Global Disease Burden Estimates of Respiratory Syncytial Virus–Associated Acute Respiratory Infection in Older Adults in 2015:

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SUPPLEMENT ARTICLE

Global Disease Burden Estimates of Respiratory Syncytial Virus–Associated Acute Respiratory Infection in Older Adults in 2015: A Systematic Review and Meta-Analysis

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Respiratory syncytial virus–associated acute respiratory infection (RSV-ARI) constitutes a substantial disease burden in older adults aged ≥65 years. We aimed to identify all studies worldwide investigating the disease burden of RSV-ARI in this population. We estimated the community incidence, hospitalization rate, and in-hospital case-fatality ratio (hCFR) of RSV-ARI in older adults, stratified by industrialized and developing regions, using data from a systematic review of studies published between January 1996 and April 2018 and 8 unpublished population-based studies. We applied these rate estimates to population estimates for 2015 to calculate the global and regional burdens in older adults with RSV-ARI in the community and in hospitals for that year. We estimated the number of in-hospital deaths due to RSV-ARI by combining hCFR data with hospital admission estimates from hospital-based studies. In 2015, there were about 1.5 million episodes (95% confidence interval [CI], .3 million–6.9 million) of RSV-ARI in older adults in industrialized countries (data for developing countries were missing), and of these, approximately 14.5% (214 000 episodes; 95% CI, 100 000–459 000) were admitted to hospitals. The global number of hospital admissions for RSV-ARI in older adults was estimated at 336 000 hospitalizations (uncertainty range [UR], 186 000–614 000). We further estimated about 14 000 in-hospital deaths (UR, 5000–50 000) related to RSV-ARI globally. The hospital admission rate and hCFR were higher for those aged ≥65 years than for those aged 50–64 years. The disease burden of RSV-ARI among older adults is substantial, with limited data from developing countries. Appropriate prevention and management strategies are needed to reduce this burden.

Keywords. Respiratory syncytial virus; acute respiratory infection; older adults; disease burden.

Acute respiratory infection (ARI), including pneumonia, constitutes a substantial disease burden in older adults ≥65 years. The Global Burden of Disease (GBS), Injuries, and Risk Factors Study 2015 estimated that lower respiratory infections have caused 1.2 million deaths (uncertainty range [UR], 1.0–1.3) and 13.5 million disability-adjusted life-years (UR, 11.7 million–14.4 million) in older adults [1]. Respiratory syncytial virus (RSV) is one of the important viral pathogens identified in older adults with ARI [2] and is increasingly recognized as a cause of illness in high-risk adults, including those with chronic lung and heart disease. A 4-year prospective cohort study indicated that RSV infection developed in 3%–7% of healthy older adults and in 4%–10% of high-risk adults [2]. Moreover, in that study, the hospitalization rate for RSV-ARI increased with age. An active surveillance study across multiple centers in the United States estimated that the hospital admission rate of RSV-associated community-acquired pneumonia in adults aged 50–64 years was 0.8 cases/10 000 persons per year, with higher rates in adults aged 65–79 years (2.5 cases/10 000 persons per year) and ≥80 years (5.0 cases/10 000 persons per year) [3]. Therefore, we formed a study group on RSV infections in adults to supplement a systematic literature review with unpublished data. We aimed to estimate the incidence, hospital admission rate, and in-hospital deaths associated with RSV-ARI in older adults in 2015, worldwide and stratified by industrialized and developing regions.

METHODS

Search Strategy and Selection Criteria

We conducted a systematic review across 9 databases (including 3 Chinese databases) following the approach detailed in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [4]. Tailored search strategies were developed and used to search Medline, Embase, Global Health, CINAHL, Web of Science, WHOLIS, China

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National Knowledge Infrastructure (CNKI), Wanfang Data, and Chongqing VIP databases (Supplementary Table 1). All searches were restricted to articles with publication dates between January 1996 and April 2018. No publication status criteria or language restrictions were applied. We included studies that fulfilled the selection criteria in Supplementary Panel 1.

Five investigators (T. S., A. D., A. K. T., I. C., and E. M.) conducted the search in English-language databases. Any disagreements were resolved after discussion. Two investigators (T. S. and X. L.), whose first language is Chinese, did searches and data extraction from Chinese-language databases (CNKI, Wanfang, and Chongqing VIP). We contacted investigators who led studies on RSV-ARI in older adults, and we identified unpublished data from 8 studies. The investigator group agreed on a common approach for data analysis and interpretation and formulated common case definitions. They used these case definitions to reanalyze data from their already published work, or they shared hitherto unpublished data from ongoing studies.

The protocol of this review was published in the PROSPERO database (registration CRD42018095111).

