Burden of respiratory infection and tuberculosis among US states from 1990 to 2019

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Abstract

Importance: Respiratory infection and tuberculosis (RIT) are major public health concerns in the US. State-level measures of RIT burden and risk factors have not been reported previously

Objective: To describe levels and trends of incidence, death and disability-adjusted life-years (DALYs) of respiratory infection (including otitis media, upper and lower respiratory infection) and tuberculosis in the US from 1990 to 2019, and discuss the risk factors driving the changes.

Design, setting and participants: Using the methodology of Global Burden of Disease (GBD), the incidence, mortality, DALYs of RIT and related risk factors were analyzed by age group, gender, and states from 1990 to 2019 in the US.

Main outcomes and measures: Incidence, death and DALYs of RIT, and attributable risk factors.

Results: In 2019, the age-standardized incidence rate of RIT was 39 702.7 (95% UI 303 183.8 to 382 353.9) per 100 000 people, a slight decrease by -0.3% (95% UI -1.3 to 0.6) from 1990. The age-standardized death and DALY of RIT were 13.6 (95% UI 12.2 to 14.4) and 384.9 (95% UI 330.6 to 458.6) per 100 000 people, improved by -40.2% and -32.5%. Lower respiratory infection attributed the highest proportion to RIT age-standardized death and DALY rate. RIT age-standardized incidence rate increased with age, but its death rate increased with age, whereas there was a small peak in the age group <1 years. Males were lower in RIT age-standardized incidence rate except tuberculosis, but much higher in RIT age-standardized death and DALY rate. Moreover, it was revealed that RIT burden was heavy in some states of East South Central, and its improvement was far from satisfactory. A strong relationship was found between SDI level and improvement of RIT age-standardized death and its changes. 89.9% and 85.8%

of RIT mortality in males and females were attributed to modifiable GBD risk factors.

Conclusions and relevance:

RIT burden varied widely in ages, genders and states. The disparities may be associated with risk exposure and SDI level. A substantial improvement of RIT burden was achieved in the US, but some states in East South Central were identified as the hotspots of RIT.

Key words: upper respiratory infection, lower respiratory infection, otitis media, pulmonary tuberculosis, United States, Mortality, Disability-adjusted life years, Trend.

Introduction

Respiratory infection including upper respiratory infection, low respiratory infection and otitis media are the most common acute respiratory tract infectious diseases in human, while lung is the most commonly affected organ in tuberculosis infection. Moreover, lower respiratory infection is the major public health concerns worldwide, and the leading cause of mortality among infectious diseases in the US, accounting 78.80% of total infectious diseases deaths in 2014[1], and in 2019 pneumonia combined with influenza ranked 9th in the leading causes of death, claiming 49 783 lives[2], while respiratory infection and tuberculosis ranked 7th causes of death in the US, and brought about 83 000 death in 2019[3]. On the other hand, tuberculosis remained a persistent low-level epidemic for years, which is still difficult to be eliminated in the US[4]. Despite a decline in mortality of RIT due to improved preventive measurement, better healthcare and effective treatments, RIT remains a health challenge to the society, because of the existing huge health burden, the antibiotics abuse and the potential outbreak of unknown pathogen, like MERS, COVID-19[1,4,5].

The epidemiological pattern of infectious disease presented large disparities across regions owing to different environment, health policy, custom and Socio-demographic Index (SDI), etc.[6-8]. Accordingly, distribution for RIT in sub-national level also varied across the country, and cartography of RIT will be beneficial to the management of risk factors and health policy-making of each state. To the best of our knowledge, no study has been carried out so far to comprehensively measure the disparities in the US. In this article, we reported the burden of RIT and discussed modifiable risk factors attributable to RIT in the US based on the most recent Global Burden of Disease Study 2019.

Method

Overview

The GBD study, conducted by Institute of Health Metrics and Evaluation (IHME), provides annual updates on the burden of diseases, injuries, and risk factors at the global, regional, and national levels. In the most up-to-date iteration, GBD 2019 have analyzed 369 diseases and injuries, and 87 risk factors systematically, and the general methods used in GBD 2019 have been published previously[3,9,10]. Here, we summarized the methods related to the estimation of RIT burden in the US. This study was approved by the University of Washington Institutional Review Board, and informed consent was waived because no identifiable data were used.

