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REVIEW

Silent Threats: Understanding the Impact of Respiratory Viruses on the Ageing Population

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Abstract

Respiratory viruses are an important cause of acute respiratory illnesses in older adults. The spectrum of illness may range from pneumonia to an exacerbation of underlying respiratory disease or acute bronchitis. Respiratory viruses can account for a significant proportion of chest infections. However, respiratory viruses, either acting as primary pathogens or in conjunction with bacterial infections, are often underdiagnosed due to less frequent viral testing compared to bacterial infections. Hitherto neglected, the coronavirus disease 2019 (COVID-19) pandemic has brought into sharp focus and generated interest in respiratory viruses and their burden in all age groups. This article addresses this interest and summarises the most prevalent and emerging respiratory viruses affecting the elderly. There is a general overview as well as specific information on how to approach, identify, and treat these viruses. We will also discuss the latest guidance on vaccination, as well as adjunctive tests like procalcitonin and point-of-care testing and the niche that these occupy in the diagnosis and management of chest infections.

Key words: respiratory viruses; elderly; epidemic viruses; diagnostics

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Introduction

Respiratory viruses are an important cause of acute respiratory illnesses in older adults. The spectrum of illness may range from consolidation on a chest X-ray (pneumonia) to an exacerbation of underlying respiratory disease or acute bronchitis (Chen et al, 2019; Jain et al, 2015). Most literature on the topic focuses on community-acquired pneumonia due to viral etiology.

Respiratory viruses, either acting as primary pathogens or in conjunction with bacterial infections, are often underdiagnosed due to less frequent viral testing compared to bacterial cultures (Branche and Falsey, 2015). This underestimation is concerning, as respiratory viruses contribute significantly to morbidity and mortality, especially in vulnerable groups such as the very young (under 5 years) and older adults (aged 50 and over), who are at much higher risk of severe outcomes (Chen et al, 2019).

In the UK, respiratory infections are a leading cause of hospital admissions and mortality in older adults, with Public Health England (PHE) reporting that seasonal viruses like influenza and respiratory syncytial virus (RSV) play a significant role in

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winter hospital pressures, particularly among those aged 65 and older. The ongoing coronavirus disease 2019 (COVID-19) pandemic has underscored the vulnerability of older adults to both new and existing respiratory pathogens, exacerbating the already significant burden of viral respiratory infections.

The burden of pneumonia, including that due to respiratory viruses, is markedly higher in the young as well as the elderly. The Etiology of Pneumonia in the Community (EPIC) trial (Jain et al, 2015) was a multicenter trial of patients admitted with pneumonia in five US hospitals in Chicago and Nashville between January 2010 and June 2012. Among 2259 patients tested, a microbiological diagnosis was made in 38%, with one or more viruses in 530 (23%), bacteria in 247 (11%), bacterial and viral pathogens in 59 (3%), and a fungal or mycobacterial pathogen in 17 (1%). The most common viral pathogens were human rhinovirus (in 9% of patients), influenza virus (in 6%), human metapneumovirus (4%), respiratory syncytial virus (3%), parainfluenza virus (3%), and coronavirus (2.5%). In comparison, the most common bacterial pathogen was Streptococcus pneumonia (5%). Mycoplasma, Legionella pneumophila, and Chlamydia pneumonia together accounted for 4% of the infections (Jain et al, 2015). There was a strong positive correlation with age of the patients and the incidence of respiratory virus infections, with influenza being 5 times and rhinovirus 10 times more common in patients aged more than 65 years (Jain et al, 2015). Nickbakhsh et al (2016) analysed 44,230 episodes of respiratory illness tested by the West of Scotland Virology centre from 2005 to 2013. At least one virus was detected in 15,302 patients (35%); with the prevalence of specific viruses as: rhinovirus 4847 (14%), influenza A virus 4244 (9.7%), respiratory syncytial virus 1786 (4.9%), coronavirus 1339 (4.1%), adenovirus 1221 (3.6%), influenza B virus 1019 (3%), metapneumovirus 345 (2.6%), parainfluenza virus-3 757 (2.2%), parainfluenza virus-4 286 (0.86%), parainfluenza virus-1 295 (0.84%) and parainfluenza virus-2 122 (0.35%) (Nickbakhsh et al, 2016).

Musher and Thorner (2014) found that the highest rates of pneumonia in adults were in those greater than 80 years of age, with the second-highest rate in adults between 65 and 79 years old.

With the UK's ageing population, the incidence of pneumonia in older adults is projected to rise. Adults over 80 years already experience the highest rates of pneumonia-related hospitalisations, with those aged 65 to 79 following closely behind. This increased susceptibility is attributed to immunosenescence (Lynch et al, 2021), a gradual decline in immune function with age, and the high prevalence of comorbidities such as chronic obstructive pulmonary disease (COPD), diabetes, and cardiovascular diseases (Chen et al, 2021). The diminished vaccine response in older adults also complicates preventive efforts, especially during recurrent seasonal outbreaks of viruses like influenza and RSV (Allen et al, 2020).

Moreover, respiratory viruses can exacerbate underlying chronic conditions in older adults, leading to worsening clinical outcomes. Influenza and rhinovirus, for example, frequently trigger acute exacerbations of COPD and asthma, increasing hospitalisation rates and mortality (Branche and Falsey, 2015). Additionally, viral infections often pave the way for secondary bacterial infections, which further complicates treatment and leads to poorer outcomes (Branche and Falsey, 2015).

However, progress has also been made in the diagnosis and treatment of respiratory viral infections. Recent advances in diagnostic methods, such as multiplex polymerase chain reaction (PCR) testing, have enhanced the detection of respiratory viruses in clinical settings. These molecular diagnostics allow for quicker and more accurate identification of viral pathogens, aiding in the early management of viral pneumonia (Allen, 2023).

This article will begin with a discussion of diagnostic methods for respiratory viruses, including blood tests, imaging, and molecular diagnostics such as PCR, emphasising their significance in clinical decision-making. Following this, it will provide an in-depth examination of key respiratory viruses affecting older adults, such as RSV, influenza, and Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2), highlighting disease manifestations, imaging findings, and laboratory markers. Additionally, the article will cover specific treatment options and vaccination strategies for each virus, along with the latest advancements in antiviral drugs and preventive measures, particularly as they relate to the unique challenges of managing respiratory health in older adults.

Diagnostics

Accurate identification of the etiology of respiratory illness, especially pneumonia, can help reduce further testing, allow appropriate infection control measures, tailor treatment, and provide accurate counselling to the patient and family. In addition, there may be a role for shortening antibiotic duration.

Blood Test Findings

Routinely available laboratory tests will often show elevated inflammatory markers like C-reactive protein (CRP), lactate dehydrogenase (LDH) and erythrocyte sedimentation rate (ESR). Lymphopenia and thrombocytopenia are also common findings in respiratory viral infections. On the other hand, neutropenia as well as neutrophilia is seen in these infections. One study conducted by Huijskens et al (2014) examining a range of clinical and laboratory findings found that only CRP helped differentiate between bacterial and viral pneumonias (median 219 mg/dL vs. 77.5 mg/dL, $p < 0.0005$).

Radiology

Whilst some viral illnesses may be associated with specific radiological patterns (details in the individual viral sections below), reliable differentiation between viral and bacterial pneumonia on chest X-ray alone is not usually possible. One study conducted by Van Den Berk et al (2023) examined the role of low dose computed tomography (CT) chest in differentiation of viral and bacterial pneumonia, and demonstrated that consolidation, while observed in both viral and bacterial pneumonia groups, was observed significantly more in those with a bacterial pathogen (Fig. 1). No significant differences for other radiological patterns (interstitial or bronchopneumonia) were found.

Other radiological features that can be seen in viral respiratory tract infections are ground glass changes, mediastinal lymphadenopathy (reactive to the chest infec-

tions), linear atelectasis, nodules, bronchial wall thickening, and even occasionally pleural effusion.

