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REVIEW

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A review of evidence for pneumococcal vaccination in adults at increased risk of pneumococcal disease: risk group definitions and optimization of vaccination coverage in the United Kingdom

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ABSTRACT

Introduction: Pneumococcal disease (PD) significantly contributes to morbidity and mortality, carrying substantial economic and public health burden. This article is a targeted review of evidence for pneumococcal vaccination in the UK, the definitions of groups at particular risk of PD and vaccine effectiveness.

Areas covered: Relevant evidence focusing on UK data from surveillance systems, randomized controlled trials, observational studies and publicly available government documents is collated and reviewed. Selected global data are included where appropriate.

Expert opinion: National vaccination programs have reduced the incidence of vaccine-type PD, despite the rising prominence of non-vaccine serotypes in the UK. The introduction of higher-valency conjugate vaccines provides an opportunity to improve protection against PD for adults in risk groups. Several incentives are in place to encourage general practitioners to vaccinate risk groups, but uptake is low-suboptimal particularly among at-risk individuals. Wider awareness and understanding among the public and healthcare professionals may increase vaccination uptake and coverage. National strategies targeting organizational factors are urgently needed to achieve optimal access to vaccines. Finally, identifying new risk factors and approaches to risk assessment for PD are crucial to ensure those at risk of PD can benefit from pneumococcal vaccination.

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1. Introduction

Streptococcus pneumoniae (pneumococcus) infection is a leading cause of morbidity and mortality worldwide [1–3]. Diseases caused by pneumococci range from mucosal infections including otitis media, sinusitis and non-bacteremic pneumonia to life-threatening pneumonia and invasive pneumococcal disease (IPD), most commonly presenting as bacteremic pneumonia, but also sepsis and meningitis. In this review, the term pneumococcal disease (PD) refers to a wider concept of pneumococcal infections (including IPD, community-acquired pneumonia [CAP] caused by pneumococcus, and pneumococcal pneumonia).

The burden of PD is considerable and leads to long-term clinical and economic impact on patients and the healthcare system in the UK. The pneumococcus was recently reported to be the leading pathogen for respiratory hospitalization among adults aged ≥65 years in England (prior to the COVID-19 pandemic) [4]. The clinical burden of PD is notably high among individuals with certain underlying comorbidities [5–10] and increases with age [5]. The increased clinical burden not only reflects higher healthcare resource utilization and costs, but also markedly impacts patients' quality of life [8,11]. Indeed, the presence of other common pandemic viral pathogens including SARS-CoV-2, respiratory syncytial virus and influenza viruses substantially contributed to the epidemiological and clinical burden of respiratory disease, potentially through viral-bacterial interaction [12–14]. However, it was recently reported that non-COVID -19 respiratory infections were still the major cause of acute lower respiratory tract infections (LRTIs) hospitalizations throughout the COVID-19 pandemic [15].

Although the burden of PD has been reported, it is likely to be an underestimate [16]. The causal pathogen is frequently not confirmed in many patients with respiratory tract infections managed in primary and secondary care. As such, underreporting together with potential under-ascertainment of PD may contribute to invalid estimates of disease prevalence, thus underestimating the true burden of PD [16].

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Article highlights

- National vaccination programs have helped reduce the incidence of vaccine-type PD in the UK, but there have been concerns on the emerging incidence of PD caused by non-vaccine serotypes (i.e. non-PCV13, non-PPV23).
- The introduction of higher-valency conjugate vaccine options (i.e. PCV15, PCV20) within the UK provides an opportunity to help address the challenges associated with serotypes replacement. These new pneumococcal conjugate vaccines provide broader serotype coverage, as these contain new serotypes (in addition to PCV13) responsible for PD cases in the UK, particularly in adults aged ≥65 years, and thus potentially offering improved and direct protection against PD for adults in risk groups.
- Two new higher-valency pneumococcal conjugate vaccines, PCV15 and PCV20, are licensed and available in the UK; both vaccines have been introduced into vaccination guidelines in the US and some European countries. In the UK, the JCVI has now recommended that PCV20 should be used for adults in risk groups.
- Within the risk categories defined in the guidelines, occupational risk factors are limited to metal workers and welders. However, other professional activities involving close contact with people with respiratory disease could be considered as relevant for pneumococcal vaccination (e.g. individuals working in residential care homes, elderly care wards, oil rigs, prisons, those living in inner city high pollution settings and healthcare workers), since they are at higher risk of exposure to respiratory infections.
- The effect of risk stacking (defined as the increase in risk of PD with the accumulation of concurrent at-risk conditions) has not yet been formally considered and should be taken into consideration when making recommendations for pneumococcal vaccines. Reassessment of risk groups deemed eligible for pneumococcal vaccination may be beneficial for prevention of PD.
- Several unmet needs and challenges for the management of PD have been identified, including the resurgence of PD cases post COVID-19 restrictions, the continuous pressure on the National Healthcare Service's capacity for delivery of patient care, and global concerns on antimicrobial resistance. Some of these issues may be addressed through pneumococcal vaccination.
- Available data suggest that the PPV23 uptake rate varies by risk factor and remains low particularly in adults with risk conditions. The PPV coverage report published by the UK Health Security Agency estimated that the PPV23 coverage up to 2021 in eligible individuals (aged 2–64 years) ranged between 38.5% for those with chronic liver disease and 56.0% for those with chronic respiratory disease, while uptake rate was 70.7% for those with cochlear implants.
- Barriers affecting vaccination uptake include vaccine hesitancy (inadequate knowledge, low awareness, negative attitudes) toward vaccinations among patients and some GPs and patient access (convenience) to routine vaccinations. We also speculate that low vaccination uptake may be attributable to organizational factors.
- Although various incentives are in place to encourage GPs to vaccinate patients at risk of PD, national strategies are still needed to optimize vaccine uptake and patient access to vaccines may be informed by learnings from vaccine delivery approaches implemented during the COVID-19 pandemic.

PD predominantly affects older adults and young children [3]. Individuals with specific clinical conditions (Table 1) are at elevated risk of PD and PD-associated morbidity and mortality [7,8,17–21]. These risk groups have been targeted for vaccination to reduce the burden of PD [3]. In the UK, five pneumococcal vaccines are authorized for protection against different serotypes, including pneumococcal polysaccharide vaccine (PPV; PPV23) and pneumococcal conjugate vaccine (PCV; including PCV10, PCV13, PCV15, PCV20) [3] (Table 2). Currently, only four licensed vaccines are available, as PCV10 is no longer marketed and in use. Since 2003, PPV23 has been routinely offered to all adults aged ≥65 years and clinical risk groups aged ≥2 years. While in 2010, PCV13 replaced PCV7 (introduced in 2006) for routine infant immunization. Indeed, in the UK, PCV13 is only recommended for adults with very-high-risk conditions (i.e. severely immunocompromised individuals defined as: patients with bone marrow transplant, acute and chronic leukemia, multiple myeloma or genetic disorders affecting the immune system [e.g. IRAK-4, NEMO], and people living with human immunodeficiency virus [PLWHIV] as described in the British HIV Association [BHIVA] guidelines) [3].

