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Expert Review of Vaccines

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ierv20

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To cite this article: Charles Reynard, James Campling, Adam L Gordon, George Kassianos, Hui-Hsuan Liu, Alex Richter, Andrew Vyse, Dexter J Wiseman, Hannah Wright & Gillian Ellsbury (2024) Adult risk groups for vaccine preventable respiratory infections: an overview of the UK environment, Expert Review of Vaccines, 23:1, 1052-1067, DOI: 10.1080/14760584.2024.2428243

To link to this article: https://doi.org/10.1080/14760584.2024.2428243

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EXPERT REVIEW OF VACCINES
2024, VOL. 23, NO. 1, 1052–1067
https://doi.org/10.1080/14760584.2024.2428243

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REVIEW

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Adult risk groups for vaccine preventable respiratory infections: an overview of the UK environment

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ABSTRACT

Introduction: Vaccine-preventable respiratory infections (VPRI) including those caused by Streptococcus pneumoniae, influenza, respiratory syncytial virus and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pose substantial challenges to health and social care systems. In the UK, routine adult respiratory vaccination programs are in place. The objective of this article is to review the current evidence on the impact of four seasonal VPRIs in adults risk group definitions and to explore the strengths and limitations of current recommendations, and to identify evidence gaps for further research.

Areas covered: Relevant evidence on UK data from surveillance systems, observational studies and publicly available government documents is collated and reviewed, as well as selected global data.

Expert opinion: Disparities exist between adult risk group categories for different respiratory vaccination programs as defined in the current vaccination guidance. The burden of multiple respiratory pathogens signifies importance of routine multi-pathogen testing with the need for a resilient and large-scale national surveillance system. Further understanding of epidemiological trends and disease burden will help guide decision-making and planning of targeted strategies for disease prevention and control. Addressing inequalities in disease burden and vaccine coverage particularly in clinical risk groups, and promoting equitable vaccine access remain a priority.

ARTICLE HISTORY
Received 2 October 2024
Accepted 6 November 2024

KEYWORDS
Acute respiratory infection; clinical risk groups; influenza; pneumococcal disease; respiratory syncytial virus; SARS-CoV-2; vaccine-preventable respiratory infection; vaccine uptake

1. Background

Respiratory infections (RI) are a leading cause of morbidity and mortality worldwide [1]. In the UK, respiratory diseases including RIs were one of the most common indications for general practice (GP) consultations and accounted for a third of acute hospital admissions even before the coronavirus disease 2019 (COVID-19) pandemic [2]. Most respiratory admissions are unplanned emergency admissions and typically double in number during winter, with the seasonal impact of RIs posing unprecedented challenges to the National Health Service (NHS) [2–4].

Some acute respiratory infections (ARIs) are potentially vaccine preventable. In the UK, several adult routine immunization programs have been established for prevention and control of vaccine-preventable respiratory diseases (VPRIs) including pneumococcal disease (PD), influenza, respiratory syncytial virus (RSV), and COVID-19 [5–7]. Respiratory vaccination programs may help maintain regular health and social care service capacity through reducing healthcare resource use (HCRU) associated with VPRIs [8].

In the current UK adult respiratory immunization programs for PD, influenza, RSV and COVID-19, all UK adults at increased risk of complications caused by VPRIs are targeted for vaccination, in particular older healthy adults and adults with certain underlying comorbidities (Figure 1). Furthermore, the Joint Committee on Vaccination and Immunisation (JCVI) provided advice that there is evidence to support introduction of an adult RSV immunization program for adults aged ≥75 years [9]. The program will target those turning 75 years of age, but the initial catch-up program will target cohorts aged 75–79 years [10]. However, JCVI risk-based guidelines for younger 'at-risk' adults have not been established [9].

In the current respiratory immunization guidelines, there are some overlaps between risk group categories for different VPRIs and bespoke risk definitions for each disease area exist (Figure 1). Whilst it remains challenging to comprehensively and optimally identify all risk groups relevant to a specific disease or vaccine, efforts focusing on harmonizing discrepant risk group recommendations across indications may alleviate the complexity of clinical decision-making during implementation.

This article reviews the current UK adult immunization guidance for VPRIs (including PD, influenza, RSV and COVID-19) and the literature underlying current risk group recommendations. It explores the strengths and limitations of approaches used to date for identifying adult at-risk

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/14760584.2024.2428243

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Article highlights

- The impact of vaccine-preventable respiratory infections (VPRIs) caused by *Streptococcus pneumoniae* (or pneumococcus), influenza viruses, respiratory syncytial virus (RSV) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is far-reaching. Acute respiratory infection (ARI) seasons caused by different pathogens often occur concurrently with increased hospital admissions and emergency department visits as well as immediate and delayed mortality, placing significant burden on health and social care systems.
- In the United Kingdom (UK), routine adult respiratory immunization programs for pneumococcal disease (PD), influenza, coronavirus disease 2019 (COVID-19), and RSV (starting September 2024) are in place to help protect at-risk populations, in particular targeting older healthy adults and adults with certain risk conditions. Whilst a comprehensive list of risk categories has been established for PD, influenza and COVID-19, disparities exist in the current risk group definitions across indications, likely due to differences in the disease characteristics (e.g. pathophysiology, seasonality), the frequency of periodic updates to guidelines, and recommendations subject to availability of clinical/epidemiological data and cost-effectiveness modeling.
- Currently, except for age, there are no adult risk categories established for RSV. The RSV vaccines have been recently operationalized for use in older adults aged 75–79 years (starting from September 2024). A decision on those aged ≥65 years is currently under review as more data becomes available.
- Specific cohorts at an increased risk from RSV are presently being established, but this is yet to be fully reflected in recommendations. In light of recently approved RSV vaccines for older adults and pregnant individuals, national surveillance may be strengthened to support the introduction of the adult routine immunization program. More research investigating this area is anticipated.
- VPRIs share certain similarities regarding seasonality, infection route and transmission mode, with disease manifested by host factors (immunity, comorbidities), pathogen behaviors (virulence) and environmental factors (other co-circulating pathogens). Given the shared similarities, risk factors for VPRIs may be generalizable across indications, but more research is needed.
- A multi-pathogen environment means that routine multi-pathogen testing, stronger laboratory capacity and surveillance system are increasingly important to help understand the current landscape of respiratory infections and interactions between pathogens as well as estimate the combined burden of respiratory pathogens.

populations. This work aims to aid optimization of existing guidelines and help inform future risk group recommendations for new respiratory vaccines entering the UK immunization program.