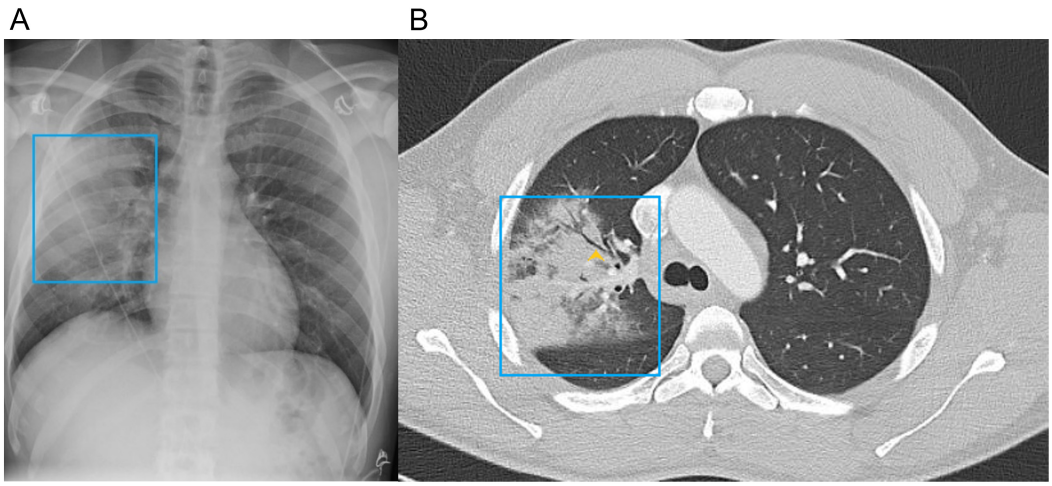

Fig. 1. Consolidation. (A) A Chest radiograph showing consolidation in a patient admitted with pneumonia (blue box). (B) Computed tomography (CT) showing consolidation (blue box) with air bronchogram (yellow arrow) in the same patient—source author.

Laboratory Diagnosis Overview

Identifying the causative virus in respiratory infections is important since clinical symptoms and radiological findings often overlap with bacterial pneumonia. There are four primary methods for viral identification: viral culture, serology, antigen detection, and PCR-based tests.

Viral Culture

This method involves growing viruses in cell lines and was first demonstrated in 1913. Although once considered the gold standard, it is a time-consuming process that requires 7–10 days for the virus to show cytopathic effects. Additional steps, such as fluorescent antibody staining, are needed for identification. It also carries a risk of infection to laboratory staff. Due to its time and resource demands, viral culture is impractical for routine hospital use. While faster methods like shell vial culture reduce the time to 2–7 days, nucleic acid amplification tests (NAATs) have largely replaced viral culture due to superior sensitivity and quicker results (Attaway and Wang, 2024).

Serological Tests

These include complement fixation (discovered in the early 1900s) and hemagglutination inhibition (developed in the 1940s). Serological tests detect antibodies in patient serum, but they have limitations, such as lower sensitivity and the need for time-consuming procedures. The hemagglutination inhibition test, particularly useful for influenza, provides detailed information on immunity and past infections, aiding in vaccine development. However, it is no longer widely used for individual

diagnoses, as it requires 7–10 days post-infection for immunoglobulin M (IgM) and immunoglobulin G (IgG) production (Vainionpää and Leinikki, 2008).

Antigen Detection

Modern immunoassays, such as enzyme-linked immunosorbent assays (ELISA) (developed in 1971), immunofluorescence assays, and radioimmunoassays, use labels (e.g., enzymes, fluorescent dyes, or radioisotopes) to detect antigens in respiratory specimens. These methods offer advantages like easier automation and quicker results, reducing false negatives associated with antibody detection. These immunoassays have also become valuable for rapid diagnosis in clinical settings (see point-of-care testing).

Nucleic Acid Amplification-Based Tests

The development of PCR in 1983 revolutionised virus detection. PCR is used for both DNA and RNA viruses; for RNA viruses, reverse transcriptase converts RNA to complementary DNA (cDNA) before PCR amplification. Real-time PCR monitors the amplification process using fluorescence, allowing for quantitative PCR (qPCR) assessment of viral load. Multiplex PCRs can test for multiple pathogens simultaneously, including combinations of respiratory viruses like RSV, COVID-19, and influenza (limited multiplex panel) as well as expanded multiplex syndromic panel (>5 pathogens), providing comprehensive diagnostic coverage in a single run (Attaway and Wang, 2024)

Specimens of nasopharyngeal swabs, sputum, nasopharyngeal washes, and bronchoalveolar lavage (BAL) fluid can be used to diagnose viral pneumonias (Miller et al, 2018). Lung tissue and BAL fluid, although invasive, are especially useful for critically ill or immunocompromised patients (Miller et al, 2018; Stefanidis et al, 2021), where precise diagnosis and detection of co-infections are essential.

In summary, nucleic acid amplification-based tests have supplanted all other methods for the detection of viruses in hospital laboratories.

Point of Care Testing Overview

Point-of-care (POC) testing offers several advantages, including quick results, ease of use, and affordability, as demonstrated during the COVID-19 pandemic.

POC testing relies mainly on lateral flow tests, which became particularly prominent during the COVID-19 pandemic. Lateral flow tests involve applying a liquid sample to a polymer strip containing antibodies specific to the target analyte. The sample migrates along the strip, and if the analyte is present, it interacts with antibodies in the detection zone, producing a visible response on the test line. These tests offer rapid, easy-to-read results and are particularly valuable for on-site testing without specialised equipment.

Rapid influenza diagnostic tests (RIDTs) based on lateral flow assays can detect influenza A and B within 30 minutes by identifying viral nucleoprotein antigens in respiratory specimens. However, RIDTs are less sensitive compared to RT-PCR tests, with a sensitivity range of 50–70% and specificity over 90% (CDC, 2024a). Digital immunoassay antigen (DIA) tests improve sensitivity to 70–80%

using fluorescence technology and handheld devices (Public Health England, 2019). Lateral flow immunoassays (LFIAs) are also used for RSV detection, with sensitivities and specificities typically above 90%, varying by manufacturer (Zhang et al, 2020). COVID-19 lateral flow tests detect nucleocapsid proteins, giving results in 15–20 minutes with 77% sensitivity, depending on sample type and user experience (UKHSA, 2021) (Fig. 2).

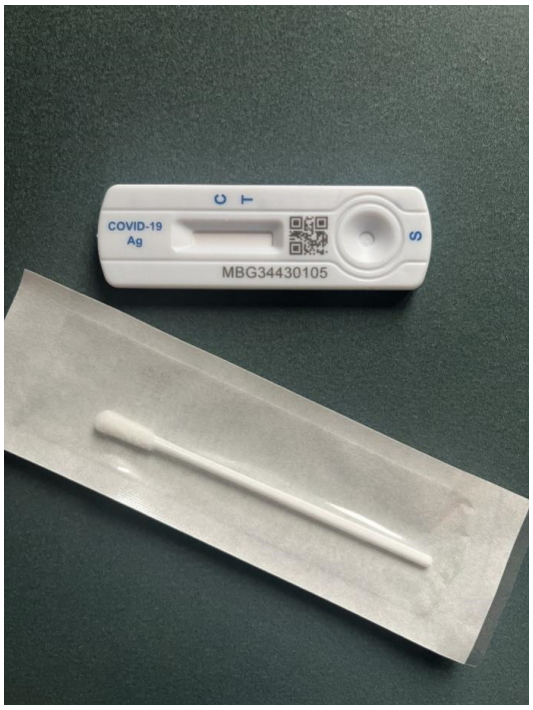

Fig. 2. Image of lateral flow test. COVID-19, coronavirus disease 2019; C, control; T, test; S, sample; Ag, antigen. Fig. 2 was taken by the author.

Use of Biomarkers to Differentiate Between Bacterial and Viral Infections

Patients with acute respiratory infections, especially if consolidation is present on imaging, usually receive antibiotics, regardless of underlying etiology (which may not be known). In addition, there may be non-infectious mimics of respiratory infections, such as acute interstitial lung disease.

Given the risk of adverse effects from the antibiotics, as well as the risk of emergence of multidrug-resistant strains, there has been an increasing interest and widespread use of the blood biomarker procalcitonin. Also, early safe discharge of patients may result in a decrease in in-hospital transmissions of viral infections.

Procalcitonin (PCT) is a peptide precursor of calcitonin, which in turn is involved in calcium homeostasis, produced in the parafollicular cells of the thyroid. PCT is located on the Calcitonin Related Polypeptide Alpha (*CALCA*) gene, whose expression in non-endocrine tissue in response to bacterial infection is substantially increased, leading to increased levels of circulating procalcitonin. Procal-

citonin levels start rising within 6–12 hours of infection, with levels strongly correlating with disease severity, adverse clinical outcomes and bacteremia. Unlike other inflammatory markers, procalcitonin release is inhibited by cytokines such as interferon-γ, which are characteristic of the immune response to viral infections (Schuetz et al, 2018). Therefore, procalcitonin is more specific for bacterial infections when compared with C-reactive protein or white cell count (Schuetz et al, 2018).