In addition to directly protecting children, the sequential introduction of PCV7 and PCV13 into the infant immunization program has induced valuable indirect protection for older age groups and consequently reduced the incidence of vaccine-type (VT)-PD across the full age range [25]. However, the subsequent emergence of non-PCV13 serotypes and concerns about the extent of protection conferred by PPV23 suggested a need to now consider the new higher-valency PCVs for optimal control and prevention of PD among UK adults with underlying comorbidities [17,26]. In late 2021 and early 2022, two new higher-valent vaccines, PCV15 and PCV20, were approved respectively within the UK and licensed for use in adults aged ≥18 years for prevention of PD [22,24]. In light of the benefits of higher-valency PCVs and the evolving epidemiology of PD, the Joint Committee on Vaccination and Immunisation (JCVI) now recommends to include PCV20 for all adults in risk groups and recognizes that PCV20 is likely to prevent more disease than PPV23 and that waning of immunity may occur at a slower rate [23].

The advantages of PCVs over PPVs have been extensively reviewed in the literature [27–30]. Compared with PPVs, PCVs are considered more effective against PD and also impact nasopharyngeal carriage, thus preventing onward transmissions and inducing direct protection [28,30,31]. While PPVs and PCVs contain the same capsular polysaccharides, the polysaccharides within PCVs are conjugated to a carrier protein which provides durable and robust immunogenicity and the ability of generating immunological memory [27–29]. New vaccine candidates are in development, including PCV21, PCV24, and PCV30 (Table 2). Such PCVs will provide direct protection against PD for adults in risk groups against a broader range of serotypes [32]. Higher-valency PCVs that include similar (or higher) numbers of serotypes to PCV20 will likely be attractive options. However, the optimal pneumococcal vaccine will change over time as the epidemiology (e.g. disease incidence, prevalence and serotype behaviors) and vaccine technologies evolve. Alongside PCVs with >20 serotype coverage in development, next-generation whole-cell vaccines and protein-based vaccines are also in early development and whilst currently unproven, theoretically have potential to protect against all serotypes and to minimize possible immune escape [33,34]. Whilst elimination of nasopharyngeal colonization (a central precursor for PD) and inducing indirect protection is an advantage associated with both new and existing conjugate vaccines, aspiring to achieve complete elimination of pneumococcal carriage with future vaccines could in fact lead to the risk of subsequent replacement with other microorganisms that can cause disease, and this may be an undesirable consequence [33,34]. Striking a balance between benefit (e.g. eliminating carriage of those serotypes with most

Table 1. Clinical risk groups recommended for pneumococcal vaccination in the Green Book [3].

	Risk group definitions
Chronic respiratory disease	• COPD including chronic bronchitis and emphysema, bronchiectasis, cystic fibrosis, interstitial lung fibrosis, pneumoconiosis, and BPD • Children with respiratory conditions caused by aspiration or a neurological disease with a risk of aspiration • Severe asthma requiring continuous use of systemic steroids
Chronic heart disease	Ischemic heart disease, congenital heart disease, hypertension with cardiac complications, and chronic heart failure
Chronic kidney disease	Nephrotic syndrome, chronic kidney disease at stages 4 and 5, and those on kidney dialysis or with kidney transplantation
Chronic liver disease	Cirrhosis, biliary atresia, and chronic hepatitis
Diabetes	Diabetes mellitus requiring insulin or anti-diabetic medication, excluding diabetes that is diet controlled
Immunosuppression	• Immunosuppression caused by disease or treatment (e.g. chemotherapy, bone marrow transplant, asplenia or splenic dysfunction, complement disorder, HIV infection at all stages, multiple myeloma, or genetic disorders affecting the immune system (e.g. IRAK-4, NEMO) • Individuals (any age) on or likely to be on systemic steroids for more than a month at a prednisolone equivalent dose of ≥20 mg per day or children (under 20 kg) on a dose of ≥1 mg per kg per day
Asplenia or splenic dysfunction	Conditions that may lead to splenic dysfunction (e.g. homozygous sickle cell disease and celiac syndrome)
Cochlear implants	Post cochlear implants
CSF leaks	Leakage of CSF caused by trauma or major skull surgery (excluding CSF shunts)
Occupational risk	Continuous occupational exposure to metal fume (welding)

The table was adapted from Green Book [3].
BPD, bronchopulmonary dysplasia; COPD, chronic obstructive pulmonary disease; CSF, cerebrospinal fluid; HIV, human immunodeficiency virus

propensity for disease) and risk (i.e. increasing the likelihood of replacement disease) is imperative, albeit challenging, in vaccine development.

This targeted literature review aimed to describe the current UK landscape in relation to the identification and vaccination of individuals at risk of PD and to identify any opportunities for optimization of vaccine delivery and uptake.

2. Evidence of pneumococcal vaccine effectiveness and impact against PD

In the UK, four licensed vaccines (PPV23 and PCVs) are currently available for use to help prevent PD [3] (Table 2). The efficacy of PCV13 against PD in adults was based on data from the CAPiTA trial (Community-Acquired Pneumonia immunization Trial in Adults), one of the largest adult vaccination randomized control trials containing the most robust data available for assessing efficacy of PCV13 against IPD/CAP in older adults [31]. Substantial efficacy of PCV13 against IPD and pneumococcal CAP was demonstrated in adults aged ≥65 years, with efficacy sustained up to five years without evidence of waning [31,35] (**Table S1**). A post-hoc analysis of CAPiTA also showed significant and persistent efficacy of PCV13 against VT-CAP in at-risk older adults [36].

Evidence demonstrating PPV23 vaccine effectiveness against PD remains inconsistent (**Table S1**). Andrews et al. (2012) and Djennad et al. (2018) showed that PPV23 provided only moderate short-term protection against IPD in UK older adults (aged ≥65 years) and achieved no impact on IPD incidence at the population level. Effectiveness of PPV23 varied by serotype and waned within 2 years after vaccination [37,38]. Whilst there is evidence demonstrating that PPV23 may provide some limited protection against hospitalized CAP in UK adults aged ≥16 years, this was not the case when adults aged ≥65 years were specifically considered [39]. Overall, it is widely accepted that PPV23 provides some limited short-term protection against IPD among adults aged ≥65 years, without significant impact on IPD at the population level [37–42]. More robust evidence is needed to demonstrate PPV23's ability to provide meaningful protection against CAP in UK adults in risk groups [40–43].

The introduction of PCV13 into the UK national routine infant immunization program has considerably reduced the incidence of PCV13 VT-IPD in older age groups through direct and indirect effects; however, the emergence of non-PCV13 serotypes as a consequence of vaccine driven serotype replacement remains a major concern particularly in adults [26,44]. Such serotype replacement has also been reported in France, Germany and Sweden, with widespread concerns that initial substantial vaccine impact is now being eroded [45].

Collectively, such serotype replacement suggests that more effective higher-valent pneumococcal vaccines now need to be considered to replace PPV23 to better protect those UK adults considered at increased risk of PD [46]. The recent JCVI recommendation to include PCV20 for adults aged ≥65 years and all adults in risk groups is therefore timely, with the potential to consider other candidate higher-valency pneumococcal vaccines that are currently in development (e.g. PCV21, PCV24, PCV30) [47–50] in the future should they be licensed (Table 2).