2. Targeted literature search

2.1. Search strategy

A targeted literature search was conducted on 16 October 2023 using PubMed. Full details on the search strategy are provided in Supplementary Methods. Briefly, the search string was developed to identify publications reporting several key areas including risk groups for VPRIs (PD, influenza, RSV and COVID-19), burden of VPRIs, and vaccination coverage, specifically focusing on the UK adult population. Whilst the search was primarily restricted to identify articles reporting UK data, relevant publications from other countries of interest were also considered to determine wider epidemiological trends (on incidence, prevalence, risk factors and disease burden) and to discuss differences in vaccination guidelines, particularly in the disease area (i.e. RSV) where UK data were scarce.

In total, 766 articles published from 2018 onwards were retrieved from the search, of which 611 articles were excluded based on title/abstract screening. Full-text screening was performed on the remaining 155 articles. A total of 76 articles were retained and included in this review; 63 were related to COVID-19, six to influenza, three to PD, three for more than one indication, and one for RSV (Figure 2). An additional 24 articles were identified from gray literature search (13 articles related to COVID-19, eight to RSV, two to influenza, and one to PD) (Figure 2).

3. Current UK respiratory immunization guidance

The UK adult respiratory immunization guidance is based on available evidence including: disease burden, epidemiology and cost-effectiveness. In the context of available licensed vaccines, the JCVI then make recommendations. The adult risk group categories for PD, influenza and COVID-19 have been well researched; further research on influenza and PD is required given some new risk groups being identified during the COVID-19 pandemic. Adult risk categories for RSV, beyond age, are beginning to be established and are yet to be reflected in recommendations [11]. Despite the evidence-based guidelines, risk group recommendations in the UK do not fully align with those in other developed countries [12].

3.1. Current UK vaccination recommendations

3.1.1. Pneumococcal disease

Streptococcus pneumoniae (or pneumococcus) commonly colonizes the nasopharynx in healthy individuals [13]. It has been shown that pneumococcal carriage in healthy adults elicits a T-cell response and boosts immunity against future colonization and disease [14]. However, such a defensive mechanism is impaired among individuals with certain risk factors including older age and certain comorbidities (e.g. asplenia/splenic dysfunction, cochlear implants, cerebrospinal fluid [CSF] leaks) due to immunosenescence and inflammation, thereby promoting pneumococcal colonization which has been shown to be a pre-requisite for PD [13].

The UK adult pneumococcal vaccination program has been established for risk groups since 1992 and was extended to include all adults aged ≥65 years since 2003 (Figure 1) [6]. Currently, all healthy adults aged ≥65 years and adults in clinical risk groups are offered one dose of 23-valent pneumococcal polysaccharide vaccine (PPV23). Revaccination with PPV23 is recommended every five years for individuals with asplenia, splenic dysfunction or chronic renal disease (CKD), but not for any other risk groups [6]. Very-high-risk groups (i.e. severe immunocompromise caused by bone marrow transplant, acute and chronic leukemia, multiple myeloma, human immunodeficiency virus infection or genetic disorders [e.g. IRAK-4 or NEMO defects]) should be offered a dose of pneumococcal conjugate vaccine (PCV13 or PCV15) in addition to PPV23 [6]. As of June 2023, the JCVI advised that either PCV20 or PPV23 could be used in the routine immunization program for all healthy adults aged ≥65 years and adults in risk groups, recognizing that PCV20 is likely to prevent more disease than PPV23 and waning immunity may

Eligibility	PD	Influenza	COVID-19[b]	RSV
Age				
Age 65+ years	✓	✓	✓	✗
Age 75 years (catch-up 75–79 years)	✗	✗	✗	✓[d]
Clinical risk				
Asplenia or splenic dysfunction[a]	✓	✓	✓	TBD
Chronic respiratory disease	✓	✓	✓	TBD
Chronic heart disease[a]	✓	✓	✓	TBD
Vascular disease	✗	✓	✓	TBD
Chronic kidney disease[a]	✓	✓	✓	TBD
Chronic liver disease	✓	✓	✓	TBD
Diabetes mellitus	✓	✓	✓	TBD
Immunosuppression[a]	✓	✓	✓	TBD
Cochlear implants	✓	✗	✗	TBD
Cerebrospinal fluid leaks	✓	✗	✗	TBD
Chronic neurological disease	✗	✓	✓	TBD
Endocrine disorders[a]	✗	✓	✓	TBD
Morbid obesity	✗	✓	✓	TBD
Pregnancy	✗	✓	✓	TBD
Severe mental illness	✗	✗	✓	TBD
Occupational risk				
Welding or exposure to metal fumes	✓	✗	✗	TBD
Frontline health and social care workers	✗	✓	✓[c]	TBD
Carer in receipt of a carer's allowance	✗	✓	✗	TBD
Staff in care home for older adults	✗	✓	✓[c]	TBD
Individuals working in poultry industry and avian animal health	✗	✓	✗	TBD
Other risk				
Primary carer of an elderly or disabled person who may be at risk if the carer falls ill	✗	✓	✗	TBD
Residents of care homes or other long-stay care facilities	✗	✓	✓	TBD
Persons who are household contacts of people with immunosuppression	✗	✓	✗	TBD
At-risk individuals at clinician's discretion	✗	✓	✗	TBD

Figure 1. UK adult respiratory vaccination guidelines and recommendations.

[a]The definition of these clinical risk groups is heterogeneous across disease areas (see Table S1 for more details).

[b]Recommendations for COVID-19 vaccines are based on the autumn 2024 booster eligibility [27]. The JCVI suggested that health and social care service providers could consider vaccinating frontline health and social care workers as well as care home staff as part of an occupational health program [28].

[c]The UK government has stated that they will offer vaccination to frontline health and social care staff, as well as staff working in care homes for older people in the autumn 2024 program [27].

[d] All adults turning 75 years of age (on or after 1st September 2024) are eligible for the routine RSV vaccination program, and a catch-up program is issued for those aged 75–79 years from 1st September 2024, with those whose 80th birthday fall before 31st August 2025 also eligible in first year of program [10].

Abbreviations: COVID-19, coronavirus disease 2019; PD, pneumococcal disease; RSV, respiratory syncytial virus; TBD, to be determined.