Procalcitonin levels less than 0.25 microgram/L generally indicate a low risk of bacterial infection (Schuetz, 2022) and can be used in conjunction with clinical and radiological features to predict a viral cause of the respiratory tract infection. One caveat is that there may be moderate or low levels in 'atypical' pneumonia when compared to 'typical pneumonia', especially Mycoplasma (Self et al, 2017) and Legionella, which can mimic respiratory viral infection

There has been emerging interest and research in the use of procalcitonin in negating or reducing the need for antibiotics, in particular if the patient tests positive for a respiratory virus. Procalcitonin is not featured in current UK guidelines on community-acquired pneumonia (CAP) (e.g., NICE, 2014; Updated 2023 Pneumonia guidelines); however, it may have most utility in early antibiotic discontinuation (e.g., 2–3 days) with appropriate risk stratification (Andriolo et al, 2017; Schuetz et al, 2018).

American Pneumonia Guidelines (Metlay et al, 2019) discuss procalcitonin testing and positive respiratory viral tests in more detail, and while still advocating standard antibacterial treatment in CAP even if testing positive for a respiratory virus, recognise the need for randomised controlled trials and more research to examine looking at earlier discontinuation of antibiotics in the context of a positive viral test.

Schuetz (2022) recommends that an approach to incorporating procalcitonin in regular clinical practice would be to use it to exclude bacterial infection in patients who have been assessed to have low pretest clinical probability of bacterial infection and low-risk clinical condition. In high clinical risk patients and/or high pretest probability of bacterial infection, empirical antibiotics should be administered. Regular monitoring of PCT levels can assist in assessing infection resolution and support decisions about the early discontinuation of antibiotics (Schuetz, 2022).

The use of procalcitonin-led therapy in other non-pneumonic respiratory infections is less clear and less evidence-based:

Acute exacerbation of COPD, the use of PCT is not mentioned in COPD guidelines (Global Initiative for Chronic Obstructive Lung Disease, 2024) and appears to have a mixed evidence base, and unclear correlation with disease activity. At least one trial showed a higher mortality in PCT-led care (Daubin et al, 2018).

Acute bronchitis, to the authors knowledge, there are no direct trials of procalcitonin led vs. standard care in acute bronchitis, although subgroup analysis of other trials and meta-analyses suggests procalcitonin can guide a reduction in antibiotic usage without an increase in adverse effects (Christ-Crain et al, 2004; Schuetz et al, 2018).

In COVID-19, the level is low in most cases and increases with disease severity (Malik et al, 2021).

C-reactive protein is a commonly tested acute-phase reactant. As mentioned above (Huijskens et al, 2014), CRP may have some role in the differentiation of viral and bacterial pneumonia.

For acute bronchitis, CRP may be used to consider the need for antibiotics in carefully selected individuals (usually under the age of 65) without medical co-morbidities (NICE CKS, n.d.), with a cut off of less than 20 mg/L as a limit below which antibiotics may not routinely be offered, and a CRP of 20–100 mg/L where a delayed antibiotic prescription could be considered (NICE CKS, n.d.).

Virus and Bacterial Coinfections

Several viral infections, including those caused by the influenza virus, respiratory syncytial virus (RSV), parainfluenza virus, and human metapneumovirus, can present as co-infections or can be complicated with secondary bacterial infections. This is of particular significance among the elderly and other high-risk groups living with underlying chronic health conditions. These bacterial infections may include Streptococcus pneumonia, Haemophilus influenzae, and Staphylococcus aureus. This often results in a more severe disease, a prolonged course and worse outcomes. The incidence of bacterial co-infections varies depending on the underlying viral infection (Morris et al, 2017).

For example, a systematic review and meta-analysis on influenza found that the frequency of bacterial co-infection ranged widely from 2% to 65% (Oliva and Terrier, 2021). The proportion of coinfection was similar in the elderly as well as the young (in fact, in all age groups) (Klein et al, 2016). Patients in the intensive care unit (ICU) had a slightly higher incidence of co-infection compared to those in other settings, although this difference was not statistically significant ($p = 0.14$) (Klein et al, 2016).

In a meta-analysis by Langford et al (2020), bacterial co-infection was identified in 3.5% of COVID-19 patients, while secondary bacterial infections were found in 14.3% of patients. Bacterial infections were more common among critically ill COVID-19 patients (8.1%). The authors concluded that bacterial co-infections are relatively rare in hospitalised COVID-19 patients, and many of these patients may not require empirical antibacterial treatment (Langford et al, 2020).

Studies on RSV-infected hospitalised patients have shown varying rates of bacterial co-infection, with lower respiratory tract bacterial co-infections affecting 17.5% to 44% of patients who tested positive for both RSV and bacterial pathogens (Oliva and Terrier, 2021).

Regarding viral coinfections, we have found some variation in their prevalence between various studies. Pott et al (2024), while studying RSV and influenza coinfection, found that it was rare and accounted for 2.39 cases per 1000 hospitalisations of patients with acute respiratory illnesses. This was based on a cohort study of hospitalised adults $\geq$50 years from the 2012/13, 2013/14, and 2014/15 influenza seasons (Pott et al, 2024). Mixed infections of SARS-CoV-2 with other respira-

tory viruses have been reported to occur infrequently, with an incidence rate of 1.4% (Aghbash et al, 2021). On the other hand, for example, when Nickbakhsh et al (2016), analysed multiplex PCR results (simultaneously testing for 11 virus groups) of 44,230 patient episodes of respiratory illness between 2005 and 2013 in West of Scotland Virology centre, found that of 9654 virus-positive patients from 27,284 episodes tested for all 11 viruses, 11% (1086/9654) had a co-infection.

Common Respiratory Viruses

After this general overview, we will proceed to discuss some of the more prevalent respiratory viruses. We will cover presentation, radiology, microbiological diagnosis, treatment and vaccination.

Respiratory Syncytial Virus

Respiratory syncytial virus (RSV), a single-stranded RNA paramyxovirus historically recognised as a paediatric pathogen, has also been found to cause severe illness in older adults, particularly those with chronic conditions like COPD and heart disease.

A retrospective study by Pastula et al (2017) examined hospitalisations among adults aged ≥20 years between 1997 and 2012 in the US. It compared 28,237 RSV-related hospitalisations to 652,818 influenza-related hospitalisations. Despite the lower number of hospitalisations, RSV was associated with more severe disease across all age groups. Among patients aged over 60, RSV-related hospitalisations showed higher in-hospital mortality rates (6.9% vs. 3.8%), increased need for mechanical ventilation (16.6% vs. 6.3%), and longer average hospital stays (6 days vs. 4.1 days) compared to influenza (Pastula et al, 2017).

RSV typically causes mild symptoms, but it can lead to severe illness in infants and older adults, with outbreaks commonly occurring in late fall, winter, or spring (Popow-Kraupp and Aberle, 2011; Stefanidis et al, 2021).

Symptoms are usually consistent with upper respiratory tract infection, which can include rhinorrhoea, pharyngitis, cough, headache, and fever (CDC, 2024b). In some cases, especially in the elderly or those with risk factors like cardiovascular, lung, renal, cirrhosis, diabetes, neuromuscular diseases, haematological or immunocompromise or obesity, this may progress to cause pneumonia (CDC, 2024b).

Diagnosis

In adults and elderly patients, chest X-ray most commonly demonstrates bilateral alveolar opacities in the form of multiple patchy infiltrates but may also show diffuse bilateral interstitial changes in the form of ground glass changes (Stefanidis et al, 2021).

On CT, RSV pneumonia showed one or more areas of ground-glass attenuation, consolidations, nodules (8 mm in maximal diameter, with halo in 71%), small pleural effusions, tree-in-bud, bronchial wall thickening (Mayer et al, 2014).

For a long time, RSV isolation in tissue culture has been considered the gold standard for confirming suspected RSV infections. However, this method is time-

consuming and requires technical expertise in specimen handling and efficient virus recovery (Popow-Kraupp and Aberle, 2011).

Testing for virus-specific antibodies is not effective for diagnosing RSV infections in the setting of acute hospital admissions. Instead, such tests are primarily used for sero-epidemiologic studies and research purposes (Popow-Kraupp and Aberle, 2011).

Traditional methods for RSV detection include enzyme-linked immunosorbent assays (ELISA) and direct immunofluorescence assays (Zhang et al, 2020). However, nucleic acid-based assays are now recognised as the most sensitive and specific diagnostic methods for RSV detection (Popow-Kraupp and Aberle, 2011). Among these, reverse transcription polymerase chain reaction (RT-PCR) was the first widely adopted nucleic acid amplification technique and remains the most widely used (Popow-Kraupp and Aberle, 2011).

Advancements in PCR technology, such as real-time RT-PCR, have further improved diagnostic efficiency. Real-time RT-PCR combines amplification and detection, significantly reducing turnaround time to just a few hours.