Currently, serotype 3 continues to be responsible for a considerable burden of PD in UK adults [26,51]. Although there is evidence that PCV13 provides some direct protection against serotype 3 PD [42,52–55], its use in UK adults and those in risk groups has been very limited, with PPV23 being the primary vaccine used in this context. The recent recommendation of PCV20 to be included in the routine vaccination program for adults aged ≥65 years and all adults in risk groups may now help address this [23]. The limited impact of PCV13 on serotype 3 carriage further indicates that any indirect protection from pediatric PCV13 programs against serotype 3 disease is compromised [56]. This is likely attributed to the unique physiological properties of serotype 3, such as its thick capsule and surface electronegativity, and its ability to confer protection against host factors [57]. These features are considered to facilitate the ability of serotype 3 to cause disease and escape immune responses [57]. Improving the ability of

Table 2. Details of licensed pneumococcal vaccines and next-generation vaccines in development.

Vaccine	Manufacturer	Serotype coverage	UK recommendation [3]
Licensed pneumococcal vaccines in the UK			
PPV23 (PNEUMOVAX®23)	Merck Sharp & Dohme	1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9 V, 10A, 11A, 12F, 14, 15B, 17F,18C, 19A, 19F, 20, 22F, 23F, and 33F	• Licensed for use in adults aged ≥65 years, people aged ≥2 years with at-risk conditions* • Revaccination (every five years) recommended for individuals with certain risk conditions (i.e. asplenia, splenic dysfunction, or CKD) • Revaccination currently not recommended for any other risk groups
PCV20 (APEXXNAR®)	Pfizer	1, 3, 4, 5, 6A, 6B, 7F, 8, 9 V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F	• Licensed for prevention of IPD and pneumonia caused by *Streptococcus pneumoniae* in individuals aged ≥18 years [22] • Recommended for routine adult pneumococcal immunization program; available for all older adults aged ≥65 years and those aged <65 years in clinical risk groups* [23] • The need for revaccination not yet established
PCV15 (VAXNEUVANCE®)	Merck Sharp & Dohme	1, 3, 4, 5, 6A, 6B, 7F, 9 V, 14, 18C,19A, 19F, 22F, 23F, and 33F	• Licensed for prevention of IPD and pneumonia caused by *Streptococcus pneumoniae* in infants, children and adolescents from 6 weeks to <18 years of age and individuals aged ≥18 years [24] • The need for revaccination not yet established
PCV13 (PREVENAR13®)	Pfizer	1, 3, 4, 5, 6A, 7F, 9 V, 14, 18C, 19A, and 19F	• Licensed for Childhood Immunization Program, people aged ≥65 years, and clinical risk groups* • Revaccination not recommended for routine immunization • Additional dose may be recommended for individuals with severe immunocompromise*
PCV10 (SYNFLORIX®)	GSK	1, 4, 5, 6B, 7F, 9 V, 14, 18C, 19F, and 23F	• Not currently recommended in the National Immunization Program • Not currently available, marketed or in use
Next-generation pneumococcal vaccines in development			
PCV30+ (VAX-31)**	VAXCYTE, Inc.	In pre-clinical development	• Not yet commercially available
PCV24 (namely AFX3772)†	GSK	1, 2, 3, 4, 5, 6A, 6B, 7F, 8, 9 V, 9N, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20B, 22F, 23F, and 33F	• Not yet commercially available
PCV21‡	Merck Sharp & Dohme	3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B	• Not yet commercially available

*Risk conditions defined in Green Book (2020) include chronic respiratory disease, chronic heart disease, chronic kidney disease, chronic liver disease, diabetes, immunosuppression, asplenia or splenic dysfunction, cochlear implants, cerebrospinal fluid leaks, and occupational risk (welding). High-risk conditions include asplenia, splenic dysfunction, and immunocompromising conditions caused by bone marrow transplant, acute and chronic leukemia, multiple myeloma, or genetic disorders (e.g. IRAK-4 or NEMO defects).

**Behrens C, et al. Development of a next generation 30+ Valent Pneumococcal Conjugate Vaccine (VAX-XP) using site-specific carrier protein conjugation. Open Forum Infectious Diseases. 2021;8(Suppl 1):S615. doi: 10.1093/ofid/ofab466.1241

†Chichili GR, et al. Phase 1/2 study of a novel 24-valent pneumococcal vaccine in healthy adults aged 18 to 64 years and in older adults aged 65 to 85 years. Vaccine. 2022;40(31):4190–4198. doi: 10.1016/j.vaccine.2022.05.079

‡Platt H, et al. Safety, tolerability, and immunogenicity of a 21-valent pneumococcal conjugate vaccine, V116, in healthy adults: phase 1/2, randomized, double-blind, active comparator-controlled, multicentre, US-based trial. Lancet Infect Dis. 2023;23(2):233–246. doi: 10.1016/S1473–3099(22)00526–6

CKD, chronic kidney disease; IPD, invasive pneumococcal disease; PCV, pneumococcal conjugate vaccine; PPV, pneumococcal polysaccharide vaccine; UK, United Kingdom

pneumococcal vaccines to protect against both serotype 3 disease and carriage may be considered in the future directions of vaccine development.

3. Current pneumococcal vaccine uptake

3.1. Vaccine uptake in risk groups

In England, it was estimated that 12.7% ($n = 6,412,685/50,479,300$) of the general population had one or more risk factors (as defined in the Green Book), and 44.8% ($n = 3,780,552/8,434,300$) in those aged ≥65 years had one or more risk factors in 2009 [6]. In 2009, the estimated proportion of the population in risk groups (aged ≥2 years) ranged from 0.01% ($n = 3,584$) for those with cochlear implants to 6.2% ($n = 3,114,844$) for those with chronic heart disease (CHD) [6].

The number of at-risk individuals has increased since 2009, particularly in those aged ≥65 years. In 2021, a total of 10,601,410 adults aged ≥65 years were eligible for PPV23 vaccination based on registration records with general practitioners (GPs), and the estimated number of at-risk individuals aged 2–64 years ranged from 5,294 for those with cerebrospinal fluid (CSF) leaks to 1,487,496 for those with diabetes [58].

Moreover, PLWHIV are at greater risk of developing IPD than the general population [59,60]. National surveillance

undertaken in England between 1999 and 2017 showed the incidence of IPD was significantly higher among PLWHIV compared than the general population (incidence rate ratio: 14.6, 95% confidence interval [CI]: 13.9, 15.4, $p < 0.001$) [60]. Of 1,453 PLWHIV who developed IPD during the study period, 70.0% developed IPD after ≥3 months of human immunodeficiency virus (HIV) diagnosis. Despite treatment with effective antiretrovirals, PLWHIV had a 4.5-fold higher rate of IPD incidence than the general population. Furthermore, 59.0% of IPD cases were caused by 11 PPV23 serotypes not covered by PCV13 (8, 12F, 9N, 10A, 22F, 15B/C, 11A, 15B, 17F, and 33F) [60]. It should be noted that these serotypes are included in PCV20 with the exception of 9N and 17F. These data indicate that higher-valent pneumococcal vaccines could offer broader protection against PD and highlight the importance of continuing to offer pneumococcal vaccines to PLWHIV according to the national recommendations.

