The Global Burden of Infectious Respiratory Diseases in Adults: Interview with Three Key Opinion Leaders

Interviewees:



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Interview Summary

According to the WHO, the proportion of the world's population aged over 60 years will almost double, from 12% to 22%, between 2015-2050. This statistic underscores the need to focus clinical attention on older adults and the risk to healthy ageing from infectious viral respiratory diseases, including COVID-19, respiratory syncytial virus (RSV), and influenza, as well as other diseases, such as pertussis, herpes zoster, and pneumococcal infections. For this article, EMJ conducted an interview in November 2024 with three key opinion leaders, Archana Chatterjee from Chicago Medical School and Rosalind Franklin University of Medicine and Science, North Chicago, Illinois, USA; Stefan Gravenstein from Warren Alpert Medical School of Brown University, Providence, Rhode Island, USA; and Tino Schwarz from the Institute of Laboratory Medicine and Vaccination Centre, Klinikum Würzburg Mitte, Standort Juliusspital, Germany, to review the global burden of infectious respiratory diseases in adults, and explore strategies to address this burden. The experts provided valuable insights into topics such as the current landscape of infectious respiratory diseases and how it is evolving, key clinical and lifestyle risk factors for infectious respiratory diseases, and the importance of surveillance. Also discussed were the challenges associated with the diagnosis of infectious respiratory diseases and treatment options for patients with these diseases. Further topics covered included non-vaccine preventive measures, adult vaccination strategies, and key challenges and barriers to the implementation of vaccination for infectious respiratory diseases in adults. The experts explored options to improve education and communication about infectious respiratory diseases and preventive strategies, including educating healthcare teams, as well as keeping patients informed and educated on this topic. Finally, the experts outlined changes they would like to see in the future to address the global burden of infectious respiratory diseases in adults.

INTRODUCTION

According to the WHO, the proportion of the world's population aged over 60 years will almost double, from 12% to 22%, between 2015–2050.¹ This statistic underscores the need to focus clinical attention on older adults and the risk to healthy ageing from infectious viral respiratory diseases, including COVID-19, RSV, and influenza, as well as other diseases, such as pertussis (whooping cough, a bacterial respiratory infection), herpes zoster (caused by reactivation of latent varicella zoster virus), and pneumococcal infections. Although the importance of these infections in older adults is well known,²⁻⁵ vaccination coverage rates in high-income countries are low.6-8 Efforts are needed to raise awareness of this issue among healthcare professionals (HCP), particularly general practitioners (GP), and improve vaccination uptake. Infectious viral respiratory diseases, specifically COVID-19, RSV, and influenza, are the main focus of this article.

CURRENT LANDSCAPE OF INFECTIOUS RESPIRATORY DISEASES

Current Landscape of Infectious Respiratory Diseases and How it is Evolving

Chatterjee described COVID-19 as a disease that is "forgotten, but not gone", with COVID-19-related deaths still reported, particularly in older populations. According to Chatterjee, there is a lack of knowledge surrounding RSV infection and pertussis among the public. Although there is awareness that these diseases can have a significant impact in children, there is little understanding of the potential for serious disease and death in adults. Chatterjee acknowledged that influenza vaccination coverage in older adults in the USA is greater than for other infectious respiratory diseases; however, there is room for improvement, particularly in the context of new emerging influenza strains.

The experts expressed concern that the highly pathogenic avian influenza A (H5N1) virus, which has entered dairy herds in the USA,^{9,10} may now spread more easily into humans. Chatterjee suggested: "As we gain control of the spread of some viral illnesses (e.g., COVID-19, RSV, and influenza), other respiratory viruses, including human parainfluenza viruses and human metapneumovirus, may take up the ecological space and start to cause proportionately more disease than we have seen with these viruses in the past."

Gravenstein pointed out that during lockdown in the COVID-19 pandemic, there was almost ablation of the other respiratory viruses, and now the infectious respiratory diseases besides COVID-19 are "flying under the radar" for adults. The post-pandemic resurgence in these respiratory infectious diseases, in the context of declining vaccination rates, was not a surprise to the infectious diseases experts, according to Gravenstein.