Definitions

We used case definitions of pneumonia and (very) severe pneumonia adapted from the World Health Organization (WHO) Integrated Management of Adolescent and Adult Illness guidelines [5]. The details of the definitions are displayed in Supplementary Table 2. RSV infection was laboratory confirmed. We categorized countries as either industrialized or developing on the basis of the United Nations Children's Fund's classification 2015 [6] and used this regional classification to report our results. The adult population estimates for 2015 were taken from the United Nations Population Division's database [7].

Statistical Analysis

For all included studies, we applied a continuity correction of 0.0005 if the number of cases or deaths was 0 [8]. This allowed calculation of an incidence rate, hospitalization rate, proportion, or hCFR for these instances and enabled their inclusion in subsequent meta-analyses. When the study period was >12 months but not in multiples of 1 year, we calculated the annualized incidence by adjusting for the population at risk. If clinical specimens were systematically collected in a proportion of eligible cases and data for all eligible cases were available, we scaled results for the proportion sampled.

We performed meta-analyses by region for the RSV-ARI incidence, the hospitalization rate for RSV-ARI, proportion of RSV positives among ARI cases hospitalised for ARI and the hCFR of RSV-ARI and reported pooled estimates (with 95% confidence intervals [CIs]) primarily for older adults but also for other age groups of interest (eg, the 50–64-year age group, when data were available). Meta-analysis was performed when there were at least 3 studies. We used the random effects model (DerSimonian-Laird method) because in-study and between-study data heterogeneity was anticipated and, thus, different effect sizes were assumed [9]. The incidence and hospitalization rate meta-estimates for RSV-ARI were applied to the ≥65-year-old regional populations to yield estimates for new episodes of RSV-ARI and cases admitted to hospitals in 2015. We validated hospitalizations for RSV-ARI estimates with an independent data set by abstracting the proportion of ARI hospital admissions that involved RSV-positive cases [10]. We then computed meta-estimates of the regional proportion and applied these to regional estimates of hospital admissions for ARI in older adults in 2015 (Shi, unpublished data). We estimated in-hospital RSV-ARI deaths by applying regional hCFR meta-estimate to the regional number of RSV-ARI hospital admissions. We estimated URs for in-hospital death by using Monte Carlo simulation (calculating estimates from 10 000 samples from log-normal distributions, with 2.5th and 97.5th centiles defining the UR). A similar simulation was performed to generate the global estimate (from regional estimates).

Data were analyzed using Stata, version 13.0, and R, version 3.0.2.

RESULTS

We identified 6593 records, and 36 articles fulfilled our selection criteria (Supplementary Figure 1) [2, 11–45]. Another 8 unpublished studies were contributed by the investigator group. Overall, 44 studies had relevant data and were included (Supplementary Figure 2). We identified 19 studies from industrialized countries, 24 from developing countries, and 1 from a mix of industrialized countries and developing countries. Nineteen studies were from urban areas, 8 were from rural areas, and 17 were from a mixed population. Among them, 9 reported the community incidence rate in older adults, 16 reported the hospital admission rate, 19 had proportion data, and 14 reported the hCFR. The full descriptions of the study characteristics and reported outcomes are available in Supplementary Tables 3–6. Most studies only reported data for individuals aged ≥65 years and did not stratify these by narrower age bands. Therefore, we decided to report our primary estimates for older adults (ie, those ≥65 years); we also reported data for those aged ≥50 or 50–64 years, when sufficient data were available.

Nine community-based studies with active case ascertainment reported the RSV-ARI incidence (Table 1). The incidence rate of RSV-ARI in older adults from industrialized countries was estimated to be 6.7 cases/1000 persons per year (95% CI, 1.4–31.5). We could not reliably estimate any rate for developing countries, owing to the paucity of data for this region (there was only 1 study from India). The estimated number of RSV-ARI cases among older adults in industrialized countries was 1.5 million (95% CI, 0.3 million–6.9 million). Only 1 study, from Wisconsin, provided data stratified by sex and subtype [12], which showed that the incidence rate of RSV-ARI in adults

Table 1. Estimates of the Incidence, Hospital Admission Rate, In-Hospital Case-Fatality Ratio (hCFR), and Number of Episodes and In-Hospital Deaths Among Older Adults Aged ≥65 Years With Respiratory Syncytial Virus (RSV)–Associated Acute Respiratory Infection (ARI), 2015