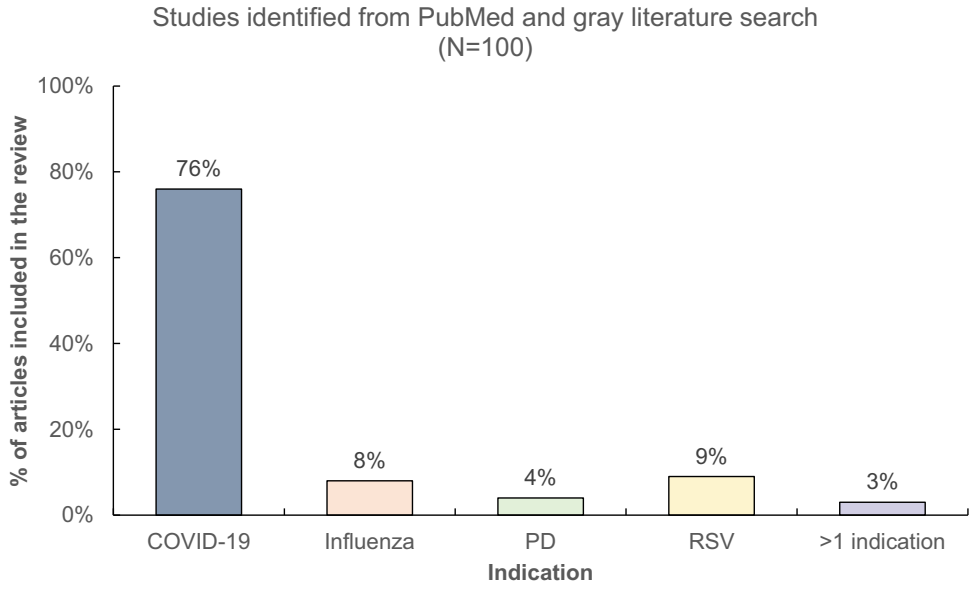


Figure 2. Target literature search outcomes.

The figure illustrates the number of included publications identified from PubMed database search and gray literature search.

Abbreviations: COVID-19, coronavirus disease 2019; PD, pneumococcal disease; RSV, respiratory syncytial virus.

occur at a slower rate [9]. The introduction of PCV20 May help address limitations with PPV23 and the emergence of serotype replacement [15].

3.1.2. Influenza

Influenza vaccination is usually deployed in early autumn before respiratory viruses start to increase in circulation [16]. Primary care services are responsible for delivering the vaccination program (e.g. identifying at-risk individuals, planning immunization appointments, ordering sufficient vaccines) [5].

Since the late 1960s, seasonal influenza vaccination programs have been established to target clinical risk groups and were further extended to all adults aged ≥65 years in 2000 [5] (Figure 1). Pregnancy and morbid obesity were subsequently added to the clinical risk category in 2010 and 2014, respectively [5]. Beyond the list of risk categories, medical practitioners should apply clinical judgment to offer vaccination to individuals who may benefit from influenza vaccines and are not in the clinical risk groups specified in the Green Book [5].

Clinical risk categories for influenza are regularly reviewed and updated to reflect the changing landscape of RIs, potentially shaped by the annual vaccine effectiveness estimated by the United Kingdom Health Security Agency (UKHSA) which develop a rich dataset to explore risk categories. In the 2020 to 2023 seasons during the COVID-19 pandemic, the influenza vaccination program was extended to healthy adults aged 50–64 years to protect the population from co-circulation of influenza viruses and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and to ease the pressure on the NHS [5]. However, the recommendation for 2023/24 season in England did not include healthy adults aged 50–64 years [17], in contrast with the guidance implemented in Scotland [18] and Northern Ireland [19].

Influenza vaccines are updated annually due to the evolving nature of the viruses. To combat this, vaccine development, production and recommendations are based on World Health Organization's decision on influenza vaccine strain selection [20]. For a decade, the quadrivalent vaccine targeting four dominant strains including two influenza A subtypes (H1N1, H3N2) and two influenza B lineages (B/Yamagata, B/Victoria) has been used in the UK [5,17,20,21]. However, vaccination guidance can be dynamic on an annualized basis in response to rapid antigenic drift that may reduce vaccine effectiveness at population levels [20,22,23]. Post-COVID-19 pandemic epidemiological trends have brought into question the need for inclusion of B/Yamagata in the vaccine; there is growing consensus that due to low circulating levels its inclusion is now longer necessary [24]. There is still an urgent need to improve influenza vaccine responses against mismatched strains, despite the recent advancement in vaccine technologies [25].

3.1.3. COVID-19

The UK COVID-19 vaccination program was launched in 2020. The aim of the program was to reduce hospitalizations and excess mortality, and ultimately alleviate pressure on the NHS and the wider social care system [7].

A vaccine prioritization strategy targeting frontline health and social care workers and nine priority groups was implemented during the primary vaccination phase and the initial reinforcing immunization, as advised by the JCVI [7]. This exercise of ranking priority was due to vaccine shortages and practicalities with vaccinating the entire adult population. This also marked a seminal time with regards to considering at-risk populations as well as comprehensively and formally defining

risk groups, necessitated by optimizing population-wide public health in a pandemic scenario.

Following the country-wide vaccine roll-out, the eligibility criteria in subsequent seasonal booster programs have been more dynamic. Vaccination guidance is regularly updated to address the emergence of new variants alongside the original strains and to reflect the rapidly evolving epidemiology [7]. In autumn 2023, a booster was recommended for adults aged ≥65 years, those aged 6 months to 64 years in clinical risk groups, and other risk groups covering pregnant individuals, residents and staff working in care homes for older adults, frontline health and social care workers, those aged 12–64 years who are household contacts of immunocompromised individuals, and carers aged 16–64 years [7]. The spring 2024 booster eligibility includes only adults aged ≥75 years, residents in care homes for the elderly, and individuals aged ≥6 months who are immunosuppressed [7]. The autumn 2024 booster eligibility is similar to autumn 2023, with advice for ≥65 years, those aged 6 months to 64 years in clinical risk groups [26,27] (Figure 1). The JCVI suggested that health and social care service providers could consider vaccinating frontline health and social care workers as well as care home staff as part of an occupational health program [28]. As there was not sufficient time for this to be operationalized, for 2024 the UK government has stated that they will offer vaccination to these groups [27].

The success of the COVID-19 vaccination program in the UK is widely recognized. The UKHSA estimated that it prevented over 230,800 COVID-19 hospitalizations, up to 24.1 million infections and up to 126,800 COVID-19-related deaths by the end of September 2021 [29]. The booster vaccination program has been estimated to have prevented approximately 192,900 hospitalizations in adults aged ≥25 years (including 159,700 hospitalizations in those aged ≥65 years, and 33,200 in healthy and at-risk adults aged 25–64 years) in England between 13 December 2021 to 20 March 2022 [30].

