A review of current data to support decision making for introduction of next generation higher valency pneumococcal conjugate vaccination of immunocompetent older adults in the UK

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ABSTRACT

Introduction: The burden of pneumococcal disease in older UK adults remains substantial. Higher valency pneumococcal conjugate vaccines (PCVs) are currently in development with adult formulations for two of these anticipated to become available in 2022. This article collates and reviews relevant candidate data now available that may be used to support cost effectiveness assessments of vaccinating immunocompetent UK adults aged ≥65-years with PCVs.

Areas covered: This article uses published data from surveillance systems, randomised controlled trials and observational studies. It focuses on local data from the UK but where these are either limited or not available relevant global data are considered.

Expert opinion: The body of relevant data now available suggests the UK is well placed to assess the cost effectiveness of vaccinating immunocompetent ≥65-year olds with new generation higher valency PCVs. Recent contemporary data provide important new and robust insights into the epidemiology of pneumococcal disease in older UK adults and help to address much of the uncertainty and data gaps associated with previous analyses. Using these data to make informed decisions about use of new higher valency PCVs for routine use in older adults will be important for public health in the UK.

Key words: adult; community acquired pneumonia; cost effectiveness; epidemiology; invasive pneumococcal disease; pneumococcal conjugate vaccines

1. Introduction

Streptococcus pneumoniae (pneumococcus) is a major cause of morbidity and mortality in children and the elderly worldwide[1, 2]. Pneumococci are Gram-positive diplococci which can be classified into 100 serotypes, based on their polysaccharide capsule[3]. Diseases caused by pneumococci include invasive infections, such as meningitis, sepsis and bacteraemic pneumonia, and mucosal infections, including otitis media, and non-bacteraemic pneumonia [4]. Pneumococci are one of the commonest causes of pneumonia [5]. The burden of pneumococcal infection is especially high in older adults, with the vast majority of cases presenting as community acquired pneumonia (CAP) [4]. A pneumococcal conjugate vaccine (PCV) that covered seven serotypes (PCV-7) was introduced in the UK for routine infant immunisation in 2006 and then replaced by a 13 valent PCV in 2010 [6].

This resulted in major reductions in vaccine type (VT) pneumococcal disease across the full age range due to both direct and indirect protection [7]. Since 2014 PCV-13 has been indicated for the prevention of invasive pneumococcal disease (IPD) and pneumococcal pneumonia in adults. However, in the UK PCV-13 is currently only recommended for adults at a very high risk of pneumococcal disease [6]. Since 2003 a single dose of the 23-valent pneumococcal polysaccharide vaccine (PPV23) has been routinely offered to all UK adults aged ≥65-years and some clinical risk groups aged ≥2 years [6]. PPV23 is a plain polysaccharide vaccine and, in contrast to PCVs, does not induce a T cell-dependent immune response which is needed for durable protection against pneumococcal disease [8]. Whilst it is generally acknowledged that PPV23 provides limited short-term protection against IPD, studies of the protection that PPV23 provides against non-invasive pneumonia give contradictory conclusions [8, 9, 10]. The extent to which PPV23 may provide older adults with meaningful protection against pneumococcal disease therefore continues to be debated with candidate PCVs under development offering potential alternatives. The Joint Committee on Vaccination and Immunisation (JCVI) considered routinely vaccinating all immunocompetent UK adults aged ≥65-years with PCV-13 in 2015 but ultimately decided not to recommend proceeding with such an approach [11]. An important contributing factor to this decision was a cost-effectiveness assessment [12], which assumed the incidence of PCV13 VT pneumococcal disease would imminently decline to such a low level in this age group in the UK due to indirect protection from the infant PCV-13 vaccination programme that a PCV-13 programme targeting those aged ≥65-years would not be cost-effective. Whilst this analysis made use of all relevant data available at the time it did recognise areas of uncertainty where data were either limited or lacking. It also assumed that key relevant epidemiological trends reported at the time of the analysis would continue for the foreseeable future.

