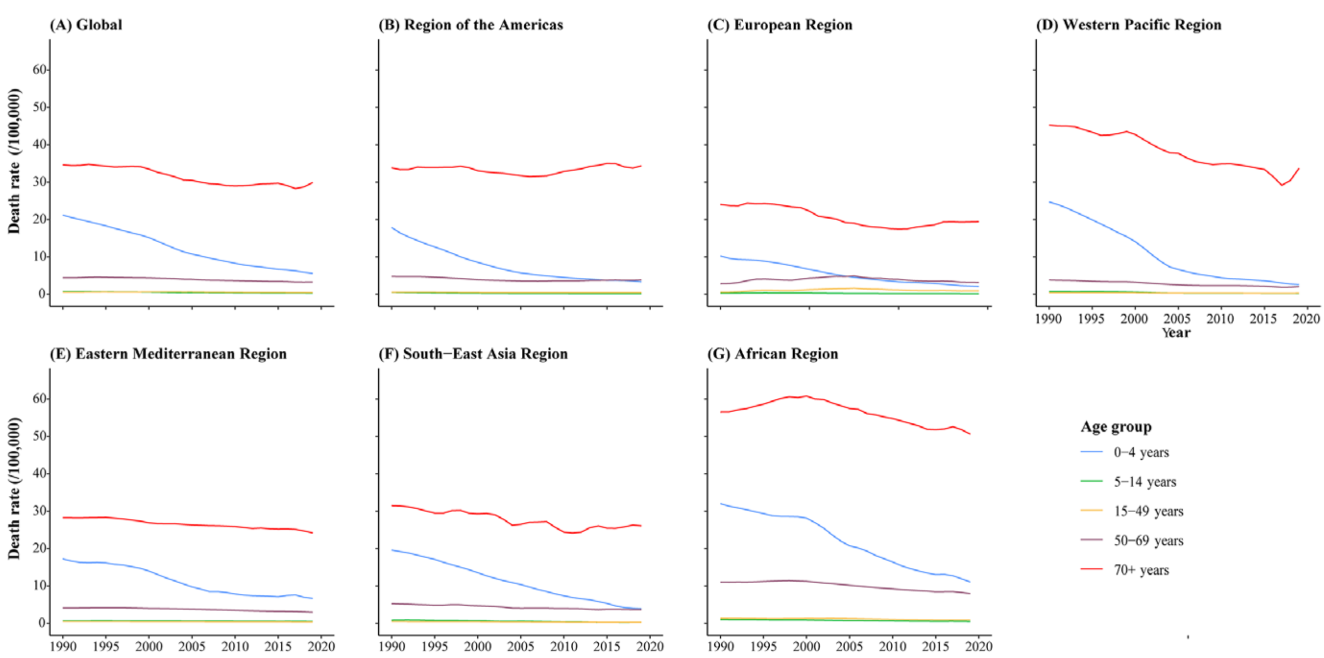

Figure 4. Age-specific temporal trends of influenza-associated lower respiratory infections among global and six WHO regions from 1990 to 2019. (A) Global; (B) Region of the Americas; (C) European Region; (D) Western Pacific Region; (E) Eastern Mediterranean Region; (F) South-East Asia Region; (G) African Region.