Treatment

The cornerstone of management in RSV infections remains supportive, which includes fluids, antipyretics and oxygen therapy as dictated by demand (Empey et al, 2010).

The antiviral, Ribavirin (nucleoside analogue which inhibits RNA synthesis), used in children, is not usually used in adults due to low evidence of efficacy and the necessity of giving it continuously over several hours (12–18) over consecutive days.

The majority of RSV antiviral drugs in clinical development are fusion inhibitors, which work by targeting viral epitopes or cell receptors to block viral binding, fusion, and entry. Drugs like Presatovir, Sisunatovir and Ziresovir, which are undergoing phase II and phase III trials in adult patients, have shown promising results in the reduction of both viral load and respiratory symptoms (Langedijk and Bont, 2023).

There is currently no role for passive immunisation against RSV infection in the elderly, with the existing licensed monoclonal antibodies against the fusion protein (Palivizumab and Nirsevimab) only for use exclusively in high-risk infants. Clesrovimab has only phase I adult data available (Langedijk and Bont, 2023). These humanised monoclonal antibodies bind to the fusion protein A on the surface of respiratory syncytial virus (RSV), inhibiting the virus from entering host cells, thereby preventing RSV infection.

As well as pharmacological treatments, robust hygiene practices have a crucial role in limiting the transmission of this infection (as well as other respiratory viral infections). Strategies such as periodic hand washing, social distancing, use of face masks and home isolation of people presenting respiratory symptoms should be utilised where appropriate. There is also an argument to institute these procedural measures in care facilities and nursing homes, as was demonstrated during the COVID-19 pandemic.

Vaccination

The 2024 Global Initiative for Chronic Obstructive Lung Disease (GOLD) report currently recommends RSV vaccination for individuals over 60 years of age and/or those with chronic heart or lung conditions (Alfano et al, 2024). In the UK, the Joint Committee on Vaccination and Immunisation (JCVI) recommends RSV vaccination for adults aged 75 years and older.

A single dose can protect patients for several years. The only RSV vaccine licensed in the UK is the Pfizer Abrysvo® Pre-F RSV vaccine (UK Health Security Agency, 2024).

Abrysvo® is a non-live, bivalent recombinant vaccine containing proteins from RSV subgroups A and B. It targets the prefusion form of the fusion (F) protein, which the virus uses to invade human cells.

Apart from older adults, it is also recommended in pregnant women.

There are some ongoing trials looking at the combination of the RSV vaccine and the human metapneumovirus vaccine (Topalidou et al, 2023).

Influenza

Influenza is an RNA orthomyxovirus. There are four types of influenza viruses: A, B, C and D. Influenza A and B cause seasonal epidemics in the winter months in the temperate regions (November to April in the northern hemisphere), whereas influenza C causes mild infection primarily in children. Influenza D solely affects cattle and pigs.

Influenza A viruses are divided into subtypes based on Haemagglutinin and Neuraminidase surface glycoproteins. Some subtypes of influenza A viruses are zoonotic (affecting swine and birds), which can sometimes jump species and cause epidemics in humans, e.g., the 1918 and 2009 swine flu pandemic caused by influenza A virus subtype H1N1 variant (A(H1N1)v) or the bird flu A(H5N1)v, which has caused sporadic but highly pathogenic flu in people who have come in contact with infected live or dead birds. The letter V denotes that these are variant subtypes, which are primarily zoonotic. Correspondingly, subtypes of influenza A viruses that are currently circulating in humans are A(H1N1) and A(H3N2). You may notice that the letter V has been dropped because although they have the same Haemagglutinin and Neuraminidase antigen, they are subtypes that primarily affect humans.

Influenza B viruses are divided into two lineages (rather than subtypes), B/Yamagata and B/Victoria. The lineages are differentiated by the Haemagglutinin amino acid sequence. They have no known animal reservoirs.

Clinically, influenza can be characterised by high fever, myalgia, rhinorrhea, sore throat, cough, sputum production, diarrhoea, vomiting, and headache. Like RSV, in certain cases, they go on to develop pneumonia.

Diagnosis

In a study on influenza A patients, Aviram et al (2010) showed that chest X-ray (CXR) findings included the following: ground-glass (69%), consolidation (59%), frequently patchy (41%), and nodular (28%) opacities. Bilateral opacities were

common (62%), with involvement of multiple lung zones (72%). Findings in four or more zones and bilateral peripheral distribution had a strong positive correlation with adverse clinical outcomes (Aviram et al, 2010).

Computed tomography (CT) findings are normal in approximately 50% of patients with laboratory-confirmed influenza virus infection (Stefanidis et al, 2021). In cases demonstrating abnormalities, the most prevalent imaging patterns include ground-glass opacities, multifocal consolidations (Fig. 3), or a combination thereof (Fig. 4). These findings are typically distributed in a peribronchovascular and subpleural pattern, resembling features of organising pneumonia. Additional commonly observed features include interlobular septal thickening and centrilobular nodules (Stefanidis et al, 2021).

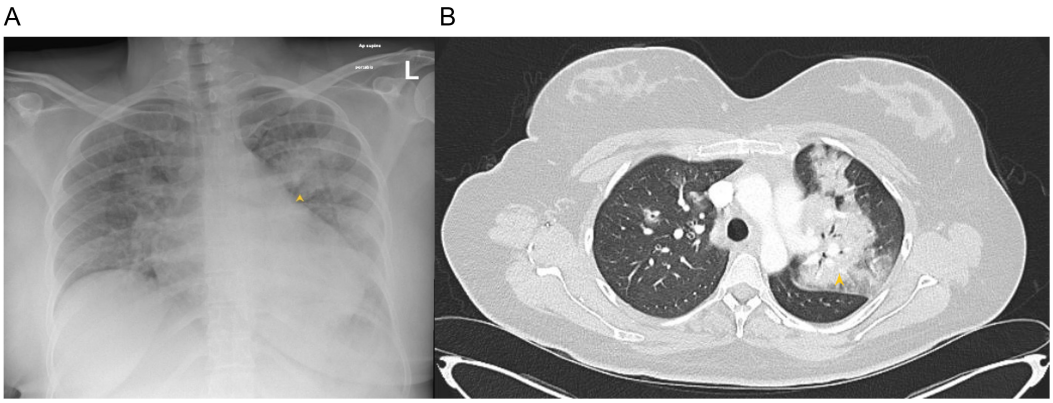

Fig. 3. Examples of radiological changes in influenza pneumonia. (A) Chest X-ray (CXR) showing consolidation in a patient admitted with influenza (yellow arrow). (B) Corresponding computed tomography (CT) showing consolidation in the same patient (yellow arrow)—source author. L, left.

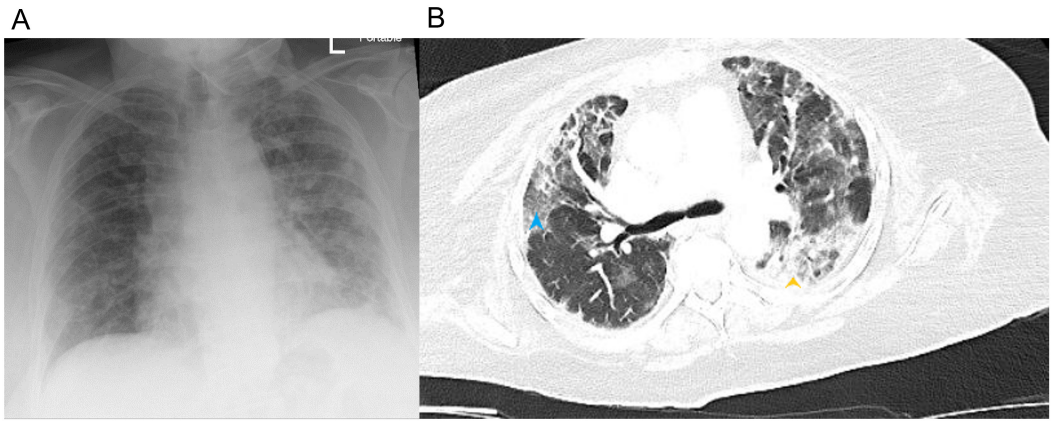

Fig. 4. Examples of radiological changes in influenza pneumonia. (A) CXR shows ground glass and reticulonodular changes in a patient admitted with Influenza. (B) Corresponding CT showing ground glass (blue arrow) and consolidation (yellow arrow) in the same patient—source author. L, left.

Viral culture is the gold standard for diagnosing influenza viral infections (Zhang et al, 2020). However, it takes 1–10 days to get results and is usually done in public health laboratories (Uyeki et al, 2022).