Data sources

RIT was defined using the International Classification of Diseases version 9 (ICD-9) and ICD-10. Diseases coded as H65-H71.93 in ICD-10 and 381-383.9 in ICD-9 were identified as otitis media, while upper respiratory infection was coded as J00-J06.9, J36-J36.0 in ICD-10, 460-465.9, 475-475.9 in ICD-9. Lower respiratory including bronchitis, bronchiolitis, pneumonia was coded as A48.1, A70, B96.0-B97.6, J09-J22.9, J85.1-J91.0, P23-P23.9, U04-U04.9 in ICD-10, and 079.82, 466-470.0, 480-484, 484.1-490.9, 510-513.9, 770.0, V12.61 in ICD-9. Tuberculosis was coded as A10-A19.9, B90-B90.9, K67.3, K93.0, M49.0, N74.0-N74.1, P37.0, U84.3 in ICD-10, and 010-019.9, 137-137.9, 320.4, 730.4-730.6 in ICD-9. The data sources used to produce estimates for the burden of RIT was extracted by GBD 2019 Data Input Sources Tool (website: http://ghdx.healthdata.org/gbd-2019/data-input-sources, http://ghdx.healthdata.org/gbd-results-tool).

Estimation of burden for RIT in the US

Considering relatively short course of respiratory infectious diseases, incidence outstrips prevalence in depicting the epidemiological trends of RIT. The incidence of RIT was defined as the new or relapse cases diagnosed within a year, and the incidence stratified by state, year, gender and age group was estimated by DisMod-MR 2.1 model, a Bayesian meta-regression tool developed for the GBD study[9].

To estimate the mortality of RIT, Cause of Death Ensemble Model (CODEm) was used. CODEm ensembles different models incorporated with various predictive covariates to analyze the cause of death, and several covariates were chosen to perform best with CODEm (**Supplement eTable1**)[3]. Moreover, disability-adjusted life years (DALYs), the sum of years of life lost (YLLs) and years lived with disability (YLDs), were estimated for the overall health loss of RIT. YLLs were calculated by multiplying of RIT related deaths in each age group by the standard life expectancy at that age, and YLDs represented the health loss associated with the severity level of RIT, from 0 (full health) to 1 (death)[9].

Socio-demographic Index

SDI was used to measure the relationship between development of each state and RIT burden. SDI is a metric consisting of 3 components: total fertility rate under age 25 years, lag-distributed income per capita, and average educational attainment in populations aged 15 years or older, and SDI value ranges from 0 (least developed) to 1 (most developed).

Attributable risk factors for RIT

The GBD study had provided the comparative risk assessment framework to quantify the burden of diseases and injuries attributable to risk factors[10]. In brief, we selected

risky factors related to RIT, like smoking, air pollution, alcohol use, temperature, child growth failure, etc., then extracted the relative risks and exposure from all available data source. The death of RIT attributable risk factors was calculated by multiplying the number of deaths for the outcome by the population attributable fraction (PAF) for the risk-outcome pair.

Uncertainty analysis

Uncertainty was propagated through all estimation by sampling 1000 draws at each calculation step. 95% uncertainty intervals (UIs) were defined as the 2.5th and 97.5th percentiles of the 1000 draws. For all estimates, a 95% UI excluding zero were considered statistically significant.

Result

Total RIT burden and its changes in the US

As shown in **Table 1**, in 2019, the total age-standardized incidence rate of RIT in the US was 339 702.7 (95% UI 303 183.8 to 382 353.9) per 100 000 people. Among RIT causes, upper respiratory infection accounted for the large majority of age-standardized incidence rate [331 560.4 (95% UI 294 985.4 to 373 552.9) per 100 000 people], while tuberculosis had the minimum age-standardized incidence rate [2.1 (95% UI 1.8 to 2.5) per 100 000 people]. Since 1990, it remained almost unchanged in total age-standardized incidence rate by -0.3% (95% UI -1.3 to 0.6), but a significant decrease was observed for tuberculosis by -72.1% (95% UI -73.9 to -70.3).

The total age-standardized death rate of RIT was 13.6 (95% UI 12.2 to 14.4) per 100 000 people, and lower respiratory infection attributed the highest proportion to RIT age-standardized death rate, which was 13.4 (95% UI 12.0 to 14.2) per 100 000 people,

followed by tuberculosis [978 (95% UI 901 to 1036) per 100 000 people]. From 1990 to 2019, the RIT age-standardized death rate decreased significantly by -40.2% (95% UI -41.9 to -38.2). Compared to about 70% decrease in age-standardized death rate for upper respiratory infection, tuberculosis and otitis media, the decrease tendency was not that remarkable for lower respiratory infection [-38.9% (95% UI -40.7 to -36.9)]. The age-standardized DALY rate and its changes for RIT was 384.9 (95% UI 330.6 to 458.6) per 100 000 people and -32.5% (95% UI -35.9 to -28.7) respectively.