The 2021 PPV23 coverage report published by the UK Health Security Agency (UKHSA) suggested that the rate of pneumococcal vaccination (PV) uptake in eligible adults was suboptimal, particularly among those with risk conditions [58]. PCV13 coverage in those UK adults with very-high-risk conditions is currently not recorded. In England, PPV23 coverage was 70.6% in all adults aged ≥65 years who were vaccinated at any time up to March 2021. Data by age group showed that PPV23 coverage in adults aged 65 years was only 34.2% and increases with age (from 45.2% in adults aged 66 years to 83.0% in adults aged ≥75 years). These data indicate that two thirds of individuals are not immunized in the year when they become eligible but in the subsequent years. Increasing vaccine coverage in older age groups suggests that opportunistic vaccination of PPV23 continues to be offered to adults aged ≥66 years in primary care [58], highlighting the importance of GP's awareness of eligibility for PPV23 and responsibility for routine monitoring of vaccine coverage/uptake. Furthermore, PPV23 coverage in at-risk individuals aged 2–64 years varied by risk category, ranging from 38.5% (chronic liver disease [CLD]) to 70.7% (cochlear implants) [58]. Lower levels of vaccine uptake were observed in eligible individuals with certain risk conditions, such as CSF leaks (38.9% of 5,294 eligible individuals), asplenia or splenic dysfunction (39.1% of 342,938 eligible individuals), immunosuppression (39.1% of 1,034,001 eligible individuals), and CHD (43.3% of 835,750 eligible individuals) [58]. Overall, PPV23 coverage was below the national standard target of 75% [61]. In those with asplenia, splenic dysfunction or chronic kidney disease (CKD), PPV23 coverage is expected to achieve 100% as they should be vaccinated every five years [3], but the uptake is low. Differences in PPV23 coverage across risk groups were likely attributable to variations in clinicians' awareness of eligibility of PPV23 according to clinical indication [58]. Despite several automated systems used to identify patients in primary and secondary care in current practice, there are some barriers to be addressed to increase vaccination uptake, including vaccine hesitancy relating to awareness of and attitudes (complacency, trust) toward vaccinations and access (convenience) to routine vaccinations [62].

Compared with vaccine coverage data published by the UKHSA, uptake rates among risk groups reported in the literature were lower [63,64] (**Table S2**). For example, Matthews et al. (2020) reported that in the UK, the rate of vaccination in risk groups rose from 13.6% to 32.0% between 2011 and 2015 [64]. Individuals with CHD, CKD, CLD, chronic respiratory disease (CRD), or diabetes were significantly less likely to be vaccinated than those with immunosuppression [64]. Vaccination uptake also varied by risk group and the lowest uptake rate included individuals with CSF leaks/shunts [63,64]. Factors influencing PV uptake were age, gender, ethnicity, region, whether individuals have additional clinical risk factors, and whether individuals are receiving annual influenza vaccination [63,64].

Patients with rheumatoid arthritis (RA) are eligible for pneumococcal vaccines, as treatment with disease modifying antirheumatic drugs and corticosteroids for RA is known to increase the susceptibility to infection [3]. However, rates of vaccine coverage remain low in this risk group [65–68] (**Table S2**). Costello et al. (2016) reported that only 50.0% of patients with RA received a PV during the 5-year follow-up period [68]. A UK audit study further found that significantly fewer patients on major immunosuppressants received or were offered pneumococcal immunization than those with other risk factors, despite a high rate of awareness of immunization [65]. These findings suggest that patients with RA may not have been appropriately targeted for pneumococcal immunization by primary care physicians, highlighting the importance of physicians' awareness and education and organizational factors in individual practices for achieving optimal vaccine coverage. Global PV coverage also remains low in RA patients: PPV23 coverage within the recommendations across 17 countries was only 17.2%, with large disparities in vaccination uptake across countries [67]. Factors consistently identified to be associated with higher PPV23 uptake in RA patients included older age (>65 years), prescription of DMARDs, and more comorbidities or additional risk factors [65–68] (**Table S2**).

Currently, there is a lack of robust official data on PV uptake among some of the high-risk groups in the UK, particularly in PLWHIV. In the BHIVA vaccination guidelines published in 2015, PCV13 vaccination is recommended for all PLWHIV, and those who meet the indications for PPV23 vaccination within the national program (typically aged ≥65 years or with a comorbidity other than HIV as defined in the Green Book) should follow general guidance and also receive a single dose of PPV23 at least 3 months after PCV13 [69]. Prior to the recent BHIVA guidelines all PLWHIV were recommended to receive a single dose of PPV23; however, uptake was low. Thornhill et al. (2015) reported that only one out of 189 PLWHIV infected with IPD had a record of PV [59] (**Table S2**). A service evaluation project at James Cook hospital, Middlesborough sought to evaluate the utility of a vaccine passport for PLWHIV [70]. This found that the uptake of pneumococcal vaccine (PCV13 in accordance with BHIVA guidelines) increased from 16.0% to 51.0% following the introduction of a vaccine passport [70].

Lastly, hematopoietic stem cell transplant (HSCT) recipients are at significant risk of PD due to adaptive immune defect

post-HSCT [71]. Joint international/national guidelines therefore recommend a comprehensive course of revaccination schedule for HSCT recipients [71]. While in the UK, there is no revaccination schedule in place for adult HSCT recipients and poor vaccination uptake in HSCT recipients has been demonstrated [72]. Factors affecting uptake include insufficient evidence to inform detailed practical guidance, variations within existing guidelines, and practical challenges of implementing international recommendations at national levels [72]. To address these issues, a joint consensus statement has established a standardized revaccination schedule for adult and pediatric HSCT recipients in the UK: a 3-dose primary schedule is recommended for all HSCT recipients from 3 to 6 months post-HSCT followed by a booster dose given at 18 months post-HSCT with either PCV13 or PPV23 [72]. These findings underline that robust vaccination programs are needed to optimize vaccine uptake, and vaccination post-HSCT to prevent PD remains a priority.

Overall, evidence suggests that there is a large gap in the PPV23 and PCV13 uptake among risk groups eligible for these vaccines. Poor compliance with UK guidelines on the immunization of at-risk individuals, and poor adherence to timely vaccination may continue to be challenging in the long term.

3.2. Factors affecting vaccine delivery/uptake and strategies for optimization

Although the adult pneumococcal immunization program is well established in the UK, the vaccination uptake remains low among risk groups. Inadequate knowledge, negative attitudes, and low levels of awareness among patients and healthcare providers remain key factors affecting PV uptake [58,73,74]. Results from a single center retrospective study showed that the rate of vaccination uptake in patients on dialysis within the last five years was significantly lower than the national average in high-risk groups in 2011 (22.0% versus 53.0%, $p < 0.0001$) [75] (**Table S2**). In this cohort, only 3.0% were up to date with PV. Sites of vaccination may also affect vaccination uptake; for instance, the dialysis unit was the preferred site of vaccination by most of the dialysis patients and GPs interviewed due to patients' regular visits [75]. Other key barriers to vaccine uptake include system organization and accessibility issues (e.g. geographical barriers), competing priorities in healthcare practices, incomplete or inaccessible documentation of vaccination records, and healthcare system delivery challenges [73,74].

Given the significant burden of PD and low levels of pneumococcal vaccination among risk groups, strategies to improve pneumococcal vaccine uptake are required. For instance, strategies targeting organizational factors may help to achieve optimal uptake. A UK audit study demonstrated that practices could achieve or exceed national targets for PV uptake rates for disease-specific risk groups through audit, feedback, and written advice on strategies for organizational change [76] (**Table S2**). After implementation of several methods to increase vaccination rates across 14 practices (e.g. accurate registers for high-risk groups, reminder systems, and practitioner protocols and reminders), rates of PV uptake significantly improved in patients with CHD ($p = 0.002$), diabetes ($p < 0.001$) and splenectomy ($p = 0.03$) and were comparable to the median standards set up across these practices [76]. Combined interventions tailored to overcome practice-specific barriers and approaches targeting individuals (e.g. improving awareness and knowledge of vaccination and attitudes toward immunization among patients and GPs) may be effective to optimize vaccine uptake. Indeed, most patient advocacy groups have endeavored to address vaccination uptake in risk groups through information sheets, websites and campaigns to enhance patients' and GPs' awareness and knowledge [77,78] – these efforts were amplified during the COVID-19 pandemic [79].