Gravenstein referred to a pilot surveillance study in nursing homes that used a pointof-care molecular test for COVID-19, influenza A or B, or RSV.¹¹ In this study, a positive result for COVID-19 prompted much more COVID testing, whereas there was little additional testing following a positive result for influenza or RSV,11 thus indicating a potential disparity in understanding of the impact of these diseases. According to Gravenstein, HCPs in nursing homes understand that COVID-19 is an important issue for older adults; however, there are signs that many believe the threat from this infectious disease is over, as shown by the limited use of masks and reduced efforts to promote vaccination.

Chatterjee was surprised to see that influenza vaccination rates have been reported to be higher than COVID-19 vaccination rates in nursing homes.¹² Chatterjee expressed that this disparity does not make sense from a medical and public health standpoint as both diseases can be severe and life-threatening in older adults. In response to this, Gravenstein explained that nursing homes are a unique environment as there are quality measures that rate these institutions based on influenza vaccine uptake, but not yet on the uptake of vaccines for other infectious respiratory diseases, although this may change in the future.

Key Clinical and Lifestyle Risk Factors for Infectious Respiratory Diseases

Gravenstein explained that there is a considerable overlap in risk factors for COVID-19, RSV, and influenza, with age being a key risk factor for all three diseases. In older adults, there is a traditional cutoff at age 65 years, above which risk is predicted to increase; however, according to Gravenstein, there is a graded risk that increases from approximately 50 years of age, with no sharp inflection point, except perhaps at menopause for females. Gravenstein outlined that this graded increase in risk is due to immunosenescence, as well as changes in IL-6, and the development of comorbidities, such as cardiovascular disease, diabetes, lung disease, obesity, and renal disease. Chatterjee identified smoking as a significant risk factor for respiratory disease across all ages.

Gravenstein referred to a key study by Kwong et al.¹³ that showed that the risk of hospitalisation for acute myocardial infarction was substantially higher in the week following an influenza diagnosis or an RSV diagnosis compared with the control interval, with an incidence ratio of 6.05 (95% CI: 3.86–9.50) and 3.51 (95% CI: 1.11–11.12), respectively.¹³ A COVID-19 diagnosis has also been shown to be a risk factor for acute myocardial infarction.^{14,15}

Gravenstein explained that the risk is not the same across the different respiratory infections, partly because of the mechanism of the respiratory disease. For example, SARS-CoV-2 causes endothelialitis¹⁶ (inflammation of the endothelium) and has a greater propensity to cause outcomes associated with hypercoagulability, such as deep vein thrombosis and pulmonary embolism, than influenza virus.¹⁷ In addition, endothelialitis can lead to the release of von Willebrand factor, further contributing to platelet dysfunction and the poorer outcomes in patients with COVID-19.^{18,19} A further consideration from Gravenstein was that at the start of the COVID-19 pandemic, older adults had immune protection to respiratory infections such as influenza, but not COVID-19; however, in the post-pandemic era, older adults are likely to have underlying immunity.^{2,20} Gravenstein concluded that the vulnerability to these infectious respiratory diseases is multifactorial.

Chatterjee noted that viral infection dampens the immune response to bacterial infection; hence, secondary bacterial infection, particularly pneumococcal, following a respiratory infection is an important risk factor, with many deaths in patients with influenza being the result of secondary pneumococcal pneumonia rather than the influenza itself. Schwarz added that there are good quality data showing a clear correlation between the RSV infection waves and the presence of invasive pneumococcal infections in children and adults.²¹

Schwarz recalled that the late Tobias Welte, a pulmonologist and "visionary in the field of respiratory health",²² described viral infections as the "door opener" to the mucosal epithelium for the invasion of pneumococci or staphylococci. In the context of this risk, the experts concurred that the pneumococcal vaccine is a potentially important tool to counter consequential (post-viral) bacterial infection, particularly as it is currently underutilised in older adults. When pneumococcal vaccination was included in national vaccination programmes for children, there was a subsequent decline in invasive pneumococcal disease in unvaccinated adults, highlighting the importance of intergenerational bacterial transmission.²³ The experts concluded that vaccination against pneumococcus in children and older adults is advantageous in combating morbidity and mortality from these diseases.