Two next generation higher valency PCVs (PCV-15 and PCV-20) are now in advanced stages of development and are currently anticipated to become available for adult use in the near future before corresponding paediatric licencing [13, 14]. These vaccines include additional pneumococcal serotypes not in PCV-13 that have recently emerged as important causes of pneumococcal disease in the UK, particularly in adults aged ≥65-years, and therefore potentially offer the opportunity to better directly protect older UK adults against pneumococcal disease [7, 15]. Table 1 shows the individual pneumococcal serotypes included in those PCVs previously (PCV-7) and currently (PCV-13) used in the UK and the two next generation higher valency PCVs (PCV-15 and PCV-20) that are in development. The importance of using vaccination to prevent common respiratory infections in adults has recently taken on greater significance following the COVID-19 pandemic that began in early 2020, with the importance of using COVID-19 vaccines to control the pandemic being paramount. However, it has been hypothesised that any inflammatory damage to the respiratory mucosal tissue caused by common pathogens such as *Streptococcus pneumoniae* and the influenza virus might potentially facilitate infection by SARS-CoV-2 with some evidence now emerging to support a synergy between the pneumococcus and SARS-CoV-2 virus [16, 17, 18]. Despite the levels of COVID-19 vaccine uptake now being achieved in older age groups in the UK new strains of SARS-CoV-2 virus with increased transmissibility are starting to emerge. Whilst there is currently no evidence these strains are demonstrating any increased clinical severity in illness the extent of any vaccine escape capability posed by these strains remains a key focus of ongoing research with concerns the virus may continue to circulate in the longer term [ref Tang 2021; Planas 2021]. Evidence gathered during the early part of the pandemic suggested only a low proportion of COVID-

19 patients hospitalised in the UK had a bacterial co-infection, with the pneumococcus rarely identified [refs Lansbury 2020; Russel 2021]. However, this research was undertaken with COVID-19 containment policies and social distancing measures in place, which greatly reduced transmission of *S.pneumoniae* [ref Brueggeman 2021]. Potential synergistic interaction between SARS-CoV-2 and other common respiratory pathogens such as seasonal influenza and the pneumococcus may therefore potentially become increasingly prevalent in the UK as social distancing measures are relaxed enabling their re-emergence with increased likelihood of co-infection with the SARS-CoV-2 virus. Therefore, in the post pandemic environment it may be increasingly important to consider maximising use of available adult vaccines that target important causes of respiratory disease. This will not only help better protect individual UK adults against respiratory disease but also contribute to helping ensure the National Health Service (NHS) does not become over-burdened [19, 20].

With two candidate next generation higher valency adult PCVs expected to become available shortly the overall aim is to summarise all currently available candidate evidence that could contribute to supporting future cost effectiveness analyses of these in older immunocompetent UK adults. In this article we review the full extent of all relevant candidate data available at the end of the second decade of the 21st century, identifying strengths and limitations. New data describing the epidemiology of pneumococcal disease in UK adults have become available since the JCVI last considered routine vaccination for immunocompetent UK adults ≥65-years with PCV-13 and assessed it cost effectiveness. These data provide important new and more contemporary insights for assessing PCV use in the older UK population and supersede much of those data previously used [12]. We therefore consider how those data previously used for key parameter inputs for the cost effectiveness model used for assessing PCV-13 in adults aged ≥65-years in the UK can be updated and identify persisting areas of uncertainty. Where local data gaps continue relevant global data generated outside the UK are summarised. In addition, we comment on new candidate data and approaches being proposed that cost effectiveness assessments of adult PCVs may now want to consider incorporating to try and more accurately reflect the full value of these vaccines. Lastly, we also consider the possible implications of the COVID-19 pandemic on future decision making for use of adult PCVs in the UK. .

