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## Disease Burden Estimates of Respiratory Syncytial Virus related Acute Respiratory Infections in Adults With Comorbidity

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# Disease burden estimates of RSV associated with acute respiratory infections in adults with comorbidity: A systematic review and meta-analysis

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## ABSTRACT

### BACKGROUND

Respiratory syncytial virus associated acute respiratory infection (RSV-ARI) constitutes a substantial disease burden in adults, especially in those with comorbidities. We aimed to identify all studies worldwide investigating the disease burden of RSV-ARI in adults with comorbidities.

### METHODS

We estimated the community incidence, hospitalisation rate and in-hospital case fatality ratio (hCFR) of RSV-ARI in adults with comorbidities based on a systematic review of studies published between January 1996 and March 2020. We also investigated the strength of the association between RSV-ARI and any comorbidity in adults. Meta-analyses based on random effects model were carried out to generate the estimates.

### RESULTS

Overall 20 studies were included. Comorbidities such as cystic fibrosis, chronic obstructive pulmonary disease, congestive heart failure, immunocompromised status and human immunodeficiency virus were reported. The annual incidence rate of RSV-ARI in adults with any comorbidity was 37.6 (95% confidence interval 20.1-70.3) per 1,000 persons per year in industrialised countries and the seasonal incidence rate was 28.4 (11.4-70.9) per 1,000 persons per season. The hCFR in industrialised countries was 11.7% (5.8-23.4). There were no studies in developing countries. There were insufficient data to generate the meta-estimate of hospitalisation rate. The likelihood of experiencing RSV-ARI was estimated to be 4.1 (odds ratio; 1.6-10.4) from studies using univariable analysis and 1.1 (0.6-1.8) from studies using multivariable analysis for those with any comorbidity compared to those without.

### CONCLUSION

The disease burden of RSV-ARI among adults with comorbidity is substantial with limited data available, especially for developing countries; appropriate prevention and management strategies are needed to reduce this burden.

Key words: respiratory syncytial virus, adults, comorbidity, acute respiratory infection

## INTRODUCTION

Acute respiratory infections (ARI), including pneumonia, constitute a substantial disease burden in adults [1]. The Global Burden of Disease, Injuries, and Risk Factors (GBD) Study 2015 estimated that in 2015 lower respiratory infections have caused 1.7 million deaths (uncertainty range [UR] 1.6-1.8) and 32.3 million disability-adjusted life-years (UR 29.9-33.9) in adults [2]. Respiratory syncytial virus (RSV) is one of the important viral pathogens identified in adults with ARI [3] 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 was observed annually in 3%-7% of healthy older adults and in 4%-10% of adults with chronic cardiopulmonary disease [3]. In this study, RSV infection was found in 10.6% of hospitalisations with pneumonia, 11.4% of hospitalizations with chronic obstructive pulmonary disease (COPD), 5.4% of hospitalisations with congestive heart failure (CHF) and 7.2% of hospitalizations with asthma in adults  $\geq 65$  years. Previously, we estimated that in 2015, there were about 1.5 million (95% confidence interval (CI) 0.3-6.9) episodes of RSV-ARI in older adults  $\geq 65$  years in industrialised countries (data unavailable in developing countries), and of these 214,000 (~14.5%; 95% CI 100,000-459,000) were admitted to hospitals [4]. The global number of hospital admissions for RSV-ARI in older adults was estimated at 336,000 (UR 186,000-614,000). We also estimated that about 14,000 (UR 5,000-50,000) in-hospital deaths in older adults were related to RSV-ARI globally. However, the disease burden in adults with comorbidity is not well characterised in spite of being increasingly recognised. In this study, we aimed to estimate the incidence, hospital admission rate and in-hospital case fatality ratio associated with RSV-ARI in adults with comorbidity, as well as the strength of association between RSV-ARI and comorbidities.

## METHODS

### Search strategy and selection criteria

We conducted a systematic review across 7 databases (including 3 Chinese language databases) following the approach detailed in the PRISMA guidelines [5]. Tailored search strategies were

developed and applied to search Medline, Embase, Global Health, LILACS, China 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 March 2020. No publication status criteria or language restrictions were applied. We included studies that fulfilled the selection criteria as indicated in Supplementary Panel 1.