Tests such as hemagglutination (HA) and complement fixation are used to detect antibodies against the influenza virus. HA relies on the hemagglutinin antigen on the virus's surface, which binds with sialic acid on red blood cells (RBCs) to form a lattice complex. Antibodies to the influenza virus can be identified by their ability to prevent this reaction. HA assays are used in serosurveys to identify influenza virus subtypes, helping determine which strains should be included in the annual flu vaccines.

Immunofluorescence assays are also employed for the detection of influenza viruses in clinical specimens. This technique involves the direct staining of respiratory epithelial cells, obtained from nasopharyngeal aspirates or swabs, using fluorescently labelled antibodies specific to influenza viruses (Uyeki et al, 2022; Zhang et al, 2020). It takes 2–4 hours for detection under a microscope. Sensitivity and specificity are 70–100% and 80–100%, respectively (Miller et al, 2010; Ravina et al, 2020).

Several ELISA-based tests are also available. However, all these conventional diagnostic methods generally have lower sensitivity and specificity relative to molecular methods. Nucleic acid amplification test (NAAT) assays based on polymerase chain reaction (PCR) detect virus-specific genetic materials (influenza viral RNA), rather than viral antigens or antibodies (Zhang et al, 2020) and have now become widespread in the detection and diagnosis of influenza.

Treatment

Influenza infections are a global public health challenge due to their ability to cause seasonal epidemics and pandemics.

Influenza viral therapy has mostly revolved around Adamantanes (matrix-2 protein inhibitors) and Neura-minidase inhibitors (NAIs), with NAIs being presently the most prescribed antiviral drugs against influenza, with demonstrable efficacy in shortening the duration of illness and causing virus clearance.

Oseltamivir and Zanamivir, which block Neuraminidase (NA) activity and viral movement from cells, while the newly developed Baloxivir, an endonuclease inhibitor, inhibits viral replication, are recommended for adults infected with influenza A and B as well as swine and avian influenza viruses.

Matrix-2 (M2) protein inhibitors like Amantadine and Rimantadine used historically, are no longer recommended owing to widespread mutations conferring drug resistance to influenza viruses. Because the M2 protein is found only in influenza A viruses, M2 inhibitors are ineffective against influenza B.

Vaccination

Vaccination is currently the best protective measure against mortality and morbidity from influenza; however, it fails to confer absolute protection often due to improper vaccine coverage, shortages and multiple circulating strains causing vac-

cine mismatch. The efficacy of influenza vaccines currently stands around 44% (Demurtas et al, 2020), limited by the rapid antigenic evolution of the virus.

The two main types of influenza vaccination currently available are the inactivated influenza vaccines (IIV) and the live attenuated influenza vaccine (LAIV), whose makeup is continually reviewed by the World Health Organization (WHO). These conventionally protect against the 3 different seasonal influenza viruses (A(H3N2), pandemic A(H1N1) and 1 of 2 influenza B lineage viruses) and are called trivalent vaccines.

Influenza vaccine has demonstrated a moderate preventive effect in the elderly along with a decrease in morbidity for influenza and pneumonia, respiratory or cardiovascular complications and risk of death (Jefferson et al, 2005).

SARS-CoV-2/COVID-19

The Severe Acute Respiratory Syndrome (SARS) coronavirus 2, the causative agent of COVID-19, is a member of the coronavirus family. Coronaviruses infect mammals and birds, and in humans, they cause a range of clinical syndromes from the common cold to lethal respiratory tract infections. Coronaviruses of various origins have spread globally, causing significant respiratory illnesses. To date, seven human-infecting coronaviruses have been identified: human coronavirus (HCoV)-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1, SARS-CoV, Middle East respiratory syndrome coronavirus (MERS-CoV), and SARS-CoV-2. Among these, SARS-CoV and MERS-CoV were responsible for major outbreaks in 2002 and 2012, respectively (Chen et al, 2020). The most recently identified, SARS-CoV-2, the causative agent of COVID-19, emerged in late 2019 and has since resulted in a global pandemic, with nearly 700 million confirmed cases worldwide to date (World Health Organization, n.d.).

COVID-19 typically presents as a flu-like illness, often accompanied by cough, dyspnea, and alterations in the sense of smell (anosmia) or taste. Routine bloods may show lymphopenia and an elevated CRP. They may progress to pneumonia, respiratory failure, venous thromboembolism and multiorgan failure. A significant percentage (12–61% Lang, 2024) also presents with gastrointestinal (GI) symptoms with diarrhoea, vomiting and abdominal pain. The underlying patho-mechanism may involve the COVID-19 virus receptor (angiotensin-converting enzyme2 [ACE2], the means of which it enters the epithelial cells), which is also abundantly present in the GI tract.

On the one hand, a proportion of patients will have asymptomatic infections, whereas others will have more severe illnesses characterised by hypoxia and dyspnoea. A subset of the latter go on to develop critical illness characterised by respiratory failure, circulatory failure or multiorgan failure.

Diagnosis

Commonly seen in COVID ground-glass opacities, which are areas of hazy opacification that obscure the lung markings and are predominantly peripheral. Accompanying these, there might be coarse horizontal white lines which can be described as linear opacities. In more severe disease, you can also see consolidation

characterised by more dense opacities with airway delineation (air bronchograms). Chest X-ray appearances are often peripheral and lower zone in distribution, often with bilateral involvement (Kohli et al, 2021; Wong et al, 2020). But with disease progression whole lung may be involved. Pleural effusions and pneumothorax are unusual X-ray findings. However, it is also possible that chest X-rays may be completely normal, especially if done early in the disease. Maximum radiographic changes can be seen on days 10 to 12 from symptom onset (Wong et al, 2020).

Chest CT imaging in COVID-19 has been broadly categorised into four stages (Pan et al, 2020). They have different radiological pictures and correspond roughly to the time from symptom onset: the early stage (0–4 days), typically showing normal findings or predominant ground-glass opacities. Nodular (round or oval) ground-glass opacities are a key characteristic that may indicate COVID-19 and prompt radiologists to consider the diagnosis (Stefanidis et al, 2021). Occasionally, a reversed halo or atoll sign may also be observed (Kong and Agarwal, 2020). This is followed by the progressive stage (5–8 days), marked by increased ground-glass opacities involving multiple lobes (Fig. 5) and the appearance of a crazy-paving pattern and/or consolidation (Fig. 5). The peak stage (9–13 days) is characterised by extensive or increasingly dense consolidation; and finally the late stage (≥14 days) also called the resorption stage shows gradual resolution of consolidation (which in the process of resolution can evolve into ground glass changes) and ground-glass opacities, with possible development of fibrotic changes such as parenchymal bands, architectural distortion, and traction bronchiectasis. Notably, crazy paving is not a feature of this stage.

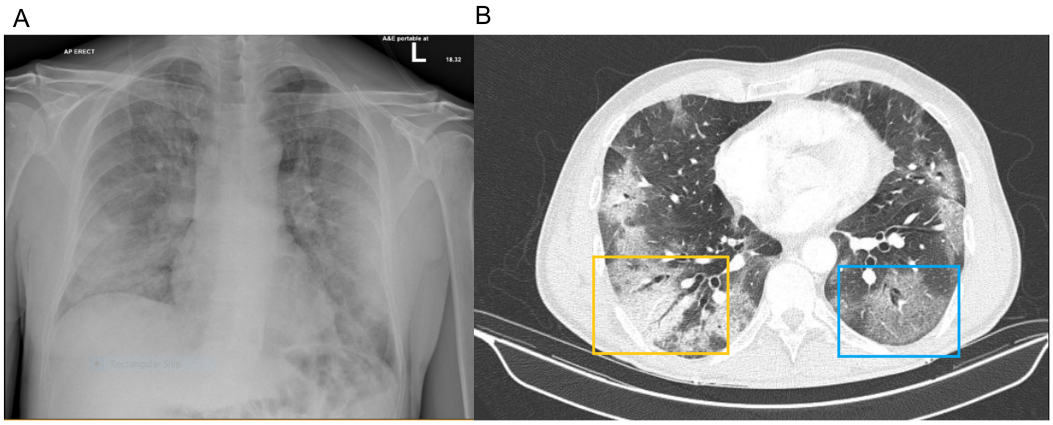

Fig. 5. Examples of radiological changes in COVID pneumonia. (A) CXR in a patient with COVID pneumonia showing ground glass and consolidation. (B) Corresponding CT patient with COVID pneumonia showing right-sided consolidation with air bronchogram (yellow box) and left-sided ground glass (blue box) changes—source author. L, left.

Molecular or nucleic acid amplification tests are recommended to diagnose acute infections. Most commonly, they are based on RT-PCR. It provides the most sensitive and specific means of confirming a clinical diagnosis.