Also, lower respiratory infection had the highest age-standardized DALY rate [247.6 (95% UI 233.8 to 256.1) per 100 000 people], and decreased by -40.0% (95% UI -41.6 to -38.3). Upper respiratory infection contributed 114.5 (95% UI 69.4 to 177.0) per 100 000 people in age-standardized DALY rate, however, there was only a slight decline[-1.9% (95% UI -3.4 to -0.8)].

RIT burden by gender in the US

Gender discrepancy existed in the burden of RIT **(Table 1)**. The total RIT age-standardized incidence rate was 329 277.2 (95% UI 293405.3 to 369916.4) per 100,000 people for males, and a bit higher for females [350 449.7 (95% UI 312 738.7 to 394 590.3)], but it showed a converse results in tuberculosis, which was 2.7 (95% UI 2.3 to 3.1) per 100,000 people for males and 1.6 (95% UI 1.4 to 1.9) for females. Besides, its decrease since 1990 was -0.5% (95% UI -1.8 to 0.8) in males and -0.2% (95% UI -1.5 to 1.0) in females.

Despite a higher RIT age-standardized incidence rate in females, RIT age-standardized death rate was lower in females [16.1 (95% UI 14.7 to 17.0) per 100,000 people] than males [11.8 (95% UI 10.3 to 12.6)], and the same pattern was found for each individual RIT cause, especially tuberculosis (males 0.249 vs. females 0.125 per 100,000 people) .

While concerning changes in age-standardized death rate, the decrease was more notable in males [-47.7% (95% UI -49.4 to -45.8)] than in females [-34.2% ((95% UI -36.5 to -31.3)]. The pattern of age-standardized DALY rate by gender for RIT was analogous to the death rate, which was 424.2 (95% UI 370.5 to 499.2) per 100 000 people for males and 352.9 (95% UI 298.3 to 429.5) for females, and its decrease was higher in males by -39.7% (95% UI -43.1 to -35.7) than in female by -25.6% (95% UI -29.3 to -22.0).

IT burden by age group

The incidence rate of RIT varied widely by age group in 2019 (**Figure 1.A**). As for upper respiratory infection, the largest proportion of RIT incidence, the incidence rate peaked in the age groups 0~5 years, and decreased with increasing age. However, the incidence of lower respiratory infection showed a U shape distribution that lowest age-standardized incidence rate turned up in age groups 15-29 years, then rose with age increasing. Otitis media mostly occurred in the age groups under 15, and shapely thinned out in other age groups. Tuberculosis presented very low age-standardized incidence rate in all age groups, and an upward trend along with ages.

On the mortality of RIT in 2019 (**Figure1.B**), it was indicated that the age-standardized death rate for RIT was bimodal, with the highest value among patients aged >95 years, and a lower one in children aged <1 years. The distribution of tuberculosis, upper respiratory infection and otitis media was also very similar.

RIT burden by regions in the US

From the cartography of RIT in the US, it was shown that RIT burden varied across the US states (**Figure 2** and **Supplement eTable 2**). As shown in **Figure 2.A**, the age-

standardized incidence was highest in the East South Central [e.g., Kentucky, 342806.4 (95% UI 306557.0 to 388755.8) per 100 000 people; Tennessee, 341642.2 (95% UI 303872.6 to 385226.8); and Alabama, 341543.8 (95% UI 304133.3 to 384800.8), etc.], and these states also ranked ahead in lower respiratory infection and otitis media (**Supplement eTable 2**). The age-standardized incidence was lower in Pacific area [e.g., Alaska 335969.9, (95% UI 298716.5 to 380039.6)] and Mountain area [e.g., Montana, 336085.0 (95% UI 300216.2 to 379560.5)]. While concerning the change of RIT incidence (**Figure 2.C**), it presented downward tendency in most states, but the situation even deteriorated in some states of East South Central, for instance, Tennessee [0.2% (95% UI -4.2 to 4.8)], Mississippi [0.2% (95% UI -4.0 to 4.7)] and Alabama [95% UI 0.1% (-4.0 to 4.3)].