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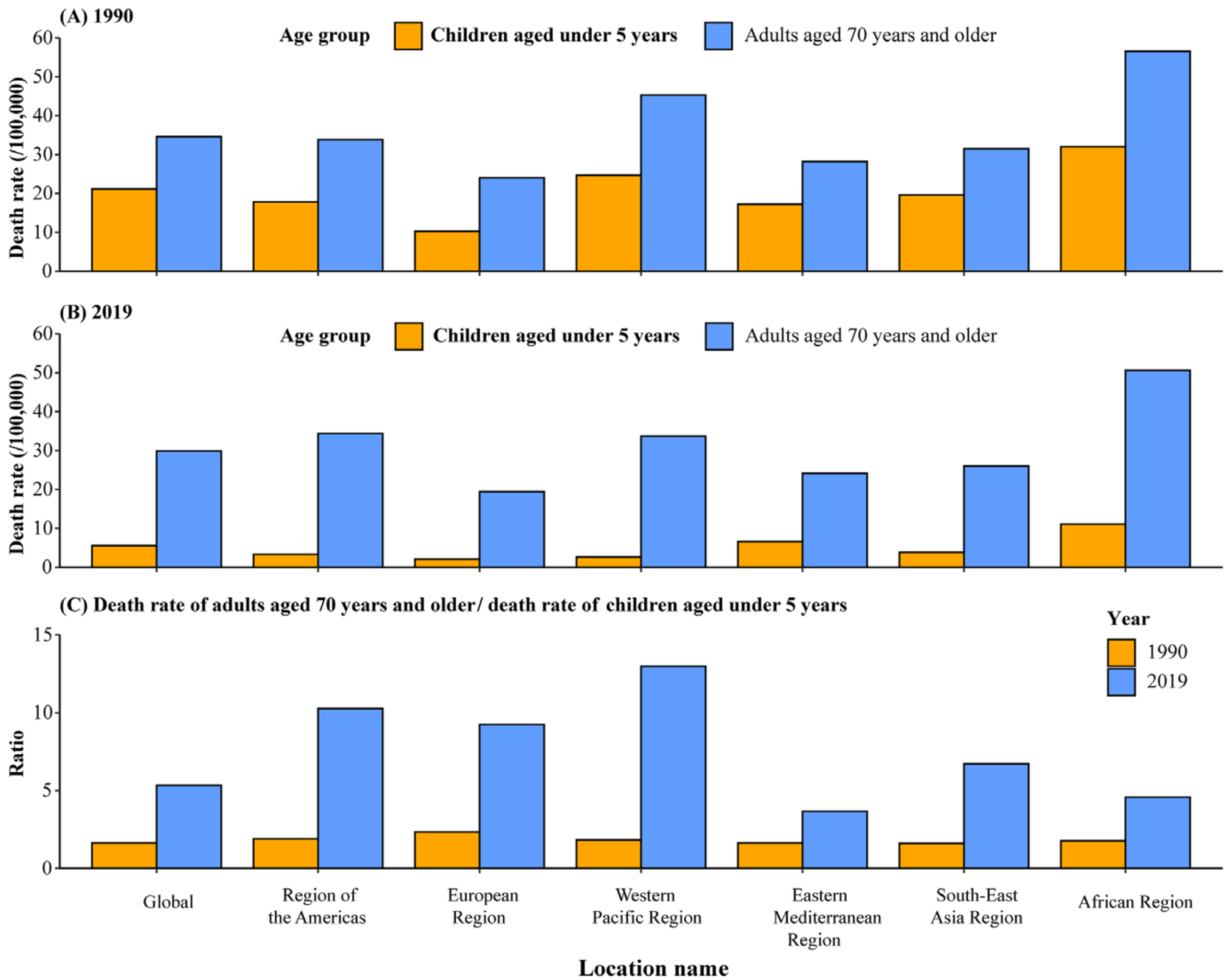

Figure 5. Deaths rate of influenza-associated lower respiratory infections in children aged 5 years and under and adults aged 70 years and older in 1990 and 2019. (A) In 1990; (B) In 2019; (C) Deaths rate of adults aged 70 years and older divided by deaths rate of children aged 5 years and under in 1990 and 2019.

Discussion

In 2019, the global ASDR of influenza-associated LRIs was 3.29 per 100,000 population. This rate was found to be higher in the African region and among adults aged 70 years and older. Additionally, there was a spatial and temporal clustering observed in the Western Pacific Region. Overall, the ASDR of influenza-associated LRIs exhibited a significant decrease from 1990 to 2019. However, there was a notable increase observed in adults aged 70 years and older during the period of 2017–2019, particularly in the Western Pacific and South-East Asia regions. Remarkable strides have been achieved in the prevention and control of influenza-associated LRI deaths among children. Nevertheless, the burden persists as a substantial challenge among the elderly population. Our study revealed differences in influenza-associated LRI deaths between males and females, which can be attributed to several factors. These factors include a higher prevalence of common infections among males, potential variations in immune responses to infections, and behavioral habits such as smoking and drinking [16,17]. Adults aged 70 years and older, who may experience malnutrition, chronic diseases, reduced antibody levels, and inflammatory responses, are more prone to developing severe illnesses and experiencing higher mortality rates [18–20]. These factors could contribute to an increased burden of influenza-associated LRIs among these populations. This emphasizes the importance of implementing timely prevention and intervention measures specifically targeting these high-risk groups.

In recent years, the increasing ratio of death rates between adults aged 70 years and above and children under 5, from 1.63 in 1990 to 5.34 in 2019 globally, suggests an uneven reduction in mortality across these age groups. When combined with their AAPC values, it becomes evident that over the past three decades, the decrease in influenza-related LRI deaths among children under 5 has significantly outpaced the decline observed in individuals aged 70 and above. Currently, the burden of influenza-related LRI deaths is primarily concentrated within the elderly population. Especially, the Western Pacific and South-East Asia regions have witnessed a significant increase in death rates among adults aged 70 years and older in recent years. This phenomenon may be attributed to a combination of factors. Firstly, inadequate vaccination coverage within this age group, possibly due to vaccine hesitancy, limited

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access to vaccination services, or suboptimal vaccine efficacy, could be a contributing factor [21]. Vaccination against influenza is extremely crucial for individuals aged 70 and above, as it significantly reduces the risk of severe illness and death associated with influenza infection [21]. Additionally, the healthcare infrastructure in these regions, including access to medical care, diagnostic capabilities, and treatment options, might have influenced the burden of influenza. Moreover, as the aging population exacerbates, there is a higher prevalence of comorbidities, which could increase susceptibility to severe influenza-related complications, leading to a higher risk of deaths [22]. It means that more attention and resources should be paid to the prevention and control of influenza infections in the elderly, so as to reduce the mortality rate of the elderly. Specifically, the government and health organizations can formulate and implement public health policies for the elderly, including vaccination promotion and disease surveillance [23,24]. Ensuring that there are sufficient medical resources, especially intensive care resources, to cope with influenza complications in the elderly during the influenza season [25,26]. Promoting public awareness of influenza prevention, emphasizing the importance of personal hygiene, healthy lifestyles, and prompt medical treatment [27,28].