2. Incidence, serotype distribution and trends

IPD (Invasive pneumococcal disease)

Public Health England (PHE) has a well-established and long-standing high quality enhanced national routine surveillance system for IPD [7, 21], encompassing all ages of patients, with serotyping of invasive pneumococcal isolates. Age stratified data are regularly published in the scientific literature giving robust, accurate and timely insight into the incidence, serotype distribution and epidemiological trends over time for IPD in English and Welsh adults. Van Hoek and Miller [12] used relevant incidence data from the latest published routine IPD surveillance data up to 2013/14 for their analysis of cost effectiveness of PCV-13 in immunocompetent English adults aged ≥65-years [21]. More recent routine IPD surveillance, including data up to 2016/17 are now published providing detailed contemporary data on the epidemiology of IPD in English and Welsh adults aged ≥65-years [7]. Furthermore, data for 27 individual serotypes that caused IPD in those aged ≥65-years in 2016/17 are also presented [7], providing insight into the most common serotypes that caused

IPD in England and Wales. This encompasses all the additional serotypes in the two new generation higher valency PCVs that are being developed and are anticipated to shortly become available (i.e. PCV-15 and PCV-20) and provides a basis for assessment of use of these vaccines for preventing IPD in older UK adults [22]. These data show that the serotypes included in PCV-13, PCV-15 and PCV-20 correspond to 21.6%, 32.6% and 64.6% respectively of the total IPD burden in English and Welsh adults aged ≥65-years in 2016/17. This equates to an incidence of 6.2, 9.4 and 18.7 per 100,000 respectively for each of these vaccines. The 10 most common serotypes that caused IPD in these adults aged ≥65-years in 2016/17 were 8, 3, 12F, 22F, 9N, 19A, 15A, 33F, 10A and 23A [ref Vyse 2020; Ladhani 2018].

An additional publication using national IPD surveillance data from 2000/01 to 2016/17[23] presents incidence data for English and Welsh adults aged ≥65 years with estimates further stratifying these data into smaller age groups. However, data are not presented by individual pneumococcal serotype with stratification limited to certain broader groups of serotypes that reflect only those pneumococcal vaccines currently used in the UK. Therefore, whilst these data may help support analyses of PCV-13 in UK adults aged ≥65-years their capacity for assessments of next generation higher valency PCVs is more limited. Additionally, these data also show that the 23 serotypes included in PPV23 corresponded to 73.1% of the total IPD burden in English and Welsh adults aged ≥65-years in 2016/17 equating to an incidence of 21.15 per 100,000. This shows that in 2016/17 the additional serotypes included in PPV23 not currently in next generation PCVs (i.e. serotypes 2, 9N, 17F and 20) caused only a small proportion of the IPD burden in English and Welsh adults aged ≥65-years [ref Djennad 2019; Vyse 2020].

Hospitalised CAP (community acquired pneumonia)

Accurate data describing the epidemiology of hospitalised CAP in older adults are particularly important when assessing PCVs for use in older adults since, in contrast to the relatively rare condition of IPD, CAP reflects a much larger disease burden [4, 24, 25, 26]. Relevant UK data are currently limited to a long-standing study of adults aged ≥16 years with CAP admitted to two university hospitals in the city of Nottingham. This study has been ongoing since September 2008 and was primarily intended to observe disease trends over time. This study stratifies data by age group, describes the trends and distribution over time for both CAP and various individual pneumococcal serotypes identified from cases of pneumococcal CAP using a multiplex urinary antigen detection assay (UAD) [15, 27]. This study also provides some insight into incidence of adult CAP and adult pneumococcal CAP but the estimates presented for older adults aged ≥65-years are very low compared to those in recently published studies of similarly aged adults in other comparable countries. For example, a meta-analysis of published data for adults aged ≥65-years hospitalised with pneumonia in industrialised countries [28] and a study of CAP in hospitalised adults aged ≥65-years in the US city of Louisville [29, 30] found incidence to be approximately 3 and 4 times higher respectively. Caution needs to be used when comparing incidence estimates in each of these studies since differing case definitions are used and there may be valid epidemiological reasons for such a low hospitalised CAP incidence in this UK population of adults from the city of Nottingham. However, it may also reflect limitations with the approach used by this study to estimate incidence. This has previously led to concerns that substantial under ascertainment may be present in this

study and cost effectiveness and modelling studies investigating use of pneumococcal vaccines in UK populations have employed scenarios that double the CAP incidence found in this study [12, 31].