Serology can be used to detect antibodies and be a surveillance tool to inform public policy (Peeling et al, 2022).

Point-of-care testing based on lateral flow assays was popular when COVID was more prevalent.

Treatment

Since the discovery of Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) as the causative agent of COVID-19, there have been more than 6.8 million deaths worldwide caused by this virus. This review aims to summarise the overall progress of COVID-19 therapeutics given the fast pace at which drugs have been developed for the entire spectrum of COVID-19 disease, ranging from mild to severe illness.

COVID-19 therapeutics currently include anti-inflammatory agents, antivirals, therapies for acute hypoxaemic respiratory failure and anti-SARS-CoV-2 antibody therapies. Numerous randomised clinical trials were set up to investigate the safety and efficacy of these drugs.

Invasive and Noninvasive ventilation (mainly continuous positive airway pressure (CPAP)) is used in the management of severe COVID-19 pneumonitis and respiratory failure. Patient selection is important with frailty and delirium are associated with a higher risk of CPAP failure and death.

The Randomised Evaluation of COVID-19 Therapy – Respiratory Support (RECOVERY-RS) (Perkins et al, 2022) trial demonstrated that, in patients with acute hypoxemic respiratory failure secondary to COVID-19, an initial strategy of CPAP significantly reduced the risk of tracheal intubation or death within 30 days of randomisation compared to conventional oxygen therapy or high-flow nasal oxygen. Also, studies have indicated that elderly, frail patients with severe COVID-19 pneumonitis who were considered unsuitable for invasive mechanical ventilation do not benefit from high-flow nasal oxygen (HFNO). Moreover, HFNO may have been associated with potential harm in this patient population (Merchant et al, 2022). A study by Ceriani et al (2022), in a cohort of 110 patients $\geq$75 years old with COVID-19 pneumonia who underwent CPAP, concluded that respiratory impairment, frailty, and delirium are key predictors of treatment failure, with frailty and delirium having a notable impact on mortality risk. CPAP support may be a viable therapeutic option for elderly patients; however, its effectiveness is significantly diminished in cases of severe respiratory impairment, advanced frailty, or the presence of delirium (Ceriani et al, 2022).

The 4C score is a validated tool to assess risk of mortality and morbidity in COVID-19 pneumonitis based on a prospective observational cohort study in adult patients admitted to 260 hospitals in England, Scotland and Wales. The total score is derived from 8 variables, which are easily available at initial hospital assessment: age, sex, number of comorbidities, respiratory rate, peripheral oxygen saturation, Glasgow Coma Scale score, urea level, and C-reactive protein. With a range of 0 to 21, the score stratifies patients' in-hospital mortality risk into low, intermediate, and very high categories. Low-risk patients might be appropriate for outpatient management, intermediate-risk patients for general inpatient care, and high-risk patients may require intensive monitoring and aggressive treatment (Knight et al, 2020).

Due to COVID-19 patients also having a high incidence of venous thromboembolic events, prophylactic anticoagulation was incorporated into guidelines for hospitalised patients.

Initial drug development for COVID-19 focused on repurposing licensed drugs and monoclonal antibodies.

COVID-19 infection leads to hyperinflammation characterised by high circulating levels of pro-inflammatory cytokines such as interleukin-6 (IL-6). Therapies, therefore, included immunosuppressive drugs such as glucocorticoids (e.g., dexamethasone) and anti-IL-6 receptor antibodies (e.g., tocilizumab). Dexamethasone was the first drug to improve survival in COVID-19, reducing deaths by about one third in ventilated patients (RECOVERY Collaborative Group et al, 2021). The RECOVERY trial subsequently identified effective repurposed drugs, including tocilizumab and sarilumab. In the Randomised Embedded Multifactorial Adaptive Platform for Community-Acquired Pneumonia (REMAP-CAP) study, the 180-day all-cause mortality was reduced among critically ill adults in intensive care who had received either of these drugs during their hospitalisation.

Nirmatrelvir plus ritonavir (Paxlovid) is recommended for treating COVID-19 in adults who do not require supplemental oxygen and are at increased risk of progressing to severe illness, including those aged 70 or older, a body mass index (BMI) of 35 kg/m^2 or more, diabetes, or heart failure, as per National Institute for Health and Care Excellence (NICE) guidance. If nirmatrelvir plus ritonavir is contraindicated or unsuitable, Sotrovimab is recommended for adults and individuals aged 12 and over who do not need supplemental oxygen, but they must weigh at least 40 kg and be at risk of severe COVID-19 progression.

Antivirals like Remdesivir and Molnupiravir are among the recommended treatment options.

Tocilizumab is recommended for treating COVID-19 in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation.

Baricitinib should be considered for individuals aged 2 years and over who are hospitalised with COVID-19, require supplemental oxygen, are receiving or have completed a course of corticosteroids like dexamethasone (unless corticosteroids are contraindicated), and have no evidence of other infections that could be worsened by baricitinib. When there is clinical deterioration despite treatment with tocilizumab, it may be appropriate to add baricitinib.

The recommended vaccines for the autumn 2024 campaign are all monovalent products containing mRNA for the spike protein of the JN.1 sub-lineage of the Omicron variant strain of the SARS-CoV-2 virus. Eligible adults aged 18 years or over can be offered either of Pfizer BioNTech 30 micrograms/dose COVID-19 vaccine (Comirnaty 30 JN.1) or a dose of Moderna 50 micrograms/dose COVID-19 vaccine (Spikevax JN.1) (UKHSA, 2024a).

Rarely reported adverse events include myocarditis, pericarditis, Guillain-Barré syndrome (GBS), erythema multiforme and thrombocytopenia. Additionally, there have been extremely rare reports of capillary leak syndrome following Moderna vaccines in individuals with a prior history of the condition (UKHSA, 2024b).

Long COVID/Post-COVID Syndrome

NICE defines ongoing symptomatic COVID-19 as signs and symptoms of COVID-19 from four to 12 weeks, and post-COVID-19 syndrome as signs and symptoms that develop during or after COVID-19 and continue for more than 12 weeks and are not explained by an alternative diagnosis.

Sathyamurthy et al (2021) examined the prevalence, patterns, and functional outcomes of post-COVID-19 syndrome in hospitalised older adults. After 90 days of recovery, the most commonly reported symptoms were fatigue (8.9%), followed by cough (4.3%), breathlessness (1.8%), dizziness (1.4%), myalgia (1.1%), loss of smell and taste (0.8%), and chest discomfort (0.7%). The risk of anxiety was observed in 7.5% of the study population, while the risk of depression was 12.2%. Overall, 23.6% of patients experienced at least one lingering symptom, and 9.3% had two or more. A comparison of the mean scores for activities of daily living (ADL) and instrumental activities of daily living (IADL) before the illness and 90 days post-recovery showed no significant statistical difference.

The mental health impact has been corroborated by Xie et al (2022), who reported an increased relative risk (RR) for mental health disorders post-COVID-19, with a notable rise in anxiety (RR: 1.35) and depression (RR: 1.39) after 12 months. What's significant is that these rates were higher than those seen after seasonal influenza, and the impact was also observed in individuals who weren't hospitalised.

Frontera et al (2021) suggested even more severe mental health outcomes, with more than 90% of patients reporting cognitive or psychiatric symptoms. This figure is quite striking and highlights the potential scope of the neuropsychiatric effects of COVID-19.

The UK Health Security Agency (UKHAS) in 2022 highlighted some important insights regarding vaccination and long COVID:

• Vaccination and long COVID risk: Vaccines seem to significantly reduce the risk of long COVID, with estimates ranging from a 30% to 80% reduction. This suggests that vaccination may play a crucial role in preventing the development of long-term symptoms following an infection.

• Vaccination and symptom improvement: For those who already have long COVID, vaccination appears to help improve symptoms in about 57% of cases. However, it's important to note that in 19% of cases, symptoms may actually worsen post-vaccination. This mixed response suggests that while vaccination can offer benefits for many, it's not a guaranteed solution for everyone suffering from long COVID.

• Antivirals: The evidence for anti-viral treatments in the context of long COVID is more uncertain, with few studies and potential confounding factors making it hard to draw definitive conclusions.

A study by Lau et al (2024) found that SIM01, a synbiotic preparation administered for six months, alleviated multiple symptoms of post-COVID-19 syndrome in a randomised double-blind placebo-controlled study.

Rhinoviruses

Rhinoviruses (RVs) are RNA viruses belonging to the *Picornaviridae* family and comprise three species (A, B, and C) with over 160 identified serotypes. RV infections are most commonly observed during early fall and late spring, presenting with a wide spectrum of clinical manifestations. These range from upper respiratory tract symptoms—such as rhinorrhea, sneezing, nasal congestion, sore throat, and pharyngitis—to lower respiratory tract involvement, including bronchitis, pneumonia, and bronchiolitis. RVs are also frequently implicated in the exacerbation of asthma and chronic obstructive pulmonary disease (COPD) (Greenberg, 2016; Stefanidis et al, 2021).