Moreover, there have been a spatiotemporal clustering event observed in the Western Pacific region. Previous studies have highlighted potential associations between incomplete health care services, an increased risk of LRI deaths due to passive smoking, reliance on solid fuels, crowded living conditions, and increased physical proximity and exposure [3,29–33]. The Western Pacific and South-East Asia regions are characterized by high population density and frequent international travel, which have contributed to the rapid spread of influenza. In the Western Pacific region, the H3N2 subtype of influenza has been dominant, partly due to antigenic mismatch between the circulating strains and the vaccine production, resulting in reduced effectiveness of the influenza vaccine. Therefore, there is a need to establish more timely and accurate surveillance systems and information-sharing mechanisms in these regions [34–38].

Although the ASDR in Africa has significantly declined over the past decades, it remains the highest compared to other regions. Katz et al. also reported that poor nutritional status, limited access to healthcare, and the presence of other factors associated with poverty may contribute as additional risk factors for poor outcomes in Africa [39,40]. Vaccination is widely recognized as the most effective method of protection against influenza and its complications. Previous studies have indicated that influenza vaccines are predominantly distributed in developed countries and regions, while many developing nations or regions face significant underutilization of these vaccines [41]. Three primary strategies and activities have been proposed to enhance vaccine utilization in developing countries or regions. These include: (i) Establishing evidence, encompassing vaccine performance, disease burden, and health economics; (ii) Formulating supportive vaccination policies, which involve guidelines for vaccination (vaccine candidates, priority target population, and timing of immunization), financing policies, and ensuring an adequate, affordable supply of prequalified vaccines; (iii) Implementing policies at the local level based on their specific characteristics and burden of influenza [21,42]. Simultaneously, it is crucial to establish an effective national influenza surveillance system to deliver timely and comprehensive estimates of the burden on high-risk populations, seasonality, circulating strains and subtypes, and the cost-effectiveness of national influenza vaccination [43].

Limitations

Our study has several limitations that should be acknowledged. Firstly, our analysis focused on influenza-associated LRI deaths, which may only represent a portion of the total deaths caused by influenza. Further research is needed to investigate the overall disease burden of influenza using multiple indicators. Secondly, comprehending the case fatality ratio is crucial for understanding the disease burden of influenza. Subsequent research efforts should aim to investigate the case fatality ratio in order to provide comprehensive evidence and strengthen support for policymaking. Thirdly, the identification of influenza depended on advancements in molecular diagnostics, such as RT-PCR. Data from surveillance systems in the 1990s and early 2000s may have been influenced by bias. Meanwhile, in certain developing countries, information regarding influenza-related deaths and their causes is limited, often relying more on model estimation. Consequently, the reported number of confirmed influenza cases to public health authorities may be lower than the actual occurrences.

Conclusion

Although the ASDR of influenza-associated LRIs has been declining globally, it continues to impose a significant burden, particularly in the African and Western Pacific Regions and among adults aged 70 years and older. There has been a noticeable upward trend in influenza-associated LRIs deaths among adults aged 70 years and older in the Western Pacific and South-East Asia regions. It is crucial to prioritize and allocate more attention to these vulnerable regions and populations.

Supplementary material. The supplementary material for this article can be found at http://doi.org/10.1017/S0950268824001559.

Data availability statement. Publicly available datasets were analyzed in this study. The data can be found here: http://ghdx.healthdata.org/gbd-results-tool.

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Author contribution. Can Chen, Dingmo Chen, Yuxia Du These authors contributed equally to this work.

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Can Chen: Writing – original draft; Methodology; Data curation; Formal analysis; **Dingmo Chen:** Writing – original draft; Data curation; **Yuxia Du:** Formal analysis; Methodology; Data curation; visualization; **Daixi Jiang:** Data curation; visualization; **Kexin Cao:** Data curation; visualization; **Mengya Yang:** Data curation; visualization; **Xiaoyue Wu:** Data curation; visualization; **Mengsha Chen:** Data curation; visualization; **Wenkai Zhou:** Data curation; visualization; **Jiaxing Qi:** Data curation; visualization; **Yue You:** Data curation; visualization; **Rui Yan:** Data curation; visualization; **Shigui Yang:** Conceptualization; Writing – review and editing.

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Competing interest. The authors declare no conflict of interest.

Ethics approval and consent to participate. The study did not require ethics approval and consent to participate because it used publicly available data.

Consent for publication. Not applicable.

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