As indicated in **Figure 2.B** and **Supplement eTable 2**, the mortality burden of RIT was also heavy in East South Central, for instance, the highest RIT age-standardized death rate of RIT, was recorded in Mississippi [20.8 (95% UI 17.7 to 24.3) per 100 000 people], then Tennessee [9.5 (95% UI 16.3 to 22.9)] and Kentucky [19.1 (95% UI 16.0 to 22.2)]. While in Florida, Oregon and Washington, the RIT age-standardized death rate was relatively low, which was 8.7 (95% UI 7.3 to 10.2) per 100 000 people, 9.3 (95% UI 7.7 to 10.9) and 9.5 (95% UI 7.8 to 11.2), respectively. Generally, there was an obvious drop in age-standardized death rate of RIT in the US, but its decrease rate ranged largely across the country, from -17.1% (95% UI -29.0 to -2.3) in Mississippi, to -56.7% (95% UI -63.3 to -48.5) in District of Columbia (**Figure 2.D**).

Collectively, the age-standardized death rate of RIT was in inverse proportion to SDI level (**Figure 3.A)**, like higher age-standardized death rate in states with lower SDI level such as Mississippi, Kentucky. However, some deviated spots were still observed, for instance, age-standardized death rate of Florida was far below Wyoming with the

equal SDI level. And the relationship between changes in RIT age-standardized death rate and SDI was very similar to the age-standardized death rate variation with SDI (**Figure 3.B)**.

Risk factors attributable to RIT mortality

In the US, 89.9% and 85.8% of RIT mortality in males and females can be attributed to GBD risk factors. However, the gender partner of risk factors was quite different (**Figure 4**). Smoking accounted for 18.1% to RIT death in males, followed by alcohol use (11.3%), and household air pollution from solid fuels (10.1%). However, in females, Child malnutrition including child wasting (14.4%), stunting (1.9%) and underweight (1.7%) attributed the most in RIT death, and household air pollution from solid fuels combined with Ambient particulate matter pollution also accounted a high proportion in RIT death of females (14.4% and 9.8%, respectively).

Discussion

In the present study, we thoroughly discussed the burden of RIT and its attributable risk factors in the US through evaluation by age, gender, and state level. Our results indicated that although the age-standardized incidence of RIT remained almost unchanged from 1990 to 2019, there was a substantial improvement in age-standardized death (-40.2%) and DALY (-32.5%) rates in the US. Meanwhile, our work revealed that RIT burden varied widely among age groups, genders and states. This assessment could provide detailed information and evidence for the US health policy makers to focus on critical issue, reduce modifiable risk factors and improve health care quality of RIT.

Upper respiratory infection accounted for the majority proportion of RIT age standardized incidence, and due to common susceptibility and easy transmission of

numerous pathogens like rhinovirus, coronavirus, etc., it is difficult to prevent people from upper respiratory infection[11], which resulted in unchanged RIT age standardized incidence, whereas notable decrease was observed in other three RIT causes, especially tuberculosis. According to CDC, the incidence of tuberculosis dropped from 10.3 to 2.7 per 100,000, and the decline was owing to the establishment of Advisory Committee for the Elimination of Tuberculosis and the following strategies such as wide screening, adequate treatment, and implement new technologies for diagnosis, treatment, and prevention[4,12]. But since 80% of existing tuberculosis cases were reactivation of latent tuberculosis acquired in the past and most from immigrants, tuberculosis still remained a persistent low-level epidemic[4]. In addition, compared to upper respiratory infection and otitis media, tuberculosis also accounted for a relatively high age standardized death rate of RIT.

Lower respiratory infection both ranked the first in mortality and morbidity of RIT causes. Despite improvements in prognosis with advances of health care and the increased access to antibiotics, lower respiratory infection still brought out heavy heath burden in the US. In 2016, lower respiratory infection, as the 7th leading cause of death and 18th leading causes of DALYs, claimed about 95,992 life, and costed 32.2 billion[6,13,14]. This severe challenge was partly due to the spread of antibiotic resistance[6], the bottleneck of novel antimicrobials in recent years [15], clusters of vaccine refusal[16] and the increasing number of immunocompromised and aging group[1,17]. It is crucial to improve quality of health care and reduce related risk factors throughout the US to improve health outcomes of lower respiratory infection.