Four investigators (TS, SV, FJ and RB) conducted the search in the databases independently and extracted data using standardised data extraction templates. Any disagreements were resolved upon discussion. The protocol of this review was published in PROSPERO database (No. CRD42020172051).

## Definitions

We adopted the case definitions of pneumonia and (very) severe pneumonia, which were adapted from the WHO Integrated Management of Adolescent and Adult Illness (IMAI) guidelines [6]. The details of the definitions are displayed in Supplementary Table 2. RSV infection was laboratory confirmed. We categorised countries as either industrialised or developing on the basis of UNICEF's classification 2015 [7] and used this regional classification to report our results.

## Statistical analysis

We calculated incidence rate, hospitalisation rate or in-hospital case fatality ratio (hCFR). We performed meta-analyses (using Stata version 14.0) by region for RSV-ARI incidence and hCFR and reported pooled estimates (with 95% CIs). Meta-analysis was carried out when there were at least 3 studies. We applied a random effects model (DerSimonian-Laird method) because in-study and between-study data heterogeneity was anticipated [9].

We calculated odds ratios (ORs) of experiencing RSV-ARI for adults with comorbidity compared to the control group (without comorbidity) with accompanying 95% CIs. ORs from univariable analysis and adjusted ORs from multivariable analysis were extracted and reported separately. Using STATA (version 14.0), we performed a meta-analysis of comorbidity associated ORs and reported pooled

estimates with corresponding 95% CIs using the random effects model due to the heterogeneity across studies as mentioned above.

## RESULTS

### *Study characteristics*

We identified 2,026 records, and 20 articles fulfilled our selection criteria (Supplementary Figure 1) [10-29]. Eighteen studies were from industrialised countries and 2 from developing countries. Nineteen studies were from urban areas and one from a mixed population. Among all studies, 7 reported the community-based incidence rates in adults with comorbidity, 2 reported hospital admission rates, 8 had hCFR data, and 5 reported odds ratios for comparison of patients with and without a comorbidity. The definitions of comorbidity in these studies are presented in Supplementary Table 3. The full descriptions of study characteristics and reported outcomes are available in Supplementary Table 4. Half (10/20) of the included studies reported data in patients  $\geq 18$  years and some focused on an older age group (e.g.  $\geq 50$  years). One study stratified the data by narrower age bands [17].

### *Incidence*

Seven community-based studies (with eight data points) reported RSV-ARI incidence in adults with comorbidity [10-16]. All of them came from industrialised countries and reported incidence rate in adults with cystic fibrosis, CHF, COPD or those with immunocompromised status due to haematopoietic stem cell transplantation (HSCT). The incidence rate of RSV-ARI in adults with any comorbidity from industrialised countries was 30.3 (95% CI 15.3-59.9) per 1,000 persons per year/season. Three studies reported annual incidence rate for adults with cystic fibrosis and immunocompromised status and its meta-estimate was 37.6 (95% CI 20.1-70.3) per 1,000 persons per year. Four studies reported seasonal incidence rate for adults with CHF, COPD and immunocompromised status and its meta-estimate was 28.4 (95% CI 11.4-70.9) per 1,000 persons per season.

*Hospitalisations*

Two hospital-based studies reported hospitalisation rate for RSV-ARI in adults with comorbidities [17, 18]. One came from South Africa and another one from US. Moyes et al. [17] estimated the hospitalisation rate of RSV-ARI in adults with human immunodeficiency virus (HIV) in three age bands (18-44 years, 45-64 years and  $\geq 65$  years). The rate in the age band of  $\geq 65$  years was 4.8 (95% CI 1.6-11.2) per 1,000 persons per year in 2012, while in the age band of 45-64 years, the rate was 2.0 (95% CI 1.5-11.2) per 1,000 persons per year and in those aged 18-44 years, the rate was 2.0 (95% CI 1.5-11.2) per 1,000 persons per year. In the study by Falsey et al. [18], the hospitalisation rate in adults with CHF or COPD aged  $\geq 65$  years was 13.2 (95% CI 6.8-23.0) per 1,000 persons per year.