Gravenstein noted that cocooning (vaccinating close contacts of highrisk individuals to protect them from infection) is an effective strategy for pertussis and pneumococcal infections, and the cocooning effect can be achieved in nursing homes with COVID-19 and influenza vaccines if vaccination rates are high enough. In alignment with this, an observational study showed that discontinuing mass immunisation for influenza in school children resulted in resurgent mortality in older individuals in Japan, indicating that vaccinating children was protective for older populations through vaccine-induced community immunity.²⁴

Schwarz posed the question: "What will be the impact on the RSV epidemic in older adults if we use monoclonal antibodies widely in young children?" Chatterjee responded that this strategy will probably not have the same impact as pneumococcal vaccination in children because monoclonal antibody is given once, mostly in the first vear of life, but RSV occurs across the lifespan. Schwarz referred to data from Galicia in Spain showing that this strategy substantially reduced infant hospitalisations for RSV-associated lower respiratory tract infection (LRTI; 89.8%), severe RSVassociated LRTI requiring oxygen support (86.9%), and all-cause LRTI hospitalisation (69.2%) when given in a real-world setting.²⁵ Schwarz specified that these results, and the cocooning strategy in general, is relevant for societies in Italy, Spain, and other countries where young children and older adults live together or are part of a close-knit community.

Gravenstein commented that there is an interesting contrast between vaccination against pertussis, where the aim is to cocoon children, and that against pneumococcal infection, where the strategy is directed at cocooning adults, adding that how cocooning will work with RSV and other viral respiratory diseases is likely a different story.

The Importance of Surveillance of Infectious Respiratory Diseases

Chatterjee stated that the COVID-19 pandemic highlighted the importance of surveillance in its various forms. For example, wastewater surveillance by public health authorities indicates the levels of SARS-CoV-2 in the community and is a bellwether to show when COVID-19 rates are going to increase in the local population.²⁶ In Chatterjee's opinion, standardising the surveillance methodology is critical to ensure consistent, comparable, and accurate monitoring and reporting of infectious respiratory diseases, which is essential for planning, and the response to the spread of these diseases.

Schwarz described a sentinel system in Germany in which the Robert Koch Institute,²⁷ a federal government agency and research institute responsible for disease control and prevention, invites GP offices to submit respiratory specimens for typing. A weekly report of infectious respiratory diseases, by region, across the country is provided throughout the winter season. Schwarz clarified that, although this report is always 1 week behind, it gives a good overview of the infectious respiratory diseases landscape across the country.

Chatterjee added that the National Respiratory and Enteric Virus Surveillance System (NREVSS) monitors respiratory viral and enteric viral activity in the USA.²⁸ Participating laboratories voluntarily report weekly to the CDC the total number of tests performed to detect these viruses and the total number of positive tests, and the CDC tracks the trends.²⁸

DIAGNOSIS AND TREATMENT OF INFECTIOUS RESPIRATORY DISEASES

Challenges Associated with Diagnosis of Infectious Respiratory Diseases

Gravenstein explained that it is hard to symptomatically distinguish between COVID-19, RSV, and influenza. Patients with these infectious diseases may present with fever, cough, wheeze, or runny nose, alone or in any combination, or they may have none of these respiratory symptoms but present with non-respiratory symptoms, such as loose stools.29 Gravenstein stated that the certainty is that the clinician cannot be absolutely certain of a diagnosis just by looking at the patient and observing their symptoms. Clinicians may use environmental cues to inform diagnosis; for example, if RSV infection is prevalent in the region but

COVID-19 and influenza are not, RSV infection may be more likely. Gravenstein acknowledged that in the absence of environmental cues and testing, the most that clinicians can provide is an educated guess when diagnosing patients based on symptoms alone.

Gravenstein pointed out that testing is not without bias; there may be an intellectual bias, or a testing bias based on which tests are available in the clinic. Furthermore, the tests for these infectious respiratory diseases are not equally equipped to diagnose; for example, the antigen-based tests are more likely to give a falsenegative result in older adults than in young children.³⁰ According to Gravenstein, many clinics base their judgement on antigen-based tests when molecular-based tests might serve them better.

Gravenstein explained that many COVID-19 cases in adults are asymptomatic, and if a molecular test is not conducted in these cases, the opportunity to implement preventive measures, such as wearing a mask, or early treatment could be missed. Multiplex tests to detect the presence of several pathogens using only a single swab³¹ are available for use in the clinic or the laboratory. Chatterjee noted that multiplex testing often reveals that patients are co-infected with more than one virus, which puts them at increased risk of secondary infections and poorer outcomes as the body is trying to fight more than one virus.