Maintaining funding for national vaccination programs is crucial for decreasing practice-associated barriers and improving patient access to vaccines. In the current landscape, funding is only available to support vaccination programs within primary care settings. As of April 2021, a new GP contract has been introduced to support the delivery and organization of vaccination and immunization services across UK primary care, and vaccination and immunization services have become an Essential Service for most routine National Healthcare Service (NHS)-funded vaccinations including pneumococcal vaccination (programs out of scope include the adult and childhood seasonal influenza program and the COVID-19 program which remain a Directed Enhanced Service) [80]. This change will undoubtedly improve PV delivery/uptake. Although opportunistic vaccination has been demonstrated to be a potential route to improve vaccination delivery/coverage during the COVID-19 pandemic, it is relatively rarely administered in secondary care despite many existing opportunities to do so for high-risk patients. Overall, pneumococcal vaccine uptake in UK adults in risk groups remains low; initiatives are needed to improve vaccine delivery.

4. Potential to expand risk group recommendations in the UK

Gaps remain in definitions of clinical risk groups in current UK vaccination guidelines. Understanding how certain disease state or factors increases risks of PD is critical for identifying additional populations at risk of PD. The following sections summarize evidence that may be used to help identify new risk factors for PD and to support the expansion of risk group definitions.

4.1. Risk stacking

The impact of concomitant, multiple risk factors ('risk stacking') for PD on clinical outcomes has been evaluated in the UK [6], US [81], and Germany [82]. Growing evidence has shown that an increasing number of underlying medical conditions is associated with a higher risk of PD and worse clinical outcomes, e.g., the risk of PD among individuals with two or more comorbidities is significantly higher than those with a single high-risk condition [6,81,82]. The concept of 'risk stacking' however is not yet formally recognized within the UK vaccination guidelines.

Using healthcare data in England, Van Hoek et al. (2012) confirmed that having one or more underlying clinical

conditions markedly increased the risk of hospital admission for IPD across all age groups (children aged 2–15 years, OR [95% CI]: 11.7 [10.2, 13.3]; adults aged 16–64 years, OR [95% CI]: 7.6 [7.3, 7.9]); adults aged ≥65 years, OR [95% CI]: 2.7 [2.6, 2.8]). The case fatality ratio (CFR) was higher in those with underlying clinical conditions versus those without risk conditions across all age groups. Notably, the highest CFR was observed among patients with liver disease aged ≥65 years (53.0%) whereas the lowest CFR was seen in non-risk children (1.8%). These findings revealed a 'risk-stacking' phenomenon among risk groups [6].

The effect of risk-stacking on clinical outcomes was evaluated by Shea et al. (2014), using US healthcare medical claims data. In at-risk individuals, absolute rates of all-cause pneumonia significantly increased with the accumulation of concomitant at-risk conditions and were progressively higher with increasing age. Of all age groups, the risk-stacking effect was most pronounced among adults aged 18–49 years; rate ratio increased from 2.5 (95% CI: 2.5, 2.5) in those with one at-risk condition to 6.2 (95% CI: 6.1, 6.3) in those with two at-risk conditions, and 15.6 (95% CI: 15.3, 16.0) in those with ≥3 at-risk conditions [81]. Furthermore, using German claims data, Pelton et al. (2015) reported that rate ratios of all-cause pneumonia among children with risk conditions increased with the number of risk conditions compared with healthy counterparts [82]. Among younger children aged <5 years, the rate ratio increased from 1.5 (95% CI: 1.5, 1.5) for those with one condition to 4.7 (95% CI: 4.6, 4.7) for those with ≥3 conditions; among older children (5–17 years), the rate ratio increased from 2.0 (95% CI: 1.9, 2.1) to 11.3 (95% CI: 11.0, 11.5). Similar patterns for adults were reported. Among adults aged 18–49 years, the rate ratio increased from 1.9 (95% CI: 1.8, 2.0) for those with one condition to 6.2 (95% CI: 5.9, 6.4) for those with ≥3 conditions; among adults aged 50–59 years, the rate ratio increased from 1.7 (95% CI: 1.6, 1.8) for those with one condition to 5.2 (95% CI: 5.0, 5.3) for those with ≥3 conditions; among those aged ≥65 years, the rate ratio increased from 1.8 (95% CI: 1.7, 1.9) for those with one condition to 4.6 (95% CI: 4.5, 4.7) for those with ≥3 conditions [82]. Both studies showed that rate ratios of all-cause pneumonia in individuals with ≥2 risk conditions were comparable with or higher than rates in individuals with a high-risk condition and that rates in individuals with ≥3 risk conditions were substantially higher than those in high-risk individuals.

4.2. Guidelines in other countries

Given the high disease burden of PD, national vaccination guidelines have been implemented worldwide. Vaccination guidance varies across countries by type of vaccine, dosing sequence (including intervals between doses), age, and risk groups deemed eligible for PV [83]. Comparison of vaccination guidelines across countries of interest is summarized in Table 3.

In risk-based guidelines, there are variations in risk factors indicated for PV across countries. For instance, the occupational risk group eligible for vaccination in the UK and Germany is limited to welders and metal workers [87], whereas occupational risk factors are currently not included in France [86]. In the US, individuals living in special environments or social settings (including Alaska Native, Navajo, and White Mountain Apache populations) are considered for vaccination [84]. In Canada, adult residents in long-term care facilities are deemed eligible for vaccination [88]. In Australia, vaccination of aboriginal and Torres Strait Islander people aged ≥50 years without risks conditions is recommended as they are at higher risk of PD compared with non-indigenous adults [90].

Specific recommendations for surrogates of comorbidity, e.g., smoking, alcoholism, illicit drug use and homelessness, are not issued in the UK, whereas some of these risk factors are included in the other countries' vaccination guidelines such as US, Canada and New Zealand (Table 3). Arguably, the most vulnerable individuals in these risk groups will be vaccinated under current UK guidelines; for example, where alcoholism has progressed to liver disease or lung disease has developed in smokers, despite no formal recommendation. Nevertheless, early vaccination of individuals with lifestyle risk factors before the associated diseases progress to the later stages would be preferable.

Age-based vaccination guidelines involve the vaccination of all older adults after a certain age, with a small variation in the recommended starting age of vaccination [83] (Table 3). For healthy older adults, eligible age for PPV23 ranges from ≥60 years in Germany, to ≥65 years in most countries (including UK, US, Canada and New Zealand), and to ≥70 years in Australia [3,83,84,87,90–92]. In contrast, vaccination of healthy older adults is not recommended in France, unless individuals have certain underlying comorbidities [83]. Indeed, older adults (≥65 years) are more susceptible to PD due to immunosenescence (e.g. increased susceptibility to infections and poor responses to vaccines) and present worse clinical outcomes than younger adults [93]. Earlier vaccination may be preferable.