3.1.4. RSV

RSV is a lesser known but recognized as an important respiratory pathogen in older adults. Until recently, vaccine development had proved extremely challenging; however, following discovery of pre-fusion and post-fusion F protein, there have been breakthrough vaccines gaining approval [31].

In June 2023, the JCVI recommended that a vaccination program for older adults was cost-effective in adults aged ≥75 years [9]. The Committee stated a preference for an initial program to vaccinate those aged 75–79 years followed by those turning 75 years [9]. The operationalization of this advice by the UKHSA was announced in June 2024 - all adults turning 75 years of age from 1 September 2024 are eligible for routine RSV vaccination program and a catch-up program for those aged 75–79 years, with those whose 80th birthday fall before 31 August 2025 also eligible in first year of program [10]. Whilst it is acknowledged that adults with comorbidities may be at increased risk of RSV [32,33], specific risk groups for RSV are not yet reflected in the JCVI's recommendations.

Insights from a UK database study suggest that individuals with chronic conditions are at an elevated risk of RSV [32], but there is a need to better define at-risk populations. Currently prospective UK-based studies investigating the total burden of RSV are limited, whilst there are extensive epidemiological data on COVID-19-related hospitalizations, despite non-SARS-CoV-2 infections contributing to significant HCRU throughout the COVID-19 pandemic [34].

Reinfection with RSV commonly occurs throughout the life course, indicating that immunity induced by natural infection does not provide long-lasting protection against reinfection [35]. A dose of RSV vaccine may offer some protection against RSV infection in adults aged ≥60 years for at least two RSV seasons [36–38]. However, the duration of vaccine-induced protection against RSV in adults remains unknown, with the need for and the frequency of booster doses (particularly for risk groups) yet to be determined. Prospective research is needed to optimally define RSV risk groups and the extent of any revaccination necessary to inform potential label updates, guiding future JCVI decision-making.

3.2. Areas for consideration in future adult risk group recommendations

Pneumococcus, influenza, RSV and SARS-CoV-2 share certain similarities regarding infection route (respiratory, contact) and transmission mode (respiratory droplets, aerosols), with disease manifested by host factors (immunity, health conditions), pathogen behaviors (mutation) and environmental factors (other co-circulating pathogens, seasonality) [39–41]. As such, a substantial proportion of adult at-risk populations could be eligible for multiple vaccines, e.g. all healthy adults aged ≥65 years and clinical risk groups (including those with certain comorbidities, e.g. immunocompromise, cardiometabolic/respiratory diseases, or with environmental risks) are eligible for PD, influenza and COVID-19 vaccines.

However, disparities exist in the current risk group definitions across indications which can be attributed to differences in the disease pathophysiology, the frequency of periodic updates to guidelines, and recommendations subject to availability of clinical/epidemiological data and cost-effectiveness modeling. Specific cohorts at risk of RSV are presently being established but this is yet to be fully reflected in recommendations, and further studies are required to generate relevant UK data to inform such decision-making.

3.2.1. Gaps in current risk group definitions

Several gaps and disparities in risk group definitions across indications are summarized below.

3.2.1.1. Age 50–64 years not in clinical risk groups. The appropriate starting age of respiratory vaccination remains debatable. In countries such as the UK, there is an argument for optimal age targeting for pneumococcal vaccination in older healthy adults [42]. Available evidence suggests that the burden of influenza starts to increase from the age of 50 years likely due to immunosenescence and continues to intensify with increasing age in the presence of comorbidity [43,44]. Thus, this is an argument in favor of lowering the threshold to ≥50 years in the influenza vaccination guidelines which had been introduced in Scotland (in September 2023) [18] and Northern Ireland (in January 2024) [19]. For 2024 Scotland

plans to raise the age threshold to ≥65 years [45], and whilst influenza vaccines for healthy adults aged 50–64 years are not NHS-funded in England or Scotland during 2024/25 season, this cohort can seek to obtain influenza vaccine privately.

The adult age threshold for the COVID-19 autumn vaccination transitioned from ≥50 years in the 2022 autumn booster program [46], to ≥65 years in autumn 2023 which was reconfirmed for autumn 2024 [7]. The spring booster program has had an age threshold of ≥75 years since spring 2022 [7]. Evidence exists that the elevated risk of COVID-19 mortality was observed as early as the age of 50 years [47,48].

Likewise, the risk of RSV infection and severe outcomes increases with advancing age. The JCVI advised that all UK adults aged ≥75 years could benefit from RSV vaccination; this was operationalized as a program targeting those aged 75–79 years [10]. While the recently approved RSV vaccines are currently licensed for healthy adults aged ≥60 years in the UK [49,50], in June 2024 an RSV vaccine gained licensure in the US for those aged 50–59 years at an increased risk for RSV [51].

3.2.1.2. Cardio-renal-metabolic diseases and endocrine disorders. Adults with chronic heart disease (CHD) are eligible for three vaccines, whilst those with vascular diseases (including atrial fibrillation, peripheral vascular disease, venous thromboembolism and stroke) are eligible for influenza and COVID-19 vaccines but not for pneumococcal vaccine (Table S1). Given the shared risk factors and pathophysiology between CHD and vascular disease [52], more research is required to investigate if they pose a similar risk to ARIs.

Endocrine disorders are important risk factors for influenza and COVID-19. Endocrine diseases can increase susceptibility and manifestation of viral infections due to endocrine tissues being a viral target, as well as chronic inflammation and altered immune response caused by diseases or certain treatment (e.g. corticosteroids) [53]. The dynamic relationship between endocrine diseases and viral infection suggests that the underlying comorbidities could worsen after infection [53]. Current pneumococcal risk groups recommendations include those with immunosuppression caused by treatment with systemic steroids at ≥20 mg/day for more than a month (Table S1). More research is needed for individuals with endocrine disorders and the risk of PD and RSV due to the possibility of disease-related immune response dysregulation.

CKD and diabetes are risk factors for PD, influenza and COVID-19, but stage 3 CKD and diet-controlled diabetes are excluded from the current pneumococcal vaccination guidance (Table S1). However, diabetes of any type with poor glycemic control was found to be strongly associated with an increased risk of hospitalization from COVID-19, influenza and PD [54].

3.2.1.3. Obesity. Severe obesity is associated with pulmonary dysfunction which further predisposes individuals to adverse outcomes from RIs [53]. Potential mechanisms underlying the link between obesity and severe respiratory outcomes have been uncovered, e.g. in the case of COVID-19, while the adipose tissue is a viral target (due to the abundant expression of the angiotensin-converting enzyme 2 receptors), the obesity-driven chronic inflammation triggers immune dysfunction leading to disease aggravation [53].