Variable	Developing Countries	Industrialized Countries	Global[a]
Incidence			
Studies, no.	1	5	6
Incidence, cases/1000 persons per y	…	6.7 (1.4–31.5)	…
Cases, no., ×1000	…	1479 (315–6939)	…
Hospital admission rate			
Studies, no.	6	6	12
Hospitalization rate, cases/1000 persons per y	0.3 (.1–.7)	1.0 (.5–2.1)	…
Cases, no., ×1000	109 (45–266)	214 (100–459)	336 (186–614)
RSV positivity among hospitalized ARI cases			
Studies, no.	8	3	11
Proportion, %	3.0 (1.9–4.9)	4.4 (3.0–6.5)	…
Cases, no., ×1000	113 (69–186)	136 (83–221)	252 (178–360)
hCFR and no. of deaths			
Studies, no.	5	3	8
hCFR, %	9.1 (2.6–31.8)	1.6 (.7–3.8)	…
Deaths, no., ×1000	10.1 (2.1–45.5)	3.3 (1.0–10.8)	14.1 (4.8–50.5)

Measures of dispersion are 95% confidence intervals.

[a]Although the overall numbers of cases and deaths were obtained by summing the region-specific numbers for each of the 10 000 samples in the Monte Carlo simulation, the point estimates and uncertainty interval limits for the overall cases are not equal to the sum of the region-specific results.

aged ≥50 years was 12.7 cases/per 1000 persons per year (95% CI, 9.9–16.3) in men and 17.8 cases/1000 persons per year (95% CI, 14.7–21.6) in women, while the rate was 8.0 cases/1000 persons per year (95% CI, 6.4–10.0) for RSV-A and 7.4 cases/per 1000 persons per year (95% CI, 5.0–9.3) for RSV-B.

Sixteen hospital-based studies with passive case ascertainment reported the hospitalization rate for RSV-ARI in older adults. We estimated the RSV-ARI hospitalization rate in older adults from industrialized countries to be 1.0 cases/per 1000 persons per year (95% CI, .5–2.1), while the rate was 0.3 cases/per 1000 persons per year (95% CI, .1–.7) in developing countries. In studies with data for adults aged 50–64 years, the hospitalization rate for RSV-ARI was 0.3 cases/per 1000 persons per year (95% CI, .1–1.7) in industrialized countries (3 studies), while the rate was 0.2 cases/per 1000 persons per year (95% CI, .1–.3) in developing countries (6 studies). The hospitalization rate was higher in industrialized countries as compared to developing countries, with overlapping 95% CIs in both age groups. The overall number of RSV-ARI cases involving hospital admission among older adults was 336 000 (UR, 186 000–614 000).

Nineteen hospital-based studies (without a clear population denominator) reported the proportion of RSV-positive cases among all hospital admissions for ARI. Using this independent data set, we estimated that 252 000 hospital admissions for RSV-ARI (UR, 178 000–360 000) occurred in older adults in 2015. Data were insufficient to provide the number of global and regional hospital admissions stratified by sex or RSV subtype.

Ten published and 4 unpublished studies reported the hCFR for older adults with RSV-ARI (17 189 cases). In industrialized countries, the hCFR meta-estimate was 1.6% (95% CI, .7%–3.8%), while it was 9.1% (95% CI, 2.6%–31.8%) in developing countries. Seven studies also reported the hCFR in those aged 50–64 years: 1.4% (95% CI, .5–3.6) from industrialized countries (3 studies) and 2.5% (95% CI, .6%–9.9%) from developing countries (4 studies). The hCFR was higher in older adults than those aged 50–64 years in both industrialized countries and developing countries. The hCFR was higher in developing countries as compared to industrialized countries, with overlapping 95% CIs, for both age groups. The overall number of in-hospital deaths in older adults was 14 100 (UR, 4800–50 500) in 2015. Data were insufficient to provide global and regional death estimates stratified by gender or RSV subtype. One study from Guatemala reported deaths in 61.5% of patients (8 of 13) aged ≥50 years with very severe RSV-ARI (ie, requiring intensive care unit admission or mechanical ventilation) [17].

DISCUSSION

This is the first systematic review to evaluate and summarize the available literature and unpublished data and estimate the burden of RSV-ARI in older adults. Our review summarized data from about 18 000 cases of RSV-ARI in older adults reported in 36 articles and 8 unpublished studies. Our study showed a substantial disease burden of RSV-ARI in older adults. We estimated that, in 2015, there were about 1.5 million episodes of RSV-ARI (95% CI, 0.3 million–6.9 million) in older adults in industrialized countries and that, of these episodes, 214 000 (95% CI, 100 000–459 000; approximately 14.5%) involved hospital admission. The global number of hospital admissions for RSV-ARI in older adults was estimated at 336 000 (UR, 186 000–614 000). A plausibility check using an independent approach with nonoverlapping data from 19 different studies was in good agreement with our hospital

admission estimates and supports their validity. We further estimated that there were about 14 000 in-hospital deaths (UR, 5000–50 000) related to RSV-ARI. Because the estimates only include individuals who were admitted to the hospital, it is most likely a gross underestimate, owing to the limited access to care and poor care-seeking behavior in developing countries.