On chest CT imaging, mild cases may demonstrate normal or near-normal appearances. However, in patients with severe rhinovirus pneumonia, a predominant peribronchial and interstitial pattern with ground-glass opacities is typically observed (Stefanidis et al, 2021).

Traditionally, RV diagnosis has relied on virus culture isolation combined with the acid-stability test. Although specific, this method is labor-intensive and time-consuming, limiting its routine clinical use (Zhang et al, 2020). Antibody-based assays have also been developed; however, due to the absence of a common antigen across RV serotypes, serotype-specific neutralising antibody assays are required. The sheer diversity of RV serotypes renders this approach impractical for widespread clinical application (Greenberg, 2016).

In current clinical practice, nucleic acid amplification tests (NAATs), particularly reverse transcription polymerase chain reaction (RT-PCR), are the preferred method for detecting rhinovirus. Multiple studies have demonstrated the superior sensitivity of RT-PCR over traditional viral culture techniques (Greenberg, 2016).

Currently, there is no cure or preventative treatment for rhinovirus infection. Treatment remains mainly supportive with symptomatic alleviation such as the use of Nonsteroidal anti-inflammatory agents, nasal decongestants and antihistamines. There have been recent efforts to develop anti-viral treatments, including blockade of the Intercellular Adhesion Molecule 1 (ICAM-1) receptor (a major cellular receptor for rhinovirus); however, these are still preliminary inquiries (Shukla et al, 2022).

Human Metapneumovirus

Human metapneumovirus (HMPV) is an RNA virus belonging to the *Pneumoviridae* family, first identified in 2001 as a cause of respiratory illness in children in the Netherlands (van den Hoogen et al, 2001). In the EPIC study, HMPV was identified as the third most common viral pathogen associated with community-acquired pneumonia (Jain et al, 2015). While HMPV infection in healthy young adults generally manifests as a mild upper respiratory tract illness, its severity increases with advancing age and the presence of comorbidities. HMPV has been implicated in the development of pneumonia and in exacerbations of asthma and COPD (Nunes-Silva et al, 2022).

Chest radiographic findings may include ill-defined patchy and nodular ground-glass opacities, bilateral peribronchial infiltrates predominantly in the central lung zones, and, in some cases, minimal pleural effusion (Stefanidis et al, 2021).

A study by Koo et al (2019) of CT findings in HMPV showed that 76% had bilateral involvement, characterised most commonly by ground glass opacities (79%), centrilobular nodules (69%), and consolidation (43%). Macronodules were seen in 45% percent of patients and bronchial wall thickening in 88%. Mediastinal lymphadenopathy (27%) and pleural effusions (22%) were less common findings (Koo et al, 2019).

In hospital laboratories, the main methods used for HMPV detection are PCR-based assays, including conventional RT-PCR, multiplex RT-PCR, and microarray-based approaches (Feng et al, 2024).

Treatment is largely supportive, although in some cases of severe illness ribavarin has been used; the efficacy of this drug has not been established (Akingbola et al, 2025). There is no vaccine for HMPV; however, there are some ongoing trials looking at the combination of the RSV vaccine and the human metapneumovirus vaccine (Topalidou et al, 2023).

Adenovirus

Human adenovirus (HAdV), a double-stranded DNA virus belonging to the Adenoviridae family, has been classified into seven species (A to G) with over 50 serotypes based on hexon and fibre protein characteristics, relative nucleic homology, immunochemical responses, biological properties, and phylogenetic relationships. The different HAdVs affect different organ systems and cause different disease manifestations, such as respiratory disease (HAdV-B, -C, and -E), gastroenteritis (HAdV-F and -G), keratoconjunctivitis (HAdV-B and -D), and meningoencephalitis (HAdV-A, -B, and -D) (Zhang et al, 2020).

Chest radiographs may appear normal in the early stages; however, with disease progression, they often reveal unilateral or bilateral parenchymal opacities (Stefanidis et al, 2021).

In a study of 104 patients with adenovirus pneumonia conducted by Park et al (2017) showed that the most common findings on CT were consolidation (92 patients), ground glass opacities (82 patients), nodules (46 patients), septal thickening (34 patients), bronchial wall thickening (32 patients) pleural effusions (16 patients) and lymphadenopathy (3 patients). The most frequently occurring CT pattern was consolidation with surrounding ground glass opacities (50 patients), with subpleural and peribronchovascular distributions. The second-most common pattern (33 patients) was consolidation, which also showed a similar distribution. The dominant nodule pattern (14 patients) exhibited mixed (64%) and peribronchovascular (100%) distributions. A dominant ground glass opacity pattern was only observed in four patients; none had central distribution (Park et al, 2017). So these findings set HAdV apart from other viruses due to the preponderance of consolidations opposed to ground-glass opacity (GGO), the latter being much more commonly seen in other viruses.

Like other viruses, the cell culture of adenoviruses to observe its cytopathic effect, with subsequent virus isolation and immunological detection, is considered the "gold standard" (Zhang et al, 2020).

Common diagnostic methods, such as immunofluorescence (IF), latex agglutination test (LAT), and enzyme immunoassay (EIA), are also commonly performed in clinical laboratories (Zhang et al, 2020).

In recent years, emerging molecular-based detection techniques have increasingly supplanted traditional methods. Among these, real-time PCR stands out as a highly sensitive and quantitative approach for diagnosing HAdV infections (Zhang et al, 2020).

Parainfluenza

Parainfluenza (PIV), an RNA virus from the paramyxoviridae family, more commonly affects young children, whereas in adults, immunosuppression and older age predispose to severe disease.

PIV-1 and PIV-2 primarily target the upper respiratory tract, leading to upper respiratory tract infections (URTIs) and being notable pathogens associated with croup. In contrast, PIV-3 replicates in the lower respiratory tract, making it the predominant serotype responsible for lower respiratory tract infections (LRTIs), including bronchiolitis, bronchitis, and pneumonias, as well as worsening asthma and COPD symptoms. Co-infections with bacteria or fungi are relatively common and should be carefully investigated and excluded during diagnosis (Nunes-Silva et al, 2022).

The radiographic features of parainfluenza virus (PIV) infections are nonspecific and may include opacities and nodular patterns. However, a predilection for involvement of the lower lobes has been observed, which may aid in distinguishing PIV from other viral infections such as influenza and respiratory syncytial virus (RSV) (Stefanidis et al, 2021).

Herbst et al (2013) analysed 24 chest CT scans from patients with PIV infection. The most common finding (13/24, 54%) was tree-in-bud opacities with an airway-centric distribution of disease, showing bronchial wall thickening, tree-in-bud opacities, and peribronchiolar consolidation (bronchitis, bronchiolitis, and bronchopneumonia) as the most common pattern (16/24, 67%). In comparison with previous data on RSV, adenovirus, and influenza virus, PIV showed tree-in-bud opacities and airway-centric patterns significantly more often than adenovirus or influenza virus. PIV and RSV showed similar CT findings and patterns of disease (Herbst et al, 2013).

In clinical practice, PIV is primarily diagnosed using RT-PCR-based assays, either as standalone tests or as part of multiplex panels that detect and differentiate between the four PIV serotypes. Traditional serological assays are much less sensitive for PIV detection (Nunes-Silva et al, 2022).

There currently exists no licensed treatment for parainfluenza virus infection. There have been reported instances of the use of ribavarin (oral, aerosolised and intravenous) in the treatment of PIV, although little data is available on the efficacy of these agents.

There have been live attenuated vaccines developed with good results in the pediatric population, but there are no studies to date in the adult and elderly population. There currently exists no licensed vaccine for PIV in the adult population.

Global Respiratory Viruses

SARS and MERS

These two are examples of coronaviruses which caused more localised epidemics. Severe Acute Respiratory Syndrome was first identified at the end of February 2003 during an outbreak that emerged in China and spread to 4 other countries (WHO, n.d.b). Middle Eastern Respiratory Syndrome, most cases of which have been reported in the Arabian Peninsula, was first reported in Jeddah, Saudi Arabia, in 2012, but to date, as many as 27 countries have reported cases (WHO, n.d.a).

Since 2004, there haven't been any known cases of SARS reported anywhere in the world (Peeri et al, 2020). Unlike SARS-CoV-1 and MERS CoV continues to be a problem. As of 3 June 2024, a total of 2625 cases of MERS, including 951 deaths, have been reported by health authorities worldwide (European Centre for Disease Prevention and Control, n.d.).