Currently, adults with morbid obesity (body mass index [BMI] ≥40 kg/m^2) are eligible for influenza and COVID-19 vaccines, as many individuals within this group may have obesity-related complications (e.g. cardiometabolic and endocrine disease) that already place them in another risk category (Figure 1). However, obesity has not been recognized as a risk factor for PD. A body of literature demonstrated that BMI ≥30.0 kg/m^2 serves as a strong prognostic factor for increased risk of COVID-19 mortality and adverse outcomes [47,55–58]. A linear association was observed between obesity and COVID-19 mortality; every 5.0 kg/m^2 increment in BMI is associated with a 11.0–13.0% increase in mortality risk [57]. In Australia, obesity with a BMI ≥30.0 kg/m^2 is officially recognized as a risk factor for influenza and COVID-19 [59], and this may be considered for UK respiratory vaccination programs.

3.2.1.4. Chronic neurological diseases. Vaccinating adults with chronic neurological diseases with influenza and COVID-19 vaccines is currently recommended (Figure 1). Such guidance may be considered for PD as previously discussed, i.e. offering pneumococcal vaccine to those with stroke or dementia [15].

3.2.1.5. Cochlear implants or CSF leaks. Pneumococcal vaccination is offered to adults with cochlear implants or CSF leaks due to an increased risk of developing pneumococcal meningitis, with recommendations based on the limited evidence on the incidence and disease etiology in the UK [60–62]. Conversely, this is not issued in the influenza and COVID-19 vaccination guidelines (Figure 1) and currently there is no research linking cochlear implants or CSF leaks to severe influenza or COVID-19. More research is needed to investigate whether both conditions are generalizable risk factors for other VPRIs.

3.2.1.6. Clinical discretion of healthcare providers. Medical practitioners are advised to offer influenza vaccines to at-risk individuals outside of recommended risk groups based on their clinical discretion [5]. Currently, such a recommendation is issued for influenza vaccination only, in contrast to pneumococcal vaccination (guided by specific risk-based recommendations) and COVID-19 vaccination guidance (remains dynamic each season) (Figure 1).

3.2.1.7. Demographic risk factors. Demographic risk factors for PD are currently limited to occupational risks associated with exposure to metal fumes and welding [6]. In comparison, a comprehensive list of demographic risk categories is established for influenza, including individuals working in poultry industry and avian animal health, frontline health and social care workers, carers, residents and staff working in long-term care homes or facilities, and household contacts of individuals with immunosuppression (Figure 1). For COVID-19, frontline health and social care workers as well as care homes residents and staff will be offered a booster vaccine in autumn 2024 [27] (Figure 1).

As previously discussed, several professional activities involving close contact of individuals with respiratory diseases may be considered as relevant for pneumococcal vaccination, e.g. individuals working in oil rigs, residential care homes, elderly care wards or prisons, and healthcare and social care workers [15]. Furthermore, emerging evidence published by the Industrial Injuries Advisory Council showed that there was an elevated risk of COVID-19 infection and subsequent illness and death among workers in the health and social care, transport, education, and leisure and retail settings [63]. In particular, workers in health and social care settings are at elevated risk of severe illness from VPRIs considering their direct exposure to patients and vulnerable groups in an isolated environment. Workplace vaccine mandate policies may be considered in health and social care settings to protect workers, patients and vulnerable groups [64].

3.2.2. Additional risk groups for further consideration

Additional at-risk populations identified from the literature may be considered as relevant for vaccination, as described below.

3.2.2.1. Frailty. The strong association between frailty and severe outcomes of PD has been discussed previously; hospitalized patients with worse frailty and morbidity scores may benefit from pneumococcal vaccination [15].

The use of Clinical Frailty Scale (CFS) for managing COVID-19 in hospitalized patients has been recommended in the COVID-19 rapid guidelines published by the National Institute for Health and Care Excellence [65]. However, the consensus guidance suggests that CFS should be used alongside other factors (e.g. age, underlying health conditions) for clinical decision-making, and that CFS cannot be applied to younger age groups or those with disabilities since the tool was only validated in adults aged ≥65 years [66]. Emerging evidence suggests that frailty may serve as an independent prognostic factor for severe COVID-19-related outcomes including mortality, hospital length of stay and post-vaccination SARS-CoV-2 infection [67–69].

3.2.2.2. Multimorbidity. Multimorbidity is a strong predictor for severe COVID-19 [70–73]. Compared with adults without any comorbidity, those with one comorbidity had 1.4-fold higher risk of COVID-19-attributable hospitalization or death while the risk level was much higher in those with ≥ 2 comorbidities (2.0-fold) [70]. Ample evidence showed that among middle-aged population, multimorbidity (≥2 conditions) was an independent risk factor for greater COVID-19-related hospitalization and death, compared with those without multimorbidity (adjusted odds ratio: 1.9; 95% CI: 1.7, 2.2). The strongest association was observed among those aged ≥60 years versus those aged <60 years (2.0-fold versus 1.2-fold; $p = 0.047$). Furthermore, the risk level of severe COVID-19 May vary by different combinations of co-occurring conditions, with the greatest risk in those with CKD and diabetes (4.9-fold higher risk versus those without CKD and diabetes) followed by heart failure and hypertension (4.5-fold higher versus those without heart failure and hypertension) [73].

The association between multimorbidity and severe COVID-19 is not unexpected, since this has also been highlighted in the context of PD and recognized as a 'risk-stacking effect,' i.e. the synergistic effect of multiple comorbidities on risk of severe outcomes [15].

In the UK, a database study examining 308 mental and physical health conditions in 3.9 million patients found that over 93.6% of the population aged ≥60 years have multimorbidity (≥2 diseases) [74]. As multimorbidity increases with age, complex multimorbidity (≥4 diseases) becomes more prevalent [75]. With an aging population, clinical risk groups for VPRIs are likely to expand and thus vaccination programs alongside interventions for multimorbidity will continue to have substantial economic and healthcare implications in the next decades.

3.2.2.3. Immunogenetic factors. Certain genetic risk factors may determine COVID-19 outcomes and affect host immune responses to viral infection or vaccines, e.g. human leukocyte antigen (HLA) polymorphisms at the HLA-DRB1 × 13:02 locus was significantly associated with increased risk of developing a symptomatic COVID-19 [76]. There may be opportunities to incorporate immunogenetic risk factors into clinical decision-making for management of COVID-19 [70,77] and other VPRIs in the future, as more genomic data are generated.