There is some inconsistency between our estimates and estimates from other studies. A modeling study showed that the annual estimate of RSV-associated respiratory and circulatory deaths was around 11 000 in the United States, which is similar to the number reported by Falsey et al (about 14 000) [2, 46]. GBD 2015 estimated that the overall number of deaths due to RSV could be as high as 54 820 in older adults globally (with 76 477 deaths for influenza and 588 961 for pneumococcal pneumonia) [1]. This might indicate that a high proportion of RSV-associated mortality could happen outside hospitals [2]. Moreover, we only included laboratory-confirmed RSV-associated cases, which could miss a number of cases with late presentation or lower viral loads [47].

Estimates vary considerably among regions and study sites. Comparisons among studies should be interpreted with caution because several factors may affect the estimates: methodological differences across studies (ie, differences in enrollment criteria, case definitions for ARI, case ascertainment method, and sample sizes of included studies), annual variations in RSV activity, clinical specimens evaluated, sensitivity and specificity of RSV diagnostic tests, variation in RSV epidemiology between study populations, and healthcare-seeking behavior of the underlying population. Although we did not include fever as part of the case definition, a few studies used a definition of severe acute respiratory infection (SARI) that required a history of fever or measured fever of ≥38°C, which could have missed some RSV cases [48]. Therefore, the true uncertainties around these estimates are larger than those expressed in the standard 95% CIs that we report. This heterogeneity might also result in differences when comparing our estimates to those from other studies [2, 46]. The hospitalization rate was higher for those aged ≥65 years than those aged 50–64 years (with overlapping 95% CIs) in both industrialized and developing countries, indicating that age might be an important risk factor for RSV-ARI–related hospital admissions among those ≥50 years. The hospitalization rate was higher in industrialized countries than in developing countries, with overlapping 95% CIs. This may be largely explained by the higher proportion of older adults and lower thresholds for hospital admission in industrialized countries and by poor care-seeking behavior in developing countries. However, the hCFR in industrialized countries was lower than in developing countries (with overlapping 95% CIs). The poorer outcome might reflect delayed presentation and less optimal case management strategies in developing countries, including lack of supportive care (including mechanical ventilation), suboptimal treatment of secondary bacterial infections, or suboptimal control of underlying conditions such as chronic obstructive pulmonary disease or diabetes.

Our estimates of RSV-ARI morbidity and mortality are limited by data availability in developing countries, where outcomes may be poorer. Of the 24 studies from developing countries, most reported the proportion of admissions of RSV-positive individuals (without a clear population denominator), and none provided community-based RSV-ARI incidence or mortality rates. Estimates from developing countries were missing for some WHO regions (the Eastern Mediterranean Region, the South-East Asia Region, and much of the African Region). The hospital admission estimates of RSV-ARI from developing countries came largely from studies where the catchment population had relatively good access to care. We expect that many adults with severe or very severe RSV-ARI in developing countries do not receive prompt hospital care. Therefore, our global and regional estimates likely underestimate the true burden of RSV-ARI in both community and hospital settings. Further estimates of the overall RSV-ARI mortality from population-based studies with demographic surveillance could provide additional data to allow more-robust estimates. Better surveillance systems, including standard case definitions and reporting practices, would substantially reduce the uncertainty in the RSV-ARI morbidity and mortality estimates. Currently an RSV surveillance pilot is being built on the WHO Global Influenza Surveillance and Response System platform, which included countries implementing community-based RSV surveillance and hospital-based RSV surveillance [49].

Few data are available stratified by narrower age groups or by sex. Therefore, the overall estimate for older adults was generated directly from the incidence or hospital admission rate for the group aged ≥65 years. Although our results showed that the hospital admission rate and hCFR increased with age, which indicates that age might be a risk factor for RSV-ARI in those aged ≥50 years, the number of available studies was limited and restricted to 2 age groups (≥65 years and 50–64 years). More studies with age- and sex-specific data are required, to provide more-robust evidence. Data were insufficient to provide estimates of the regional incidence or hospitalization rate stratified by RSV subtype. One community cohort study reported that both RSV antigenic groups circulated each year without significant differences in the proportion of each subtype among both outpatients and inpatients [12]. Moreover, only 1 study provided the hospital admission rate and hCFR for older adults with very severe RSV-ARI [17].