The key aspects of infectious respiratory disease diagnosis, according to Gravenstein, are recognising that COVID-19, RSV, and influenza have overlapping clinical symptoms; starting with a high index of suspicion; being aware of atypical presentations; and acknowledging the possibility that patients are shedding virus before and after a negative test result. Following on from this, Chatterjee emphasised that patients with COVID-19 may test negative multiple times before they test positive, even if they are symptomatic, because of issues with sample collection and testing. Chatterjee proposed that early testing for COVID-19 and influenza can be justified because there are treatments available for these infectious diseases, and early intervention can be effective. In contrast, supportive care is the mainstay of treatment for RSV, therefore, testing could be seen as a purely academic exercise.

Subsequently, Schwarz specified that it is important to know which pathogen is causing the patient's respiratory symptoms in the hospital setting because this has an impact on how the patient is managed. A confirmed diagnosis of COVID-19, RSV, or influenza would prompt isolation of the patient, whereas there is no need to isolate following a rhinovirus diagnosis. Also, in outbreaks and other situations where there is a shortage of hospital beds, testing would enable patient cohorts to be formed based on their diagnosis.

As well as providing an opportunity for directed treatment, Chatterjee outlined that testing is beneficial because patients want to know what illness they have, the clinician can provide a prognosis based on the type of infection, and the need for further diagnostic tests, empirical antibiotic use, and additional expense is reduced. Importantly, this antimicrobial stewardship limits the development of antibiotic resistance.

Continuing the discussion on antimicrobial stewardship, Gravenstein described a study on the use of antibiotics following a COVID-19 versus an influenza diagnosis in nursing homes.³² There was a substantial reduction in antibiotic use after a COVID-19 diagnosis but not following an influenza diagnosis. Gravenstein speculated that this may be related to the nascent education around COVID-19 and the understanding that antivirals can be used to treat this disease, and an atrophy of knowledge about treatment strategies for influenza. Gravenstein clarified that in older adults, "watchful waiting", even for just a day or two, after timely administration of an effective antiviral following a diagnosis of viral infection, may result in a reassessment of clinical improvement and spare antibiotic use.

Treatment Options for Infectious Respiratory Diseases

Gravenstein summarised that treatment options available for COVID-19 include a nirmatrelvir–ritonavir combination, remdesivir, and molnupiravir.³³ Gravenstein disclosed that these antivirals provide an opportunity to prevent hospitalisation or escalating disease severity in older, highrisk patients. Corticosteroids are used to reduce mortality in hospitalised patients with COVID-19 who require oxygen.³³ IL-6 inhibitors are also recommended for patients with inflammatory markers, and JAK inhibitors can be used alongside corticosteroids.³³

There are several antivirals available to treat influenza, including oseltamivir, zanamivir, and baloxavir.³⁴ Oseltamivir is renally cleared, hence, there are dosing considerations with this treatment. Oseltamivir and zanamivir require multiple doses, whereas baloxavir is given as a single dose. Other differences include that zanamivir is inhaled, whereas oseltamivir and baloxavir are taken orally.

Supportive care is currently the primary treatment option for patients with RSV infection. The experts commented that there is a lot of excitement in the RSV space, and the development of new, efficacious treatments for this infectious disease is awaited with interest.

PREVENTIVE MEASURES FOR INFECTIOUS RESPIRATORY DISEASES

Non-vaccine Preventive Measures

Schwarz noted that the COVID-19 pandemic highlighted the importance of hand hygiene as a non-vaccine preventive measure, and hand sanitisers are now widely implemented in locations such as public toilets, restaurants, sports centres, hospitals and other healthcare facilities, and airports to help reduce the spread of infectious respiratory diseases. Chatterjee described a study in which a non-vaccine preventive measure was implemented in a children's hospital during a pertussis outbreak in 2004, to combat the sharp rise in exposure of hospital employees to patients infected with pertussis.³⁵ Personal protective equipment, including child- and adult-sized masks, hand sanitisers, and tissues, was provided at the entrances to the hospital emergency room, outpatient clinics, and lobby for patients and their attendants.³⁵ This control measure, alongside a "Cover Your Cough" poster campaign, effectively interrupted employee exposure to patients with pertussis symptoms.³⁵ Chatterjee disclosed that although this was a simple study that was not hypothesis driven, the study publication was selected as a seminal paper at a congress (17th Annual Society for Healthcare Epidemiology of America Annual Meeting, Baltimore, MD, 15–17 April 2007) as an early example of successfully engaging the public in infection prevention.