Patients with SARS commonly present with fever, cough, and/or myalgias. Dyspnoea and hypoxemia typically develop during the second week of illness, with a subset of patients experiencing rapidly progressive respiratory failure (Greenberg, 2016).

In patients infected with MERS-CoV, nonspecific initial symptoms are frequent, including fever, chills, and sore throat. Respiratory symptoms are also prevalent, and respiratory failure can develop within a few days of onset (Greenberg, 2016).

Acute renal failure is a notable complication of MERS, often occurring in the second week of illness and occasionally requiring dialysis. A similar condition has been observed in a small percentage of SARS patients. Other reported non-respiratory manifestations include diarrhoea (7–25% of cases), nausea, vomiting, pericarditis, and arrhythmias (Greenberg, 2016).

There is no specific antiviral treatment for MERS. There are no approved vaccines for MERS.

Hantavirus

Hantavirus is spread mainly via rodents. They have not been known to cause human-to-human transmission. Humans are infected after exposure to rodents' droppings, urine, saliva or rarely even bites.

Hantavirus can cause two syndromes—hantavirus cardio-pulmonary syndrome (HCPS) and hantavirus haemorrhagic fever with renal failure syndrome.

Old World hantaviruses (those present in Europe, Asia and Africa) tend to cause haemorrhagic and kidney disease, whilst New World hantaviruses tend to cause severe respiratory disease (Public Health England, 2008).

Very few cases of hantavirus infection have been confirmed in the United Kingdom, although there are seroprevalence data to suggest that exposure does occur (Public Health England, 2008).

The only hantavirus known to cause human-to-human transmission is the Andes virus—a New World hantavirus found in Argentina and Chile and known to cause HCPS. Rare cases of travel-associated Andes virus (ANDV) infection have also been reported (Public Health England, 2021). In an outbreak involving 16 individuals, resulting in 9 fatalities and 15 secondary cases, eight infections were suspected to have occurred within healthcare settings. Among these were five physicians, three of whom had been directly involved in the clinical care of a patient with Andes virus-associated hantavirus cardiopulmonary syndrome (ANDV HCPS). Three of the physicians and a clinic receptionist succumbed to the illness (Public Health England, 2021).

If this is what your patient has, then you need help from the following Imported Fever Service (IFS) (24-hour telephone service: 0844 778 8990), Rare and Imported Pathogens Laboratory (RIPL) and Airborne High Consequence Infectious Disease (HCID) Treatment Centre.

Conclusion—Navigating the Challenges Posed by Respiratory Viruses in the Elderly

Respiratory viruses in older adults represent a growing challenge for clinicians and public health systems. This age group is disproportionately affected due to age-related changes in immunity and the presence of multiple chronic conditions. As highlighted in studies like the Etiology of Pneumonia in the Community (EPIC) study, viruses such as influenza, rhinovirus, and respiratory syncytial virus (RSV) are frequently detected in cases of community-acquired pneumonia (CAP) when systematic viral testing is performed (Jain et al, 2015). These viruses often contribute significantly to the disease burden in older adults, either as primary pathogens or alongside bacterial co-infections.

Immunosenescence and the Ageing Immune System

Ageing is associated with a decline in immune function, a process known as immunosenescence, which affects both the innate and adaptive arms of the immune system (Lynch et al, 2021). This decline leaves older adults more vulnerable to infections, with a slower and less effective response to pathogens. Importantly, the ageing immune system also responds less robustly to vaccines, making the prevention of respiratory viral infections more difficult in this population. For instance, older adults often have a suboptimal response to the influenza vaccine, requiring the use of high-dose or adjuvanted formulations to boost efficacy (Thompson et al, 2003). Even then, vaccine protection may be reduced compared to younger adults.

Moreover, the concept of "inflammaging"—chronic low-grade inflammation that occurs with age—can amplify the severity of viral infections. Infections like influenza and COVID-19 can trigger an exaggerated inflammatory response, leading to complications like acute respiratory distress syndrome (ARDS) and multiorgan failure, which are more likely to result in hospitalisation or death in older adults (Ruan et al, 2020).

Diagnostic Complexities in Viral Infections

Diagnosing respiratory viral infections in older adults is not always straightforward. Many viral infections in this population present with non-specific symptoms such as fever, cough, and shortness of breath, which overlap significantly with bacterial infections (Falsey et al, 2005). Traditional diagnostic tools, including chest radiography, often do not offer sufficient clarity to differentiate between viral and bacterial causes of pneumonia. For example, ground-glass opacities and bilateral lung involvement on chest X-rays are seen in a range of viral infections, including RSV, influenza, and rhinovirus, but they are not unique to any specific virus (Ruan et al, 2020).

Molecular diagnostics, particularly polymerase chain reaction (PCR)-based tests, have significantly improved the ability to detect respiratory viruses quickly and accurately. PCR allows for the identification of viral RNA or DNA, often within hours, making it a valuable tool in clinical settings (Mahony, 2008). However, the use of PCR in routine clinical practice remains limited, partly due to cost and accessibility issues, especially in resource-limited healthcare settings (Loeffelholz and Tang, 2020).

Preventive Strategies: The Role of Vaccination

Vaccination remains the cornerstone of prevention against viral respiratory infections in older adults. The seasonal influenza vaccine, for instance, has been widely adopted, though its effectiveness can vary year to year depending on the circulating strains and the individual's immune response (Grohskopf et al, 2021). Newer vaccines, such as the recently approved RSV vaccines, offer hope for reducing the burden of disease in older adults (Walsh et al, 2023).

The COVID-19 pandemic has also brought the issue of respiratory viral infections in older adults to the forefront. Vaccination efforts, particularly with mRNA vaccines, have been pivotal in reducing severe outcomes in this population. However, the emergence of variants and waning immunity over time has highlighted the need for booster doses and potentially new formulations to ensure ongoing protection (El Sahly et al, 2021).

Clinical and Public Health Implications

The high incidence of respiratory viral infections in older adults, especially in institutional settings like nursing homes, has broad public health implications. Outbreaks in long-term care facilities can have devastating consequences, as was seen during the COVID-19 pandemic. Infection prevention strategies, including vaccination, regular screening, and strict infection control measures, are critical in these settings (McMichael et al, 2020). From a clinical perspective, there is also a growing recognition of the need to avoid unnecessary antibiotic use. Because viral and bacterial pneumonia can be difficult to distinguish based on clinical and radiological findings alone, antibiotics are often prescribed empirically. This contributes to the growing problem of antibiotic resistance. Biomarkers like procalcitonin, which tend to be lower in viral infections, may help guide clinicians in making more informed decisions about antibiotic use (Schuetz et al, 2011). How-

ever, more research/trials are needed before it can be incorporated into standard practice.

Future Directions and Research Needs

There are several areas where future research could make a meaningful impact. First, there is a need for better vaccines that are specifically tailored to the ageing immune system. While current vaccines offer some protection, the response in older adults is often suboptimal. Adjuvants and high-dose vaccines are steps in the right direction, but more research is needed to develop vaccines that provide long-lasting and robust immunity in this population (Thompson et al, 2003).

Finally, more comprehensive surveillance systems are needed to monitor emerging respiratory viruses and their impact on older populations. With the ongoing threat of pandemics, preparedness efforts must prioritise the protection of vulnerable groups, including older adults.

Conclusion

In conclusion, respiratory viruses remain a significant cause of illness and death in older adults, driven by age-related changes in immunity and the presence of chronic conditions. While diagnostic and therapeutic advancements have been made, there is still much to be done to reduce the burden of these infections. Vaccination, timely diagnosis, and appropriate management are essential components of care, but ongoing research is needed to address the unique challenges posed by ageing and to improve outcomes for this vulnerable population.

Key Points

- Respiratory viruses are a common cause of acute respiratory illness, including pneumonia, in the elderly either in isolation or concomitant with bacterial infection.
- Detection is important to tailor treatment, appropriate infection control measures and reduce further testing.
- RSV in particular is emerging as an important respiratory virus in older adults, and a vaccine has recently been licensed.
- Ongoing trials and research are needed to see if a positive respiratory virus test, in conjunction with a biomarker such as procalcitonin, can be used to shorten or stop antibiotic courses.

Availability of Data and Materials

All data included in this study are available from the corresponding author upon reasonable request.

Author Contributions

SP, RR, SF and GH designed the work. SP drafted the manuscript. All authors contributed to the important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Written informed consent for publication of images has been obtained from patients. The research was conducted in strict accordance with the ethical principles outlined in the Declaration of Helsinki.

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Conflict of Interest

The authors declare no conflict of interest.

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