In addition to PPV23, PCV13 is provided for all adults aged ≥65 years without risk conditions in the US, Canada and New Zealand, but not in the UK, France and Germany despite being introduced in the National Childhood Immunization Program (Table 3). As of January 2022, the US Advisory Committee on Immunization Practices (ACIP) recommends the use of PCV15 in series with PPV23 or PCV20 alone in PCV-naïve adults aged ≥65 years or adults aged 19–64 years with certain medical conditions [85]. In 2023, the Canadian and Australian guidelines have also been updated to introduce these two next-generation vaccines [89,90]. As of June 2023, the JCVI recommends to include PCV20 alongside PPV23 in the routine vaccination program for adults aged ≥65 years and all adults in risk groups [23].

4.3. Identification of new risk factors

As the population ages, multimorbidity becomes more prevalent and certain health conditions are more common in different life stages [94]. Using phenotyping algorithms to map the course of the 50 most common health conditions at different life stages, Kuan et al. (2019) illustrated that: hypertension and dyslipidemia commonly occurred in individuals aged 40–49 years; cancer and type 2 diabetes were

Table 3. Comparisons of pneumococcal vaccination guidelines across countries.

Country/Region	UK	US	France	Germany	Canada	Australia	New Zealand
References	[3,23]	[84,85]	[86]	[87]	[88,89]	[90]	[91]
Vaccines recommended in current guidelines							
PPV23	✓	✓	✓	✓	✓	✓	✓
PCV13	✓	✓	✓	✓	✓	✓	✓
PCV15		✓		✓	✓	✓	
PCV20	✓*	✓			✓	✓	
Structure							
Childhood pneumococcal vaccination program	✓	✓	✓	✓[b]	✓	✓	✓
Age-based guidelines	✓[a]	✓[a, b, c]	✓[d]	✓[a]	✓[a, b, c]	✓[a, b]	✓[a, c]
Risk-based guidelines	✓	✓	✓	✓	✓	✓	✓
Risk groups included in current guidelines							
Asplenia/splenic dysfunction	✓	✓	✓	✓	✓	✓	✓
Immunosuppression	✓	✓	✓	✓	✓	✓	✓
Chronic respiratory disease	✓	✓	✓	✓	✓	✓	✓
Chronic heart disease	✓	✓	✓	✓	✓	✓	✓
Chronic liver disease	✓	✓	✓	✓	✓	✓	✓
Chronic Kidney disease	✓	✓	✓	✓	✓	✓	✓
Diabetes	✓	✓	✓	✓	✓	✓	✓
Cochlear implants	✓	✓	✓	✓	✓	✓	✓
CSF leaks	✓	✓	✓	✓	✓	✓	✓
Occupational risks (exposure to metal fumes, i.e. welders and metal workers)	✓			✓			
Additional risk groups							
Persons living in special environments or social settings		✓[e]					
Residents of long-term care facilities					✓		
Certain ethic groups (indigenous people)						✓[f]	
Smoking		✓			✓		✓
Alcoholism		✓			✓		✓
Illicit drug use					✓		
Homelessness					✓		
Risk-stacking concept							
≥2 risk conditions (Recommended)[g]							✓

*As of June 2023, PCV20 is recommended for adult pneumococcal immunization program by the UK Joint Committee on Vaccination and Immunisation, and it is now available for adults ≥65 years and all adults in clinical risk groups as defined in the Green Book (2020).

[a]PPV23 vaccination of healthy older adults is recommended. Eligible age: ≥60 years for Germany; ≥65 years for UK, US, Canada and New Zealand; ≥70 years for Australia. Revaccination of PPV23 every five years is recommended for most countries, while Germany recommends revaccination with PPV23 at intervals of at least 6 years. In the UK, revaccination of PPV23 is only recommended for the highest risk group of IPD, including those with asplenia, splenic dysfunction and chronic kidney disease.

[b]In the US, PCV20 alone or PCV15 following a dose of PPV23 is recommended for vaccine-naïve adults aged ≥65 years and adults aged 19–64 years with certain medical conditions or risk factors. In Canada and Australia, PCV20 (or PCV15 following a dose of PPV23 as an alternative option) is recommended for vaccine-naïve adults aged ≥65 years and those aged 18–64 years with risk conditions. In Germany, PCV15 is currently recommended for use in children and adolescents aged 2–17 years.

[c]PCV13 is recommended for use in all healthy adults who are aged ≥65 years without risk conditions. In the US, if the decision is made to administer PCV13, it should be given at least 1 year before PPV23. In Canada and New Zealand, it is recommended that a dose of PCV13 should be given first followed by PPV23 at least 8 weeks later.

[d]PPV23 vaccination is only recommended for adults aged ≥18 years with certain medical conditions; revaccination every five years is recommended.

[e]Includes Alaska Native, Navajo, and White Mountain Apache populations.

[f]Indigenous population includes aboriginal and Torres Strait Islander people.

[g]PCV13 and PPV23 are recommended but not funded for the following individuals: immunocompetent adults (aged ≥18 years) at increased risk of pneumococcal disease or its complications due to chronic illness (e.g. chronic heart, renal, liver or pulmonary disease, diabetes or alcohol dependency); adults with CSF leaks; immunocompromised adults at increased risk of pneumococcal disease (e.g. those with nephrotic syndrome, multiple myeloma, lymphoma and Hodgkin's disease); individuals of any age who have had one episode of invasive pneumococcal disease; smokers. CSF, cerebrospinal fluid; PCV, pneumococcal conjugate vaccine; PPV23, pneumococcal polysaccharide vaccine; UK, United Kingdom; US, United States.

prominent in individuals aged 60–79 years; CVD and renal disease became more common in individuals aged ≥80 years [94]. These findings imply that clinical risk groups for PD with multiple underlying conditions are likely to expand with an aging population.

Despite the comprehensive list of risk conditions for PD as defined in the Green Book, some risk factors that are currently not included in the guidelines could also predispose individuals to respiratory infections including PD and lead to severe outcomes. These risk factors include prevalent diseases (e.g. COVID-19 infection, stroke, dementia) [95,96], prescription of certain medication (e.g. proton pump inhibitors) [97], and lifestyle or environmental factors (e.g. cigarette smoking, vaping, alcoholism, occupational exposure to inorganic dust or fumes) [98–101]. Among these risk factors, alcoholism and smoking could be considered for the UK guidelines as local data suggest potential associations with IPD and recurrent hospitalization with pneumonia [98–100].

Evidence exists that occupational or environmental exposures to inorganic dust and fumes (including tobacco smoke) increase the risk for IPD [101–103]. A 5-year cumulative occupational exposure to silica dust or fumes was associated with over two-folds of risk of IPD with pneumonia [101]. Tobacco smoking, passive smoking among non-smokers, and vaping are strong independent predictors for IPD, while cessation of tobacco smoking reduced the risk IPD [102–104]. These findings suggest that efforts should be made to reduce environmental or occupational exposures to dust and fumes and

control tobacco smoke and vaping. The use of pneumococcal vaccines could also be considered for UK populations with such exposures to help prevent PD.

Several socioeconomic and demographic characteristics are also associated with increased risk of PD infection, including living with children aged <6 years who attend day-care centers, low educational level, low income, and household crowding [102]. In addition, accumulated evidence showed that homeless people are at higher risk of PD compared with the general population, potentially associated with deprivation, poor living and access to healthcare services, and higher rates of chronic alcohol abuse, illegal drug use and tobacco smoking [105–108]. Currently, PPV23 vaccination of the homeless is only recommended in Canada (Table 3). More research is required to support the consideration of prioritizing vaccination for populations with these characteristics in the UK vaccination guidelines.