Gravenstein proposed that another nonvaccine preventive measure is to educate patients on infectious respiratory diseases and vaccines to offset misinformation on these topics. Gravenstein suggested that data derived from target trial emulation³⁶ could be used to create public messaging, as this strategy provides a more rigorous way to present observational real-world data about vaccine effectiveness and side effects. For example, a nursing home setting provides a closed population with equal access to vaccines, access being one of the main confounders in outpatient populations, thus providing a more formal estimate of effectiveness and safety, as has been shown for COVID-19 vaccines.37-39

Adult Vaccination Strategies

There are currently three licensed vaccines authorised by the European Medicines Agency (EMA) for use in the EU,⁴⁰ and the Centers for Disease Control and Prevention (CDC) for use in the USA:⁴¹ two mRNA vaccines (Pfizer-BioNTech and Moderna), and one protein-based vaccine (Novavax). There is a further protein-based vaccine recommended in Europe only (HIPRA Human Health S.L.U.).⁴⁰ Schwarz acknowledged that there are no head-to-head trials for COVID-19 vaccines, and the window of opportunity for these trials has passed, in the context of the high level of hybrid immunity (i.e., acquiring immunity both by vaccination and incidental infection) in the population. There are also no head-tohead trials for the RSV vaccines licenced in Europe and the USA. Clinicians have to rely on manufacturers' data for both COVID-19 and RSV vaccines, and the efficacy of these vaccines cannot be directly compared.

Schwarz alluded to the excellent data on the high-dose and adjuvanted influenza vaccines in Europe and the USA, which show similar efficacy, and the recombinant influenza vaccine (USA only, not available in Europe), with all these influenza vaccines being well tolerated.⁴²

Registered real-world efficacy and safety data on vaccine effectiveness are available from Kaiser-Permanente for influenza vaccine.⁴³ Schwarz looks forward to seeing registered data from the USA for COVID-19 vaccines and RSV vaccines.

Key Challenges and Barriers to Implementation of Vaccination for Infectious Respiratory Diseases in Adults

Chatterjee expressed concern about the potential impact on vaccination rates of having vaccine sceptics in prominent political positions in the USA, and the possible re-emergence of vaccinepreventable diseases, such as measles and polio, if vaccine coverage greatly reduces. In terms of vaccine access, Chatterjee suggested that there is a need to think beyond the traditional model of patients going to the physicians' office to get vaccinated, particularly for homebound patients and nursing home residents, and that pharmacists are key to improving access to vaccines. Chatterjee remarked on the impressive power of AI and advocated for creative thinking on how to utilise this tool to improve the identification of under-vaccinated populations, vaccine access and education, record keeping, and monitoring of health status.

In Gravenstein's opinion, the vaccination process in adults is more complicated than in children because there is a wellestablished method of sharing vaccination data for children, whereas for adults there are barriers to health information exchange. The solution, Gravenstein suggested, is to create a transparent platform where vaccination information for adults is stored and is accessible to patients, healthcare providers, and pharmacies.

According to Schwarz, one of the main obstacles to implementing vaccination for infectious respiratory diseases in adults in Europe is that vaccinations are typically administered in GP offices rather than in hospitals,⁴⁴ due to a lack of trained staff and funding.⁴⁵ Schwarz pinpointed this as a missed opportunity to vaccinate a large cohort of vulnerable patients in the hospital setting.