A low RSV detection rate in older adults may be due to the low awareness of RSV infection, challenges in diagnosing RSV in clinical practice, difficulty in obtaining appropriate clinical specimens for testing, insensitivity of some of the current diagnostic tests, and relatively high cost of polymerase chain reaction analysis. Moreover, older adults usually have atypical or delayed clinical presentations with very low viral loads, which

further decreases the sensitivity of diagnostic tests, particularly those for antigen testing [47]. They may not have detectable virus when they visit the clinics or hospitals, owing to a shorter duration of shedding, delay in presentation for care, or inappropriate specimen collection [11].

Although age might be a risk factor for RSV-ARI in adults aged >50 years, the majority of older adults who have been studied had underlying medical conditions, such as congestive heart failure and chronic obstructive pulmonary disease, which are associated with an increased risk of RSV-ARI and poor outcome. Moyes et al [37] reported that the hospital admission rate among individuals with RSV-ARI was around 1.0–4.8 cases/1000 persons per year in HIV-infected older adults, while the rate was 0.2 cases/1000 persons per year in those without HIV infection (which translates to a relative risk between 5 and 24). Thus, comorbidities should be taken into consideration when evaluating the role of age in RSV-ARI hospitalizations. Most studies included participants with and those without comorbidities and did not report comorbidity-specific disease burdens. One study presented the hCFR of RSV-ARI in patients with and those without immunocompromised status among individuals aged ≥60 years (7.0% vs 6.8%) [24]. Falsey et al [2] reported that the hCFR of RSV-ARI in older adults hospitalized with acute cardiopulmonary conditions was 7.6%, which is higher than the hCFR from our meta-estimate for industrialized countries. Further research into the high-risk profiles of older adults admitted to hospitals with severe RSV-ARI could help guide management strategies, reducing RSV-ARI hospitalization and improving outcomes.

According to Falsey et al, in US residents aged ≥65 years, RSV infection accounted for 10.6% of hospitalizations for pneumonia, 11.4% for chronic obstructive pulmonary disease, 5.4% for congestive heart failure, and 7.2% for asthma [2]. Therefore, the estimate from this report on RSV-ARI could underestimate the overall disease burden attributable to RSV infection. Moreover, our study was limited to hospitalized patients and did not account for the substantial outpatient burden of RSV disease.

Causal attribution of RSV infection in older adults is best assessed in case-control studies. However, asymptomatic RSV infection is uncommon, occurring in only about 10% of asymptomatic participants [50]. Our recent meta-analysis suggests that there was strong evidence for the association, indicating possible causal attribution for RSV in older adults presenting with ARI, compared with those without respiratory symptoms or healthy older adults [50]. Among individuals with RSV-ARI, ARI is causally attributable to RSV in about 88%.

In conclusion, this study provides a review of the existing evidence regarding the RSV-ARI burden in community and hospital settings in older adults aged ≥65 years. RSV-ARI is an important disease among older adults. More high-quality data (including detailed age-stratified data) on RSV-ARI morbidity and mortality with larger sample sizes will improve the disease burden estimate and help guide targeted interventions, such as vaccination.

STUDY GROUP MEMBERS

Respiratory Syncytial Virus Consortium in Europe investigators are Harish Nair, Harry Campbell, Ting Shi, Shanshan Zhang, and You Li (University of Edinburgh); Peter Openshaw and Jadwicha Wedzicha (Imperial College London); Ann Falsey (University of Rochester); Mark Miller (Fogarty International Center, National Institutes of Health); Philippe Beutels (Universiteit Antwerpen); Louis Bont (University Medical Centre Utrecht); Andrew Pollard (University of Oxford); Eva Molero (Synapse); Federico Martinon-Torres (Servicio Galego de Saude); Terho Heikkinen (Turku University Central Hospital); Adam Meijer (National Institute for Public Health and the Environment); Thea Kølsen Fischer (Statens Serum Institut); Maarten van den Berge (Academisch Ziekenhuis Groningen); Carlo Giaquinto (Fondazione PENTA for the treatment and care of children with HIV-ONLUS); Rafael Mikolajczyk (Martin-Luther University Halle-Wittenberg); Judy Hackett (AstraZeneca); Bing Cai and Charles Knirsch (Pfizer); Amanda Leach and Sonia K. Stoszek (GlaxoSmithKline); Scott Gallichan, Alexia Kieffer, Clarisse Demont, and Angeline Denouel (Sanofi Pasteur); Arnaud Cheret, Sandra Gavart, and Jeroen Aerssens (Janssen); and Robert Fuentes and Brian Rosen (Novavax).

Supplementary Data

Supplementary materials are available at The *Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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