There is therefore some uncertainty regarding the published incidence estimates available for adults aged ≥65-years hospitalised with CAP in the UK. Whilst estimates are now available up to 2017/18 [15, 27], these should be used with caution due to concerns regarding potential under ascertainment. This suggests using these incidence estimates in conjunction with a suitable multiplier may be most appropriate for assessing adult PCV use in the UK as has been used by other analyses that have considered the burden of hospitalised CAP in UK adults[12, 31]. This also highlights that further studies are needed that can provide more robust estimates for hospitalised CAP incidence in older UK adults.

Although the incidence of CAP might be underestimated in the Nottingham study, the distribution of serotypes is likely representative and provide reliable information on epidemiological trends between 2008 and 2018 for UK adults hospitalised with CAP. These are stratified by age group and further stratified into pneumococcal CAP and broad groups of serotypes reflecting those current pneumococcal vaccines used in the UK. Since 2013/14 the multiplex UAD assay used has extended the number of individual serotypes that could be detected to include all contained in PCV-13 and PPV23 [32]. Whilst data for individual serotypes are only presented for all adults aged ≥16-years for each epidemiological year of the study this still provides valuable data describing recent epidemiological trends and distribution for these individual serotypes over time. Importantly this includes all the serotypes in the two new generation higher valency PCVs currently in development that are expected to shortly become available. It also enables an estimation of the current proportion of adult pneumococcal pneumonia these vaccines could potentially address [22].

Pneumonia in adults in primary care

The previous analysis did not consider the burden of CAP in older UK adults treated in primary care when assessing routine PCV-13 use in adults aged ≥65-years [12]. Previously relevant UK data describing this aspect were both limited and historical, reflecting data from the 20th and very early 21st centuries [26, 33, 34, 35]. A new study using electronic data records from the UK Clinical Practice Research Datalink [36] reported that clinically diagnosed pneumonia in UK primary care has been increasing over time, particularly since 2010, with an estimated incidence of 2.22 cases per 1000 person-years in 2017 for all age groups combined. However, trends showed incidence of clinically diagnosed pneumonia decreased over time for those aged <15 years but increased in those aged ≥15 years, especially amongst older adults. Collectively these data suggest a potentially large proportion of the burden of adult pneumonia in the UK may be being treated in primary care and future analyses assessing the cost-effectiveness of new PCVs in UK adults may want to include these cases. Whilst the financial cost to the NHS will likely be small compared to that treated in secondary care, pneumonia treated in primary care may still reflect a significant burden to the UK NHS. Given the pneumococcus is a common cause of pneumonia [ref Reynolds 2010], higher valency adult PCVs could usefully contribute towards reducing the burden of adult pneumonia that is seen in primary care . Whilst there are now more contemporary UK data, the body of data providing relevant insight remains limited. To robustly assess this aspect further studies investigating the contemporary epidemiology of pneumonia in UK adults that is treated outside secondary care are therefore needed.

3. Projecting future epidemiological trends for pneumococcal disease in older UK adults and the contribution of indirect protection

Projecting the future longer-term incidence of pneumococcal disease caused by vaccine serotypes was an important and influential component of the previous cost-effectiveness assessment of vaccinating UK adults aged ≥65-years with PCV-13 [12, 37]. To make a realistic projection of the future incidence of vaccine-type IPD and CAP in this age group for the next five years this analysis accounted for the indirect protection induced by the childhood pneumococcal vaccination programme. Trends for pneumococcal disease available at the time extended to 2013/14 and were primarily defined using IPD surveillance data from England and Wales. These data showed that collectively PCV-13 vaccine type IPD incidence in older English and Welsh adults aged ≥65-years had been declining steadily with time as a result of indirect protection from routine paediatric immunisation. It was reasonably assumed at the time that this trend for IPD incidence in older UK adults would remain consistent and continue for the foreseeable future, so it was extrapolated for the subsequent five years. The future incidence of CAP in this age group was similarly estimated based on the projected IPD incidence and a multiplier approach (the ratio between observed for IPD and CAP between 2008 and 2013). This prediction suggested that PCV-13 vaccine type pneumococcal disease would continue to decline post 2013/14 in older UK adults aged ≥65-years reaching very low near elimination levels by 2018/19. This projected incidence was an important contributor to the conclusion that introducing a routine PCV-13 programme to directly protect the immunocompetent elderly in the UK would not be cost-effective.