Occupational risks in the current UK guidelines cover welders or metal workers [3]. However, other professional activities involving close contact with people with respiratory disease could be considered as relevant for vaccination (including individuals working in residential care homes, elderly care wards, oil rigs, prisons, those living in inner city high pollution settings and healthcare workers), as they are at higher risk of exposure to respiratory infections [109–111]. Indeed, several measures were implemented to control infections during outbreaks, including isolation, hand/respiratory hygiene practice, personal protective equipment, and use of antimicrobials [110]. Utilizing vaccination would be more strategic for employers to prevent PD and its severe outcomes.

In certain patient groups, clinical characteristics and prior history of disease exacerbation may increase patients' susceptibility to PD. In patients with chronic obstructive pulmonary disease (COPD), for whom PPV23 is recommended in the UK, those who had moderate airflow limitation and heightened cardiovascular risk, factors including prior exacerbation history of COPD, body mass index <25 kg/m^2, and greater impairment of lung function (FEV1 <60%), were strongly linked to pneumonia risk [112]. This study indicates that risk of PD could vary within patient group and the risk assessment for PD may be tailored based on individual clinical characteristics.

Moreover, evidence showed that frailty and Charlson Comorbidity Index (CCI) score may serve as prognostic factors for severe clinical outcomes of respiratory diseases (e.g. hospitalization, intensive care unit [ICU] admission, deaths) [5,100,113,114]. Szakmany et al. (2021) assessed the influence of frailty on mortality in patients with pneumonia in Wales between 2010 and 2018. Results showed that increased frailty scores (assessed by either electronic frailty index or hospital frailty risk score) were significant risk factors for ICU admission and in-patient mortality among patients with pneumonia [113]. A study using the Clinical Frailty Scale found that frailty was an independent predictor for 1-year in-hospital mortality for CAP among older patients aged ≥65 years [114]. Similarly, CCI could be a strong predictor for adverse outcomes of PD. Trotter et al. (2008) demonstrated that higher CCI scores were significantly associated with increased odds of 30-day in-hospital mortality among patients with pneumonia in England, after controlling for known confounders (odds ratio (OR) [95% CI] for mild, moderate and severe CCI: 1.6 [1.6, 1.6], 2.5 [2.4, 2.5], 3.7 [3.7, 3.8]). Szakmany et al. (2021) also reported that higher CCI score was significantly linked to higher odds of ICU admission (OR: 2.6, 95% CI: 2.5, 2.8) and in-hospital mortality (OR [95% CI] for CCI 1–10: 1.2 [1.1, 1.2], CCI > 10: 2.5 [2.4, 2.6]). Frailty and multimorbidity are likely to increase notably in the UK population in the coming decades.

These findings indicate that the risk categories currently defined in the UK vaccination guidelines may need to be revised to better manage and prevent clusters of PD, e.g., including additional risk conditions (e.g. COVID-19 infection, stroke, dementia and illicit drug dependency), expanding occupational risks (e.g. healthcare workers) and considering vaccination of hospitalized patients with worse frailty and morbidity scores.

Overall, there is a lack of international consensus around risk group definitions. To address this gap, there may be an opportunity to develop a tool for identifying individuals who are at risk of PD and severe outcomes after respiratory infection. In 2020, a novel risk assessment tool, QCovid®, was developed to predict severe outcomes of COVID-19 infection using a data-driven approach; factors including age, medical conditions, vaccination status and background infection rate are included to establish a risk prediction model [115]. A similar digital tool/calculator may also be considered to identify risk groups for PD.

Lastly, vaccine programs in the UK must be shown to be cost-effective nationally to justify their introduction, and therefore modifying eligible groups for routine vaccination requires a minimum evidence base to assess this. There will also be a budgetary impact due to the change in the number of patients eligible for vaccination. During the COVID-19 pandemic, non-pharmaceutical interventions (i.e. mask wearing and isolation) that were intended to limit the spread of SARS-CoV-2 had a profound impact on other respiratory infections, including the pneumococcus. However, public willingness to routinely adopt such measures, particularly on an ongoing basis, is questionable and vaccination is perhaps a more pragmatic intervention.

5. Current environment

PD causes a significant burden in adults in the UK, despite a relatively high level of health preventive and intervention measures and treatment guidelines [4,26,38]. An understanding of the current landscape and wider challenges and identifying any unmet needs for the management of PD – especially in high-risk groups – will be crucial to help address the resurgence and burden of PD.

5.1. Epidemiological trends of PD before and after the pandemic

Despite the substantial reduction in the IPD cases over time achieved by the well-established routine childhood PCV program in the UK, the overall incidence of IPD has increased since 2013/2014, driven by a rapid increase in non-vaccine serotypes and mainly in the older age groups (≥65 years) [26]. Similarly, there has been an increasing trend of the

incidence of pneumococcal septic arthritis (an uncommon form of IPD) in older adults and those with underlying comorbidities over the last decade, primarily caused by non-vaccine serotypes and PPV23/non-PCV13 serotypes [17]. However, the epidemiological landscape of the pneumococcus recently changed dramatically with the emergence of SARS-CoV-2 and non-pharmaceutical interventions that were intended to limit the spread of this virus.

Following the introduction of non-pharmacological interventions in March 2020, large reductions in IPD were subsequently concomitantly observed across all age groups in England [13]. As the third national lockdown was lifted in July 2021 in England, the incidence of IPD in those aged <15 years rapidly increased to exceed the levels observed before the COVID-19 pandemic [116]. However, levels of IPD in UK adults have re-emerged more slowly and have not yet returned to pre-pandemic levels [117]. A similar pattern of epidemiological trends for IPD was reported in Germany: the incidence of IPD across all age groups largely declined coinciding with the implementation of national COVID-19 measures in 2020 and has exceeded the pre-pandemic levels (2015–2019) after national COVID-19 restrictions were lifted in 2021 [118]. Despite these temporal changes in IPD epidemiology as a consequence of COVID-19 pandemic, distribution of serotypes has remained consistent and reflects those observed before the COVID-19 pandemic in the UK and Germany [13,118,119]. Insight into how pneumococcal pneumonia in the UK was impacted remains limited although there is evidence suggesting that incidence of non-SARS-CoV-2 related all-cause hospitalized CAP remained largely unaltered [17].

5.2. Pressure on the healthcare system

PD imposes a significant economic burden on the NHS in the UK. The estimated mean costs of hospitalization for CAP in 2019 was £3,904 per adult, accounting for a total cost of £731 million per annum to the NHS [120]. For those receiving critical care, the mean cost was £11,654 per person. The mean costs for hospitalized CAP varied by risk group, ranging from £4,458 for patients with diabetes to £5,215 for those with CHD aged <65 years, and £4,356 for those with CHD to £4,751 for those with CLD aged >65 years [120]. However, the costs for PD could be underestimated especially for patients aged ≥65 years due to complications which contribute to additional costs [42]. The COVID-19 pandemic has also significantly increased the pressure on the NHS, and limited its ability to deliver patient care because of absence of staff due to isolation and long-term illness post infection [121,122].

Therefore, improved pneumococcal vaccine uptake in older adults aged ≥65 years or those with the highest risk of PD with higher-valent PCVs could contribute to relieving the continuous pressure on the NHS [42], and more importantly, to help reduce mortality in hospitalized patients and those with unrecognized/undocumented PD in the community.