*hCFR*

Eight studies reported hCFR of RSV-ARI in adults with comorbidities [15, 17, 19-22, 28, 29]. Six studies (with seven data points) came from industrialised countries and another two from developing countries. Four studies reported data in adults  $\geq 18$  years and the rest focused on an older age group, e.g.  $>45$  years. Comorbidities such as HIV, CHF, COPD and immunocompromised status were reported. Overall, the hCFR meta-estimate was 11.0% (95% CI 6.8-17.9) in adults with any comorbidity. In industrialised countries, it was 11.7% (95% CI 5.8-23.4).

*Associations*

Five studies reported the associations between the occurrence of RSV-ARI and the history of comorbidity (ies) in adults [23-27]. All of them were hospital-based studies and came from industrialised countries. Three studies reported the results using univariable analysis, one study used multivariable analysis and one study reported both. Three studies reported data in adults  $\geq 18$  years, while one focused on  $\geq 21$  years and another one focused on  $\geq 50$  years. Comorbidities such as asthma, CHF, COPD, diabetes and immunocompromised status were reported. Their comparison groups were adults without this comorbidity. The meta-estimate OR from studies using univariable analysis was 4.1 (95% CI 1.6-10.4) based on 16 data points while it was 1.1 (95% CI 0.6-1.8) from those using multivariable analysis based on 6 data points for RSV-ARI hospitalisation in patients with a



comorbidity comparing to those without the comorbidity. When focusing on CHF, the meta-estimate OR was 3.3 (95% CI 0.2-44.9) based on univariable analysis from three data points.

## DISCUSSION

This is the first systematic review to evaluate and summarise the available literature that estimates the burden of RSV-ARI in adults with comorbidities. Our review summarised data from about 11,000 cases of RSV-ARI in adults with comorbidities reported in 20 articles. Our study shows a substantial disease burden of RSV-ARI in adults with comorbidities. We estimated that the annual incidence rate was 37.6 (95% CI 20.1-70.3) per 1,000 persons per year and seasonal incidence rate was 28.4 (95% CI 11.4-70.9) per 1,000 persons per season in industrialised countries. The hCFR was 11.7% (95% CI 5.8-23.4) for industrialised countries. The overall hCFR was 11.0% (95% CI 6.8-17.9) in adults with any comorbidity. The association between RSV-ARI and a comorbidity in adults was 4.1 (95% CI 1.6-10.4) based on univariable analysis and 1.1 (95% CI 0.6-1.8) from multivariable analysis.

The incidence rate of RSV-ARI in adults with comorbidities in our study was much higher than the rate reported in general population (with or without comorbidities): 37.6 (95% CI 20.1-70.3) compared to 6.7 (95% CI 1.4-31.5) per 1000 persons per year in industrialised countries [4]. However, the latter estimate was focusing on those aged  $\geq 65$  years, while our estimate included also younger patients. We observed a similar pattern for hCFR. In industrialised countries, hCFR of RSV-ARI was 11.7% (95% CI 5.8-23.4) for adults with comorbidity, while it was 1.6% (95% CI 0.7-3.8) for general population [4]. This indicates that adults with comorbidities could have a higher risk of experiencing RSV-ARI infection and tend to have a poorer outcome. We could not reliably estimate any data for developing countries due to paucity of data from this region (none reported incidence rate, one reported hospitalisation rate and two reported hCFR).

Variations in estimates from different studies should be interpreted with caution, because several factors may affect the estimates: methodological differences across studies (e.g. differences in enrolment criteria, case definitions for ARI, case ascertainment method, definition of comorbidity, age group of study population and sample size of included studies), annual variations in RSV activity, clinical specimen, sensitivity and specificity of RSV diagnostic tests, variation in RSV epidemiology between study populations, and healthcare seeking behaviour of the underlying population. Although we did not

include fever as part of the case definition, one study used severe acute respiratory infection (SARI) that required history of fever or measured fever of  $\geq 38\text{ C}^\circ$ , which could result in missing some RSV cases [30]. Moreover, the in-hospital CFR was defined as 90-day overall mortality or death at 100 days in two studies, which might have overestimated the actual in-hospital CFR. Therefore, considering the variations across study sites, the true uncertainties around these estimates are larger than those expressed in the standard 95% CI that we reported.