More recent data for both IPD and CAP obtained within the UK from English and Welsh residents and English residents respectively present contemporary observed trends for PCV-13 serotype disease in older adults and shows how these have changed since 2013/14 [7, 15, 23, 38, 39]. In contrast to the predicted trend, these data show that incidence of PCV-13 serotype pneumococcal disease in older adults did not continue to decline. Rather, the trend unexpectedly reversed, and post 2013/14 incidence began to increase in older adults aged ≥65-years with levels in 2016/17 considerably higher than in 2013/14. This highlights the difficulty of accurately predicting future pneumococcal disease trends that are associated with indirect protection. Furthermore, this collective trend for the serotypes in PCV-13 is largely driven by serotypes 19F, 19A and especially 3 which all began to increase in incidence in older UK adults after 2013/14 [7, 15]. There is speculation this could be because higher thresholds of protection maybe required for these serotypes which may have implications for the ability of PCV-13 to impact carriage of these serotypes in young children [22, 40, 41, 42, 43, 44]. Pneumococcal disease in UK adults due to the remaining ten PCV-13 serotypes has continued to decline post 2013/14 though the extent to which the very low near elimination levels anticipated by 2018/19 has been achieved is debatable, particularly when adult pneumococcal CAP is considered [7, 15].

Adult formulations of higher valency next generation PCVs now in the late stages of development will be available before the corresponding paediatric formulations, with PCV-13 therefore expected to continue to be routinely used in the UK paediatric immunisation programme, at least in the short term. This suggests that when assessing the cost effectiveness of vaccinating older UK adults with next generation higher valency PCVs the previous approach used to project the extent to which indirect protection from the paediatric PCV-13 programme may impact the pneumococcal disease burden in older adults in future years will require revision [37]. This will need to reflect the new

trends observed post 2013/14 and account for the current observed burden of PCV-13 type pneumococcal disease in older UK adults, which is considerably larger than was previously anticipated, and estimate how trends for these serotypes will likely continue. These data also suggest that relying on indirect protection induced by paediatric PCV programmes alone may not always optimally reduce the corresponding disease burden in adults, particularly for certain serotypes, with more consideration needing to be given to the public health value and importance of directly protecting older adults with PCVs. In this context consideration may need to be given to the observation that some emerging serotypes that are now major causes of pneumococcal disease in older UK adults (e.g. serotypes 8 and 12F) have rarely been detected in younger age groups by recent UK carriage studies, with these younger age groups traditionally considered to be the main carriers and transmitters of the pneumococcus [7, 15, 45, 46, 47]. Whilst this finding may reflect limitations with the methodology used for these carriage studies it nevertheless questions the extent to which indirect protection will be induced against these serotypes specifically by a routine paediatric PCV program. This possibly suggests that direct vaccination may especially be needed to optimally protect older adults against disease caused by these pneumococcal serotypes. Estimating the future extent of indirect protection for older adults induced by paediatric PCV programmes may therefore be more complex than previously thought, need to incorporate insights from the latest and most contemporary local data available and may require more sophisticated approaches.

Future trends for pneumococcal disease in older UK adults aged ≥65-years due to those additional serotypes included in higher valency next generation PCVs but not in PCV-13 will need to be carefully considered when use of these vaccines in older UK adults is assessed. Recent data shows that incidence due to several of these serotypes (e.g. serotypes 8 and 12F) unexpectedly began to rapidly increase post 2013/14 and these are now among the leading contributors to the adult pneumococcal disease burden in the UK [7, 15]. This observation is not confined to the UK with serotypes 8 and 12F also having emerged in recent years to become leading causes of IPD in various other European countries [ref ECDC 2017]. There is, as yet, no clear explanation for this phenomenon nor is it known for how long this trend might continue [7]. Relevant data post 2013/14 should therefore be used to define current trends for pneumococcal disease due to these serotypes individually, explore how they may evolve in the future and for estimating the potential impact of directly vaccinating older adults with higher valency next generation PCVs.