3.2.2.4. Household contacts and caregivers of infants. The burden of influenza disproportionately affects infants and young children. In England, the influenza hospitalization rate was highest among infants aged <6 months [78]. However, currently there are no influenza vaccines licensed for widespread use in this young age group, and to date passive protection using a monoclonal antibody has been restricted to a small group [11]. Evidence showed that maternal influenza vaccination conferred protection against laboratory-confirmed influenza, influenza-like illness, and influenza-related hospitalization and clinic visits in infants aged <6 months [79]. Immunization of household contacts and caregivers of infants aged <6 months with influenza vaccines is issued in the US [80].

3.2.2.5. Sociodemographic risk factors. Several sociodemographic risk predictors for PD have been highlighted, e.g. living with children <6 years who attend day-care centers, low educational level, low income, household crowding, living in inner-city high pollution settings, and homelessness [15]. Furthermore, deprivation was also a risk predictor consistently identified for worse clinical outcomes of influenza [81] and COVID-19 [68,71,82–84] across different age groups, potentially attributed to inequalities in vaccine uptake. For example, a study reported a higher proportion of people with the least social deprivation received ≥ 2 doses of vaccines compared with those with the most social deprivation across all waves (e.g. 88.0% versus 71.0% in wave 5) [85]. The UKHSA estimated that 2022/23 seasonal influenza vaccine uptake was lowest among those with the most social deprivation across different risk groups (including those aged ≥65 years, adults in clinical risk groups aged 16–64 years, and pregnant women) [86]. Thus, strategies are needed to foster equitable access to

vaccines among all target populations. Moreover, ethnic minority groups were more likely to experience severe COVID-19 illness compared with the white population [55,71,82,83,87,88]. This observation could be associated with lower vaccination coverage [85] and the distinct demographic characteristics (e.g. multigenerational household living, deprivation) among ethnic minority groups compared with the white population [89]. Collectively, addressing clinical and social inequalities is critical in planning respiratory disease prevention and intervention strategies.

3.2.2.6. Lifestyle and environmental factors. Several lifestyle or environmental factors associated with increased susceptibility to PD have previously been discussed, including exposure to cigarette smoke, vaping or inorganic dust or fumes, and alcoholism [15]. Notably, smoking appears to have a sizable effect on COVID-19 mortality risk [57,58]. A smoking history (current, former or ever smoker) was associated with greater risk of COVID-19-related death, compared with never-smokers [57].

As extensively discussed in the literature, smoking is a significant independent risk factor for viral and bacterial respiratory infections and severe clinical outcomes while smoking cessation reduces the risk of infection and provides greater health benefits [90]. Notably, cigarette smoking is formally recognized as a risk factor for COVID-19 and influenza in the US [91] and Australia [59], respectively. Therefore, national strategies are urgently required to promote smoking cessation to prevent subsequent disease burden, and vaccination may help reduce disease severity.

3.2.3. Considerations for potential RSV risk groups

The burden of RSV is commonly characterized in the context of children and their parents/caregivers [92], in contrast to PD, influenza and COVID-19. Despite limited evidence derived from adults, it is widely suggested that adults ≥60 years and those with comorbidities experience high risk of severe illness from RSV infection (e.g. RSV-attributable hospitalization and mortality) [32,33,93–98].

UK-based evidence suggests that there is a considerable proportion of RSV-attributable hospital admissions and deaths among older adults aged ≥65 years [32,93–95,97]. The burden of seasonal RSV in older adults aged ≥65 years was found to be comparable to or exceed that of influenza [32,95]. Sharp et al. (2022) estimated that the mean seasonal rate of RSV-attributable respiratory hospital admissions was 71 and 251 admissions per 100,000 persons among adults aged 65–74 years and adults aged ≥75 years in England, respectively [95]. The mean number of seasonal RSV-attributable respiratory admissions was significantly higher than influenza (45 and 119 admissions per 100,000 adults in those aged 65–74 years and adults aged ≥75 years, respectively) [95]. These results demonstrated that RSV was one of the leading causes of winter respiratory admissions in older adults in England, and the burden of RSV was greater than influenza. Furthermore, adults with clinical risk conditions indicative of risk for severe influenza (as per recommendation in the Green Book) were found to have 2.0-fold higher risk of RSV-related episodes of GP visits or deaths and 4.0-fold higher risk of RSV-related hospitalization, compared with those without these conditions [32]. Further evidence from a modeling study using Scottish registry data demonstrated that RSV hospitalization rates among adults aged 45–64 years with underlying comorbidities were higher compared with the overall population [96]. RSV has also been associated with exacerbations of chronic obstructive pulmonary disease (COPD); thus, adults with COPD may benefit from preventive measures [98]. The burden of RSV in older healthy adults and clinical risk groups (based on influenza risk group categories) has been estimated using a statistical modeling approach [32,95–97], but this may underestimate the burden [99] and more prospective research is required to capture the true burden of RSV infection.

In the US, ongoing clinical and surveillance data suggest that certain underlying medical conditions are associated with increased risk of RSV hospitalization among adults aged ≥18 years [100], and most of these chronic conditions are currently deemed as risk factors for influenza or COIVD-19 as per vaccination guidance. Notably, a greater risk of severe RSV is observed in older adults with multimorbidity (≥3 versus 1–2 chronic conditions), those with any chronic medical condition (versus none), or those who live in long-term care facilities [100]. While implementing RSV vaccination program for older adults aged ≥60 years, the evaluation of benefits of vaccines for adults with certain chronic conditions is still ongoing and will inform future RSV vaccine policy [100].

4. Conclusion

VPRIs including PD, influenza, RSV and COVID-19 place significant burden on health and social care systems in the UK. Routine adult immunization programs are in place to help protect at-risk populations, in particular targeting older healthy adults and/or adults with certain risk conditions. However, there are discrepancies in risk group definitions across PD, influenza and COVID-19. Specific cohorts at an increased risk of RSV are presently being established and yet to be fully reflected in recommendations. A strong systematic approach was undertaken to define risk groups for COVID-19 through necessity, but this was not implemented for other VPRIs. In the area of PD, there is less evidence to enable optimal risk stratification compared with influenza and COVID-19.