Our results indicated that most age standardized death of RIT occurred in the aged >70 years, and elderly people were much more susceptible and vulnerable to respiratory infection. Much of global initiatives about lower respiratory infection were focused on

children younger than 5 years, but globally, the mortality rates have remained consistently high in the elderly people worldwide since 1990, meanwhile, aging of population prompts an urgent on protecting the elderly people[6]. In addition, we found that the death rate of tuberculosis in young and middle age should not be ignored because of a high incidence rate in these population.

A distinct gender difference was found that males had a lower RIT age-standardized incidence rate (except tuberculosis), but severer outcomes as a higher age-standardized death and DALY rate, which accorded with many previous studies concerning respiratory infection disease[18]. For instance, the ratio of male to female was 1:1.27 in US nationwide population-based acute respiratory infection study involved 9 763 710 outpatients[19], but the male to female ratio of tuberculosis was 1.88:1 in 1999[20], moreover, the hazard ratio of mortality for male was 1.33 in active tuberculosis[21] and 1.59 in the COVID-19[22]. The reasons for this disparity might be due to different hormone influence, inflammatory response, and other important factors involved were environment, behavioral and metabolic risk factors, which outweighed in males[6,10,18]. Smoking is associated with increased risk and consequences of respiratory infection and COPD[23], and it was estimated that 26.2% of males and 15.7% of females consumed tobacco products in 2019, bringing about critical health burden in the US[13,24]. Air pollution, especially household air pollution, was also largely related to health loss of respiratory infection in females because of more exposure, and it was reported that household air pollution increased risk of acute respiratory infection (pooled RR=1.53 in adults) [25]. Another noteworthy risk factor was child undernutrition, also had a high prevalence in pneumonia children patients, and associated with bad health outcomes[6,26]. Through analysis by subnation, some states in East South Central area like Alabama, Mississippi, Tennessee, Kentucky were identified as the hotspots of RIT, which had not

only the highest age-standardized incidence and death rate, but also the minimal improvement in RIT burden. Persistent hotspot suggested resource inclination and policy interventions in these states. The reasons behind RIT burden disparities within the US were complex, for instance, environmental, demographic, behavioral, socio-economic factors, and among these factors, socio-economic factor was most substantial[8]. Our results showed an inverse proportion in age-standardized death rates and its change with SDI in the US, which corroborated the relationship between fatality of lower respiratory infection/tuberculosis and SDI in global level[6,27]. According to CDC data about behavioral factors involved, discrepancy of smoking and alcohol use in each state might be also associated with the RIT burden disparities [24,28].

Limitation

There were several limitations in our study, firstly, although environment, behavior, metabolic factors were included into RIT burden analysis, some important factors affecting RIT burden like ethnicity, urban and rural, cultural and immigration background could not be assessed through GBD study. Secondly, seasonal variations of upper/lower respiratory infection also could not be revealed by the annual reports of GBD. Thirdly, respiratory infection is very common in chronic diseases like COPD, heart failure and diabetes, and extra-pulmonary tuberculosis and pulmonary tuberculosis often coexisted in one patient, therefore, this may affect the precise quantitative assessment of RIT as a single contributor to health loss and death.

Conclusion

RIT remained a major cause of health loss in the US but its burden varied widely across states, ages, and genders. The major burden of RIT was from lower respiratory infection.

The burden and its improvement rate were strongly associated with SDI level, and 89.9% (males) and 85.8% (females) of RIT death was related to modifiable risk factors. We found that RIT burden had improved for all states, but some states in East South Central area were identified as the hotspots of RIT. Our work can provide evidence for health worker about management and prevention of RIT to reduce the future burden of this condition.

Conflict of interest

None declared

Founding

Reference

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Figure legends.

Figure 1. The burden of RIT stratified by age groups: the proportion of age-standardized incidence rate **(A)** and death rate **(B)** of tuberculosis, otitis media, upper and lower respiratory infection in each age group.

Figure 2. RIT burden of each state in the US: **A.** Age-standardized incidence rate of RIT in 2019. **B.** Age-standardized death rate of RIT in 2019. **C.** Change in age-standardized incidence rates of RIT, 1990-2019. **D.** Change in age-standardized death rates of RIT, 1990-2019.

Figure 3. A. The correlation of age-standardized death rate of RIT and SDI of every states in 2019. **B.** Trends in age-standardized death rates changes of RIT in each state by SDI.

Figure 4. RIT mortality attributable to different risk factors by gender.