The latest data highlights the unpredictability of pneumococcal disease epidemiology and the difficulties in accurately projecting future trends in older adults [7, 38]. Transmission between paediatric and unvaccinated adult age groups may also be more complex than previously thought with previous assumptions about the extent and consistency of indirect protection induced by routine paediatric PCV programmes over time possibly over optimistic [37, 48]. New research suggests that carriage of *Streptococcus pneumoniae* in adults may previously have been underestimated, with significant transmission between older adults more likely than had previously been thought. This may have implications for interpreting the dynamics of pneumococcal transmission and the value of vaccinating older age groups with pneumococcal conjugate vaccines [9, 49, 50, 51].

A further issue that arises when considering possible future epidemiological trends for pneumococcal disease is the extent of population level impact that may potentially be achieved by directly vaccinating older adults with higher valency PCVs. Despite compelling evidence that PCV-13

is efficacious in adults aged ≥65-years it has been difficult to detect a measurable impact on vaccine type IPD following the introduction of routine vaccination with PCV-13 in this age group in the United States in 2014 when trends using US Active Bacterial Core Surveillance are considered. However, these data may need interpreting with caution as coverage of PCV-13 in older US adults has been low until more recently and this may contribute to the lack of impact observed. Furthermore, it is notable that IPD incidence in US adults has remained stable since routine PCV-13 vaccination for older adults began in 2014. This contrasts with data from the UK where older adults are not routinely vaccinated with a clear trend of increasing incidence post 2013/14 for PCV-13 serotype IPD in those aged ≥65-years [ref Vyse 2020]. Whilst higher valency PCVs are also anticipated to be efficacious, achieving appropriate uptake amongst older UK adults will be important if meaningful impact on the pneumococcal disease burden is to be observed at the population level.

4. Serotype 3

Previously all thirteen serotypes included in PCV-13 were assessed collectively, with PCV-13 considered efficacious against all thirteen when vaccinating immunocompetent UK adults aged ≥65-years [12]. Local data available at the time showed that post introduction of PCV-13 into the UK routine childhood immunisation programme in 2010 trends for serotype 3 IPD had declined for all individual age groups [52] and that adult pneumococcal CAP due to serotype 3 had also declined [27]. This therefore suggested that PCV-13 would provide some direct protection against serotype 3 disease for UK adults aged ≥65-years.

However, more recent data now available show that the declining trend for incidence of serotype 3 disease in UK adults ceased in 2013/14 and has subsequently increased substantially [7, 15]. Whilst serotype 3 continues to be a rare cause of IPD in young children in the UK, incidence in those aged under 5 years has also risen post 2013/14 [7]. This unexpected change in trend for serotype 3 disease in the UK remains to be explained [38] with recent genomic data suggesting the emergence of a new clade of serotype 3 pneumococci post 2014 [53]. Whilst it is hypothesised this clade might be able to more successfully evade the host immune system and possibly compromise the serotype 3 component of PCV-13 any clinical implications are yet to be determined with further research needed. In addition to these changes in trend for serotype 3 disease, vaccine effectiveness estimated for PCV-13 against serotype 3 IPD in UK children aged <5-years using routine national IPD surveillance data to June 2018 suggested protection was low compared to that for the other serotypes in PCV-13 though this estimate lacks precision due to the rarity of serotype 3 IPD cases in UK children [54]. Collectively these data have subsequently led to the ability of the serotype 3 component of PCV-13 to directly protect against serotype 3 disease to be questioned in the UK with the suggestion that future analyses might legitimately assume the serotype 3 component of PCV-13 to be a non-vaccine serotype [7, 15, 54]. This assumption was recently used in a study modelling the impact of using a reduced primary dosing schedule of PCV-13 in the UK [31]. However, there are other data that support direct PCV-13 protection against serotype 3 IPD in children[42, 44]. These are now supported by a review of publicly available IPD surveillance data from a range of countries which suggest that PCV-13 provides some direct and indirect protection against serotype 3 at the population level[55]. Further evidence that PCV-13 protects paediatrics against serotype 3 disease is