Evidence derived from this targeted literature review revealed that research on risk groups understandably focused on the COVID-19 pandemic in the past five years, with large evidence gaps in the burden of RSV among UK adults. With the newly approved RSV vaccines for use in older adults, more research focusing on adult RSV is expected and the RSV surveillance may be strengthened to support the recent introduction of routine RSV vaccination program [10]. Furthermore, additional risk groups for each indication identified from the literature may be considered as relevant for vaccination. Given the shared characteristics of VPRIs, most risk categories may be generalizable across indications. Learnings from the COVID-19 pandemic demonstrate that a data-driven, risk prediction model has helped to rapidly and accurately identify relevant risk groups for severe COVID-19 in real-time and can be validated to reflect the evolving

epidemiology [101]. Such a tool may be adopted for other VPRIs to ensure wider at-risk populations are optimally identified and to inform targeted strategies/policies for infectious disease prevention and control, as more surveillance data become available.

5. Expert opinion

5.1. State of the literature

Vaccination guidance is regularly updated for influenza and COVID-19 to reflect the changing epidemiology and viral evolution. Conversely, periodic updates of the guidance for PD adult risk groups are not performed, while updates for RSV are anticipated as more insights into RSV risk groups and the duration of protection of RSV vaccines emerge. A more regular and systematic update to vaccination guidelines, in particular risk group eligibility, is critical to ensure validity of recommendations as new vaccines becomes available (e.g. combination vaccines, higher-valency PCVs, new influenza and COVID-19 vaccines, and vaccines targeting other respiratory pathogens). Having an available risk predictor tool for seasonal RIs ready to deploy would be useful before novel vaccines or treatments are developed and approved, as this could help early identification of risk groups and accelerate vaccine deployment. With more data generated and further understanding of the disease, a risk-assessment tool for COVID-19 was developed to accurately identify risk groups, which helped inform a more targeted and precise guidance and facilitated prioritization strategies for vaccine deployment [102]. An evidence-based prediction tool may be developed for other VPRIs to identify relevant at-risk groups in real-time, rather than the traditional 'condition-based' approach.

The COVID-19 pandemic increased the awareness of the disproportionate high risk of severe VPRI outcomes in immunocompromised individuals. Despite being recognized as a clinically extremely vulnerable group for VPRIs for decades and following COVID-19 outbreak, immunocompromised individuals are often underrepresented in respiratory vaccine trials (including PD, COVID-19, and influenza) [103]. While it is convention that pivotal phase 3 trials are conducted under standard experimental conditions and can only include participants with limited or stable comorbidities, post-licensure surveillance allows for assessment on vaccine effectiveness and safety in wider real-world populations with broader health conditions [104]. Thus, conducting post-licensure studies to monitor and evaluate vaccine effectiveness is critical to ensure trial vaccines provide the anticipated level of effectiveness in those who need protection. Collectively, it is imperative to maximize the efforts in protecting immune vulnerable groups against VPRIs (e.g. using a combination of early identification, diagnosis and intervention).

Indeed, there are additional risk groups to be considered as relevant for vaccination against PD, influenza and COVID-19, while adult risk groups for RSV are yet to be officially defined. Risk group recommendation requires robust evidence on disease burden and cost-effectiveness analyses, but data derived from specific risk populations are not always available or sufficient since most clinical trial data are based on healthy individuals. HCRU and operational considerations also need to be assessed prior to any risk group recommendation.

It has been extensively recognized that the immune function has begun to decline after the age of 50 years [105], lowering the eligible age to 50–64 years for routine respiratory vaccination may be considered. Moreover, different age recommendations across VPRIs may create barriers to implementation for clinical practice and confusion among the public. Given the literature cardio-renal-metabolic diseases, endocrine disorders, obesity and multi-morbidity could also be considered as generalizable risk factors for VPRIs. Standardizing discrepant recommendations may support the delivery of vaccination programs. This needs to be balanced by the duration of protection from vaccine, the frequency of revaccination, and cost of the program.

In the UK, adult risk categories for influenza or COVID-19 May be adopted as a standard set for initially establishing RSV risk groups before sufficient surveillance data are obtained. Risk groups for adult RSV have only recently been investigated in earnest, which creates promising opportunities for current/future research. Risk factors for other VPRIs and data from other countries may be used to guide which risk group candidate to examine, e.g. those with chronic cardiac and pulmonary disease, renal disease, diabetes and immunocompromised conditions [106], as well as sociodemographic risk factors [107,108]. There was variation in the risk of COVID-19 for the subcategories of the immunosuppressed, with transplant recipients, hematological malignancy and systemic steroid use found to be at an increased risk of COVID-19. These subcategories could be a priority for research in other VRPIs [109].

Moreover, existing RSV surveillance in the UK utilizes sentinel site data from primary and secondary care, including data collected by the Royal College of General Practitioner's Research and Surveillance Centre (RCGP-RSC) and laboratory-confirmed RSV cases from hospitalized patients with ARIs [21,110]. Given the recent approval of RSV vaccines [49,50] and other vaccine candidates in late-stage development [111], RSV surveillance may be strengthened particularly with routine testing for RSV. A rise in research on RSV is anticipated to support the recent introduction of a routine immunization program targeting healthy adults aged 75–79 years and may offer opportunities to help define RSV risk groups. Importantly this will enhance understanding of which risk groups could benefit from indirect protection and being directly protected individually.

There is a dilemma between categorizing risk groups on a pragmatic basis rather than solely on gold standard practice. For example, if the majority of care home residents are eligible via another risk category, vaccinating all residents may be operationally simpler/efficient. However, a large number of care home residents may have practical implications for the operational aspects of a vaccine program.

Learnings from the COVID-19 pandemic demonstrate that health economic modeling plays a pivotal role in underpinning public health policy. In the situation of incomplete/missing data, mathematical modeling was used to estimate the landscape of the pandemic (e.g. disease transmission and impact), assess the impact of intervention (e.g. vaccines) on resource utilization/allocation and determine vaccine priority

groups [112,113]. Employing such modeling approaches may be useful for future pandemic preparedness and ensure the efficiency of intervention strategy for ARIs. Nevertheless, there are opportunities for at-risk individuals to receive relevant vaccines privately outside of current risk categories, e.g. those with relevant occupational risks where employers could organize/fund vaccines to ensure their workforce is not compromised by VPRIs (e.g. sickness absence, presenteeism).