There are a few limitations of this study. First, our estimates of RSV-ARI morbidity and mortality in adults with comorbidity are limited by data availability in developing countries where outcomes may be poorer. Of the 20 studies, only two were from developing countries, reporting the hospitalisation rate or hCFR. We expect that many adults with severe or very severe RSV-ARI in developing countries do not receive prompt hospital care. Further estimates of RSV-ARI morbidity and 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 in both industrialised and developing countries. Second, most studies (4/5) used RSV negative ARI patients as the control group to investigate the strength of association which might not reflect the true association between RSV-ARI and comorbidity in general population. Third, most studies did not report age group specific rate except Moyes' study, where the hospitalisation rate in adults with HIV seemed to increase with age: 1.1 (95% CI 0.9-1.2) per 1,000 persons per year in adults with 18-44 years, 1.4 (95% CI 1.0-1.9) in 45-64 years, and 3.9 (95% CI 0.8-11.3) in  $\geq 65$  years. This indicates that age might be an important risk factor for RSV-ARI related hospital admissions among adults with HIV. More studies with age specific data are required to provide more robust evidence for HIV and other comorbidities (e.g. COPD, cardiorespiratory) [31, 32]. Fourth, we only included laboratory confirmed RSV cases which could miss a number of cases with late presentation or lower viral loads [33]. In addition, the estimate from this report on RSV-ARI could underestimate the overall disease burden attributable to RSV infection. For example, it would be helpful to include exacerbation of underlying heart and lung disease rather than only those diagnosed as ARI. Fifth, there were insufficient data to

provide regional incidence or hospitalisation rate estimate. Also, estimates by RSV sub-type or gender-specific estimates were missing.

In conclusion, this study provides a review of the existing evidence regarding RSV-ARI burden in community and hospital settings in adults with comorbidities. RSV-ARI is an important disease among this population. Further research into the high-risk profiles of adults will improve the disease burden estimate on RSV-ARI morbidity and mortality in adults with comorbidities. This will help guide management strategies and guide targeted interventions such as vaccination against RSV.

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## **RESCEU Investigators**

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## **Conflict of interest**

HN reports grants from Innovative Medicines Initiative, during the conduct of the study; grants and personal fees from Sanofi Pasteur, personal fees from Janssen, personal fees from AbbVie, grants and personal fees from World Health Organisation, personal fees from Bill and Melinda Gates Foundation, and grants from NIHR, outside the submitted work. All other authors report no potential conflicts.

**Table1:** Meta-estimates of the incidence, hCFR and OR of RSV-ARI in adults with any comorbidity from industrialised countries

	<b>Industrialised countries</b>
<b>Incidence rate of RSV-ARI</b>	
<b>Number of studies</b>	7 (8)
<b>Incidence rate (annual)</b>	37.6 (20.1-70.3)
<b>Incidence rate (seasonal)</b>	28.4 (11.4-70.9)
<b>hCFR of RSV-ARI</b>	
<b>Number of studies</b>	6 (7)
<b>hCFR</b>	11.7 (5.8-23.4)
<b>OR of RSV-ARI (univariable)</b>	
<b>Number of studies</b>	4 (16)
<b>OR</b>	4.1 (1.6-10.4)
<b>OR of RSV-ARI (multivariable)</b>	
<b>Number of studies</b>	2 (6)
<b>OR</b>	1.1 (0.6-1.8)

RSV=respiratory syncytial virus. ARI=acute respiratory infection. hCFR=in-hospital case fatality ratio. OR=odds ratio. Incidence rate (annual) is presented as per 1,000 persons per year. Incidence rate (seasonal) is presented as per 1,000 persons per season. hCFR is presented as %. Incidence rate, hCFR and OR are presented with 95% CIs. Data in parentheses indicate number of data points.

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