additionally now reported by a study of otitis media in children aged 5-35 months which found effectiveness of PCV-13 to be 89% (95%CI 23.9-98.4)[56]. However, the possibility is recognised that routine childhood immunisation programmes with PCV-13 may have only limited impact on carriage of serotype 3 pneumococci which may compromise the extent of indirect protection induced against adult serotype 3 disease[43]. In the context of adult pneumococcal disease a recent analysis of data from a large randomised controlled clinical trial (RCT) showed PCV-13 provided some protection against serotype 3 CAP in adults aged ≥65-years (efficacy 61.5%; 95%CI 17.6-83.4) using subjects that met a clinical definition of CAP regardless of radiologic findings [57]. This finding has subsequently been supported by a systematic review and pooled analysis of published literature describing the effectiveness of PCV-13 against serotype 3 CAP in hospitalised adults aged ≥65-years. Whilst this study was based on a relatively small number of serotype 3 CAP cases (n=67) it estimated vaccine effectiveness to be 53.6% (95%CI 6.2-75.9) and similarly suggested that PCV-13 provides some direct protection against serotype 3 CAP in adults aged ≥65-years [58]. Some local expert opinion in the UK is also now supportive of this conclusion [10].

Published data describing PCV-13 efficacy or effectiveness specifically against serotype 3 IPD in older adults are currently not available. However, pneumococcal vaccines have consistently been found to provide better protection against invasive than non-invasive disease [59] with compelling data from a large RCT showing that collectively for all serotypes PCV-13 efficacy is considerably higher for IPD than for CAP in adults aged ≥65 years [60]. Given the emergence of data showing that PCV-13 is efficacious in protecting older adults against serotype 3 pneumonia some, potentially substantial, protection against serotype 3 IPD in adults aged ≥65-years might therefore also be expected from PCVs that include serotype 3. In this context a recent analysis of Spanish surveillance data between 2009 and 2019 suggests a reduction in serotype 3 IPD has been achieved in those Spanish adult populations aged ≥65-years directly vaccinated with PCV-13 [61].

Overall, emerging data therefore support the ability of PCVs that include a serotype 3 component to provide adults aged ≥65-years with some meaningful protection against serotype 3 pneumococcal disease. Baseline assumptions in analyses that consider a serotype 3 component of adult pneumococcal vaccines as a non-vaccine serotype should therefore be used with caution.

5. Mortality

Previously a 30-day case fatality rate (CFR) of 30% and 10% respectively was used for UK adults aged ≥65-years hospitalised with IPD and CAP [12]. However, relevant data to support these estimates were limited at the time and they were considered uncertain.

The 30% estimate used for 30-day CFR following IPD in UK adults aged ≥65-years was based on a study of IPD patients in England undertaken between 2002 and 2009 which found the 30-day CFR in adults aged ≥65-years to be 31.5% [62]. However, this period reflects the pre PCV era and the first years of PCV-7 use prior to the introduction of PCV-13 into the routine UK childhood immunisation programme. The epidemiology and pneumococcal serotype distribution in the UK is now very different and this will have implications for the contemporary 30-day CFR associated with pneumococcal disease [7]. Two recent UK studies are now available that provide more recent insight into the 30-day CFR in UK adults following IPD. Houseman et al [63] showed a trend of declining 30-day CFR between 2006 and 2016 in patients with IPD in the north-east of England. Whilst the trend of declining 30-day CFR was associated with each age group studied, 30-day CFR increased with

increasing age and varied by individual serotype. The mean 30-day CFR for adults aged ≥65-years estimated across the full study period was 30% and reflects the estimate previously made by Van Hoek et al [62]. This estimate may not accurately reflect the 30-day CFR following IPD now experienced by UK adults aged ≥65-years ten years after the introduction of PCV-13. More recent UK data are used by Amin-Chowdhury et al [64] where routine national IPD surveillance data from England between 2014 and 2018 were analysed reflecting the PCV-13 era alone. This study estimated the 30-day CFR following IPD for English adults aged ≥65-years to be 24.8% across the study period. Additionally, 30-day CFR estimates for older adults are further stratified into those aged 65-79y (16.4%) and 80+y (34.4%) illustrating the increase in CFR with age in older adults. This study also showed that the emerging serotypes that are becoming important causes of IPD in the UK have a lower 30-day CFR. These new data suggest that the 30-day CFR following IPD in adults aged ≥65-years has declined following the introduction of PCV-13 and suggest an estimate of ~25% for this age group is now more appropriate to use rather than the previous estimate of ~30%. An important factor contributing to the decline in CFR is likely to be serotype replacement following the introduction of PCV-7 in 2006 and PCV-13 in 2010 which targeted those serotypes associated with the most severe outcomes, with new emerging pneumococcal serotypes having a lower propensity for mortality.