Lastly, available data exhibit variations in vaccination coverage for PD, influenza and COVID-19 by risk group with uptake mostly below the national target of 75% coverage [114]. The uptake in vaccines programs for PD, influenza and COVID-19 among adults aged ≥65 years was 71.5% (up to 2022), 77.8% (2023/24 season) and 70.3% (2023/24 season in England) [115–117]. Vaccination coverage remains low among adults in clinical risk groups. Among individuals aged 2–64 years in clinical risk groups, the estimated PD coverage (up to 2022) ranged from 38.5% (chronic liver disease) to 70.5% (cochlear implants) [118]. A low vaccination coverage for influenza and COVID-19 was also observed among immunosuppressed individuals in England (48.5% for influenza in those aged 16–64 years in winter 2023/24; 40.1% in those aged 5–64 years for COVID-19 in autumn 2023) [116,119]. Improving vaccine uptake among clinical risk groups remains as a high priority. Strategies are required to address individual factors for vaccine acceptance and discrepancies in vaccine access driven by existing clinical and social inequalities [120]. Insights into uptake and acceptance of the current licensed respiratory vaccines may be used to inform targeted approaches for candidate vaccines in development as they become available (e.g. human metapneumovirus vaccine). There may be opportunities to help optimize vaccination coverage with candidate combination vaccines currently in clinical development that include some or all of influenza, COVID-19 and RSV components [121–124]. Combination vaccines may benefit patients and healthcare system, but clinical decisions on applying these combination vaccines to risk groups may be complex due to variations in current risk group definitions across indications.

5.2. Multi-pathogen environment

The shared seasonal pattern of many common respiratory viral and bacterial pathogens has long been recognized. The circulation of respiratory pathogens typically increases in the autumn and peaks in the winter [125–127], occurring concurrently with the rise in hospital/ICU admissions and mortality [22]. Although PD is reported all year round, its distinct seasonal variability may be attributed to other co-circulating pathogen [125,128]. Evidence suggests that respiratory viruses can act as co-factors in the pathogenesis of PD [129], and viral infections may increase the susceptibility to the existing pneumococcal carriage through enhancing pneumococcal colonization and virulence, and vice versa [130,131].

In the multi-pathogen environment, coinfections including preceding and secondary coinfections remain as a concern. Respiratory viral or viral/bacterial coinfection exerts synergistic effects that can aggravate disease severity and outcomes [129,132–137], potentially imposing additional pressures on the NHS and social care system as the season approaches. Thereby, diagnosis of causal pathogens becomes increasingly important for planning targeted prevention and intervention in the current multi-pathogen environment.

In most UK centers, testing for respiratory pathogens in hospitalized patients is performed based on clinical suspicion, using laboratory-based PCR diagnostics rather than point-of-care testing (POCT) [138]. Rapid microbiological POCT platforms (single, dual and multiplex) for respiratory viruses are implemented in some UK hospitals but not yet in primary care [139]. There are multi-panel POCT systems alongside pathogen-specific POCTs (e.g. influenza) available to distinguish common respiratory viral and bacterial pathogens [140]. These platforms may facilitate effective clinical decision-making on patient management (e.g. the need for antimicrobials or antiviral prescriptions) and foster antimicrobial stewardship [140]. However, there is still a need to develop more accurate diagnostic technologies, e.g. sequencing or subtyping-based system. Importantly, efforts are required to improve awareness among clinicians and the wider public as to the burden of RSV in older adults and adults with risk factors. In practice, suitable testing is not performed unless RSV is suspected or suggested. Evidence shows that in the US, RSV testing is often not considered in most hospital admissions for lower respiratory tract infections, even among at-risk groups (e.g. adults aged ≥65 years) [141].

In England, the basis for a large-scale surveillance system is available. The RCGP-RSC network, established since 1957, is a nationally representative infectious disease sentinel surveillance network of > 2,000 practices across England and Wales [110,142]. The RSC collects the virology (including POCT and potentially self-swabbing at home) and serological surveillance data from primary care and shares with the UKHSA, enabling continuous monitoring, prediction and management of respiratory infection outbreaks including influenza, COVID-19 and RSV [142]. However, a larger system is required, and GPs are encouraged to undertake swabs from patients with ARIs and increase sample collection to escalate data collection/synthesis. Crucially, there is an urgent need to improve current surveillance system to capture more insights into risk groups affected by RIs, identify any unmet needs in seasonal RIs and inform risk group recommendations for vaccines. Until the system is enhanced, it remains challenging to make recommendations on clinical risk groups eligible for vaccination, in particular for RSV which has a large need for further studies. In light of lessons learned from the COVID-19 pandemic, there is an argument for developing a resilient surveillance system integrating a broad respiratory pathogen surveillance (including RSV, influenza, COVID-19) across Europe, with detailed level of pathogen subtyping data [143]. Routine multi-pathogen testing becomes increasingly important to guide healthcare decision-making as it provides epidemiological trends of variants that may potentially be influenced by vaccination [143].

Collectively, more accurate multi-pathogen testing and stronger laboratory capacity and surveillance system are crucial to help understand the current landscape of RIs and interactions between pathogens and estimate the combined

burden of respiratory pathogens. Ultimately, this will also help support developing targeted strategies for infectious disease prevention and control.

There is a positive outlook regarding intervention of VPRIs. Over the next decade, the wider implementation of multiplex POCT will improve diagnostics in primary and secondary care. Vaccine development has advanced and continues to evolve, and new vaccines targeting other common RIs likely enter the UK immunization program in the next decade. Therefore, achieving greater vaccine awareness and uptake while continuing to develop future-proof surveillance methodology and tools for risk stratification is paramount.

Abbreviations

ARI	acute respiratory infection
BMI	body mass index
CFS	Clinical Frailty Scale
CHD	chronic heart disease
CKD	chronic kidney disease
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CSF	cerebrospinal fluid
GP	general practice
HCRU	healthcare resource use
HLA	human leukocyte antigen
ICU	intensive care unit
JCVI	Joint Committee on Vaccination and Immunisation
NHS	National Health Service
PCV	pneumococcal conjugate vaccine
PD	pneumococcal disease
POCT	point-of-care testing
PPV	pneumococcal polysaccharide vaccine
RCGP-RSC	Royal College of General Practitioner's Research and Surveillance Centre
RI	respiratory infection
RSV	respiratory syncytial virus
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
UKHSA	United Kingdom Health Security Agency
VPRI	vaccine-preventable respiratory infection

Funding

This study was funded by Pfizer Ltd, UK. Medical writing support was provided by Hui-Hsuan Liu at OPEN Health and was funded by Pfizer.

Author contributions

All authors have (1) substantially contributed to the conception and design of the review article and interpreting the relevant literature and (2) have been involved in writing the review article and have revised it for intellectual content.

Declaration of interest

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Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose

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Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

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