IMPROVING EDUCATION AND COMMUNICATION ABOUT INFECTIOUS RESPIRATORY DISEASES AND PREVENTIVE STRATEGIES

Educating Healthcare Teams about Infectious Respiratory Diseases

Schwarz explained that there are no strategies in place for vaccination in hospitals in Europe; therefore, hospital doctors may have little experience in vaccination strategies and administering vaccinations. Schwarz highlighted: "There is no national immunisation programme in many European countries, and efforts to educate and engage HCPs and increase the vaccination coverage in Europe are lacking. Vaccines are a fantastic tool for prevention, but they are not implemented adequately; this is a real issue." Schwarz proposed that information and training on infectious respiratory diseases and vaccines should form a larger part of the education of medical students at university. and should be introduced into hospitals and GP practices in an effort to increase vaccination rates and coverage.

Keeping Patients Informed and Educated about Infectious Respiratory Diseases

Gravenstein emphasised the importance of communicating information to patients in ways that they prefer to receive it. For example, individuals who have issues with numeracy and cannot relate to statistics about vaccination would not benefit from receiving complex data. Furthermore, Gravenstein explained: "We [HCPs] are trained to deliver traditional education in a traditional way; however, younger and now increasingly even older adults do not get their information in the traditional way anymore. We have to figure out how to reach patients, and if their trusted source is an influencer, we have to become that influencer."

Chatterjee remarked that topical, accessible information about infectious respiratory diseases, ideally delivered via relevant social media platforms to reach different age groups and populations, is needed to raise awareness of the threat of these diseases in adults. In addition, Chatterjee specified that HCPs need to keep the vaccine conversations going and "meet people where they are", including striving to understand the reasons behind any hesitancy towards vaccine acceptance, as well as making every effort to dispel myths and misconceptions surrounding vaccines. Chatterjee suggested that trusted faith leaders and other authority figures could be invited to deliver vaccine messaging to the public in the drive to improve vaccination rates.

The experts agreed that it is essential to acknowledge and respect an individual's right to choose what to do with their body and which healthcare interventions they accept. Furthermore, the terminology used to describe individuals who are reluctant to accept vaccination was considered crucial for patient engagement, with the experts preferring the term 'vaccine-inquisitive' rather than 'anti-vaxxers' as this was "likely to get us further in the conversation to acceptance". Schwarz described a public education campaign on RSV and herpes zoster that is currently being conducted in Germany with some success. The campaign has led to patients requesting vaccination from their GPs rather than waiting for or being prompted by GP recommendation. Schwarz considered that well-conducted consumer activities that inform patients about infectious diseases and preventive measures may lead to increased demand for vaccines and improved vaccination coverage rates.

The experts considered that pharmacists could have an even greater role in providing vaccinations, but the use of pharmacists as vaccine providers is not widely implemented. Chatterjee suggested: "Communication between healthcare providers and pharmacists is a critical aspect of vaccination provision that needs to be addressed. Nonetheless, greater utilisation of pharmacists for providing vaccinations is a key step in improving vaccine access and vaccination rates."

In response, Schwarz emphasised: "The important point is that pharmacies are a low barrier to vaccination for patients. We need to get the vaccine to the patient, not the patient to the vaccine. Any activity that improves vaccination strategies and administration is highly recommended."

Gravenstein indicated that presumptive recommendation, with patients being told by healthcare providers or pharmacists that they are due for a vaccination, rather than being asked whether they want the vaccine, is a key communication strategy to encourage vaccination. Furthermore, Gravenstein suggested that providing information about the risk reduction for heart attack with influenza vaccination being equivalent to stopping smoking or taking statins or blood pressure medications can be a persuasive approach for patients who are hesitant to accept vaccination.⁴⁶

ADDRESSING THE GLOBAL BURDEN OF INFECTIOUS RESPIRATORY DISEASES IN ADULTS IN THE FUTURE

Gravenstein would like to see the vaccines for infectious respiratory diseases considered all together in a "basket" rather than individually, and suggested that patients should be advised to "stay up-todate" with their vaccinations rather than using terminology surrounding booster doses.

Chatterjee hopes to see further progress in the development of combination vaccines, as these will reduce the burden of injections for patients, may reduce costs, and could improve vaccine acceptance and vaccination rates.⁴⁷

Schwarz concluded: "When you go on safari, you hope to see the big five (lions, leopards, elephants, African buffaloes, and rhinoceroses).⁴⁸ Now, we have to promote the big six for healthy ageing: vaccines for COVID-19, RSV, influenza, pertussis, herpes zoster, and pneumococcal infections."

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