5.3. Concerns on antimicrobial resistance

Antimicrobial resistance (AMR) is now a widespread, urgent global public health threat of high priority to the WHO and wider global society [123]. Many adults in risk groups have a heightened risk of intercurrent infections including respiratory tract infections which are the leading clinical indication for antibiotic prescriptions in both primary and secondary care worldwide [124,125]. Antibiotics such as co-amoxiclav and cephalosporins are known to be important contributors to AMR [126].

Given that pneumococcal infection is a leading cause of LRTIs worldwide (responsible for 197.05 million episodes and 1,189,937 deaths in 2016) [1], the use of vaccines can help to address the global issue of AMR through direct and indirect effects including [123]:

- prevention of bacterial/viral infections and viral diseases prone to bacterial coinfections or superinfections requiring antibiotics,
- its mechanism of actions less prone to inducing resistance,
- reducing incidence of infections and hence decreasing antimicrobial use,
- prevention of resistant strains from occurring and spreading, and
- prevention of antimicrobial misuse.

Evidence revealed that universal coverage by PCVs in children aged <5 years led to approximately 47.0% reduction in the amount of antimicrobials used for pneumococcal infections [127]. Utilizing PCVs also reduced 64.0% of AMR pneumococcal infection in children and 45.0% in adults aged ≥65 years in 2011 in the US [127]. The significant impact of PCVs on the control of AMR through restricting the need of antimicrobials and reducing the incidence of resistant strains in other countries has also been reported [128]. These studies highlight the important role of vaccinations in the prevention of PD from occurring and spreading as well as addressing the global issue of AMR.

6. Conclusion

The UK JCVI now recommends that PCV20 may be used in addition to PPV23, with a number of even higher valency conjugate vaccines in development that may become available for consideration in the future. Despite the well-established UK immunization programs and guidelines, uptake of PPV23 among clinical risk groups and all adults aged ≥65 years remains unsatisfactory. Improving pneumococcal vaccine uptake in adult risk groups is therefore critical to ensure they are optimally protected. Thereby, national strategies are urgently required to optimize vaccination access and coverage. In light of growing evidence, a number of gaps exist in risk group definitions in current vaccination guidelines which should now be revised to cover wider populations at risks of PD.

7. Expert opinion

Whilst it is well established that individuals with a range of underlying comorbidities are at an increased risk of pneumococcal disease, more robust, detailed evidence is needed.

Detailed insight into incidence in risk-group patient populations is lacking, particularly relating to pneumococcal pneumonia. COVID-19 highlighted the need to better understand the spectrum of comorbidities that increase the risk of respiratory tract infections. Given this, there could be a benefit from a reassessment of the risk groups that are currently eligible for pneumococcal vaccination. Furthermore, the increased likelihood of pneumococcal infection in patients with multiple risk factors suggests that risk stacking should be taken into consideration when making recommendations for pneumococcal vaccines.

Viral-bacterial coinfections and superinfections are relatively common, as preceding or concurrent viral infection of the respiratory tracts is widely known to increase the susceptibility to secondary bacterial coinfection, or vice versa [129,130]. Viral-bacterial coinfections are often synergistic, leading to adverse outcomes [130,131]. Recent evidence showed that individuals aged ≥65 years who had received PCV13 had a lower incidence of COVID-19 infections, hospitalization and mortality compared with non-PCV13 recipients [131]. These findings not only suggest a possible synergistic interaction between pneumococci and SARS-CoV-2, but also highlight some protection afforded by PCV13 against the outcomes of COVID-19 [131]. Given the presence of several common pandemic viral pathogens including SARS-CoV-2, respiratory syncytial virus and influenza viruses, prevention of PD becomes increasingly important to avoid subsequent burden of respiratory diseases caused by viral-bacterial coinfections.

There is a financial incentive in place to encourage GPs to vaccinate UK adults at risk of pneumococcal infection, i.e., adults aged ≥65 years or those in risk groups aged 2–64 years. Data suggest that uptake varies significantly by risk factor and overall uptake is currently low in adults in risk groups but higher in adults eligible for the age-based recommendation. This demonstrates the success of implementing age-based recommendations and the challenges regarding recommendations for specific groups within the population. Current pneumococcal vaccination uptake in risk groups is only reported broadly and is not stratified by risk. Improved vaccine uptake data stratified by specific risk groups would be valuable as it could help to highlight those risk groups where uptake is particularly low at present. This may in part reflect a poor understanding and awareness by both the general public and some healthcare professionals of the threat posed to patients in risk groups by pneumococcal infections or other factors such as concern regarding the efficacy of PPV23.

The recent JCVI recommendation to include PCV20 in addition to PPV23 for UK adults at increased risk of PD provides an opportunity to improve the protection they receive against PD. With several even higher valency PCVs in development, it is anticipated that in the future it may be possible to further improve the extent to which UK adults risk groups are protected against PD. The ability of a single dose of PPV23 to provide long-term protection, particularly for younger adult patients with risk factors is questionable and needs further research.

The NHS is facing capacity challenges particularly following the COVID-19 pandemic, so all opportunities to help prevent infection should be taken. In addition to ensuring that adults with underlying comorbidities are protected against influenza and COVID-19, all opportunistic efforts should be made to ensure adults at increased risk of PD also receive a pneumococcal vaccine.

The response to the COVID-19 pandemic highlighted the variety of ways in which vaccines can be provided to the public, including those at increased risk of respiratory disease. Learnings from this experience and the use of the associated and existing vaccination program framework, should be applied to optimize the delivery of pneumococcal vaccines to adults in risk groups.

Infectious disease control and prevention is the responsibility of everyone involved in patient care and helps to mitigate AMR. Whenever patients in pneumococcal risk groups see their specialist consultant or present acutely to hospital care, there is an opportunity to review their vaccine status. Where necessary a recommendation for pneumococcal vaccine should be documented in follow-up correspondence with their GPs. The role of opportunistic vaccination in the secondary care setting or other innovative approaches should also be explored.

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Declaration of interests

J Campling, A Vyse, H Wright, and G Ellsbury are employees of Pfizer Ltd, UK, and may hold stock or stock options. HH Liu is an employee of OPEN Health. M Slack has received personal fees from GlaxoSmithKine, Pfizer, Merck, AstraZeneca, and Sanofi Pasteur as a speaker at international meetings and as a member of advisory boards and has undertaken contract work for Pfizer. RR Reinert is an employee of Pfizer Inc, France, and may hold stock or stock options. M Drayson owns equity/stocks in Abingdon Health outside the submitted work. D Singh has received consultancy fees from Aerogen, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, CSL Behring, EpiEndo, Genentech, GlaxoSmithKline, Glenmark, Gossamer Bio, Kinaset Therapeutics, Menarini, Novartis, Orion, Pfizer, Pulmatrix, Sanofi, Synairgen, Teva, Theravance Biopharma, and Verona Pharma. G Barlow is Senior Clinical Lecturer at Hull York Medical School at the University of York and an Honorary Consultant in Infection at Hull University Teaching Hospitals NHS Trust. Within the last three years, G Barlow has received advisory board or consultation fees from Advanz Pharma, Pfizer UK and Biomerieux. G Kassianos works as a National Immunisation Lead RCGP, President British Global & Travel Health Association, Board Member European Working Scientific Group on Influenza, and Chair RAISE Pan-European Group of experts in influenza, and has participated at meetings organized by all vaccine manufacturers in the UK. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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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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