The 30-day CFR estimate of 10% previously used for adults aged ≥65-years hospitalized with CAP was based on limited local UK data available at the time [27, 65] and data from a large RCT undertaken outside the UK [60]. However, this estimate was acknowledged as being a compromise due to the wide range of CFRs reported by these sources (from 1.8% to ≥20%). Rodrigo et al [27] also only provided CFR data for adults aged ≥16-years rather than for those aged ≥65-years specifically. Relevant new data from the UK now available[15] describes a continuation of the study reported by Rodrigo et al [27] to 2017/18 but again only presents 30-day CFR for adults aged ≥16-years hospitalised with CAP. This was 7.5% and closely reflects the 6% previously reported [27]. Other UK data now available suggest the 30-day mortality for adults hospitalised with CAP is considerably higher. A British Thoracic Society (BTS) audit of CAP in British hospitalised adult patients aged ≥16-years (median age of patients 77 years) undertaken between 2009 and 2014 found overall 30-day mortality to be 18% with a trend that declined with time across the study period [66]. The 6th British Thoracic Society (BTS) national audit of CAP in adults presents data obtained between 1st December 2018 and 31st January 2019 [67]. This reports a 30-day CFR of 13.6% for UK adults hospitalised with CAP but again this is for all adults aged ≥16-years (median age of patients 75 years) and is not further stratified by age. A further finding highlighted by this audit is that mortality in UK adults hospitalised with CAP has been decreasing over time and is currently at its lowest level for 10 years. Therefore, whilst some new UK data are now available, a 30-day CFR estimate following CAP remains uncertain for UK adults aged ≥65-years. Historical UK data describing hospital admissions for pneumonia between 1997 and 2005 also indicate that 30-day mortality is considerably higher in those aged ≥65-years compared to those aged <65-years, highlighting the relevance of having contemporary data specifically for older adults with pneumonia [65]. This also emphasises a need for future studies that investigate the CFR following hospitalised CAP in UK adults aged ≥65-years specifically to help address this local data gap.

In the absence of published local data describing a 30-day CFR following hospitalization with CAP for UK adults aged ≥65-years two recent studies undertaken outside the UK provide insight for this age

group specifically. Arnold et al [29] reports a 30-day CFR of 17% for US adults aged ≥65-years hospitalised with CAP in the city of Louisville between 2014 and 2016. Shi et al [28] presents a meta-analysis of global data from 1996-2017 for older adults hospitalised with pneumonia. The meta-estimate of 30-day mortality for those aged ≥65-years living in industrialised countries was 15.9% (95% CI 13.0-19.3). Lastly, a systematic review of global data describing clinical outcomes for hospitalised patients with CAP is also now available and gives some insight into mortality [68]. This shows that data describing mortality are limited but is an important clinical outcome that occurs in 10-15% of cases overall.

Collectively these data therefore suggest that for future analyses a 30-day CFR for UK adults aged ≥65-years hospitalised with CAP should be at least 10%. Whilst there is evidence that 30-day CFR in UK patients has been declining over the last decade the most contemporary data suggest an estimate of 13-15% could be considered reasonable for UK patients aged ≥65-years who are hospitalised with CAP.

There are currently only very limited and now historical UK data from a single study that provide some insight into mortality following pneumonia treated in primary care [35]. This study estimated 30-day mortality in this context to be 18.5% in participants with a mean age of 57.6 years. However, when deaths in patients with probable hospital discharge diagnoses were excluded this reduced to 5.6%. This lower estimate reflects a 30-day mortality estimate of 5.3% from a study of pneumonia and non-pneumonia lower respiratory tract infections in primary care in the Netherlands that included adults aged 60+ years [69]. Contemporary data on mortality following outpatient pneumonia is therefore lacking, with more research needed to obtain robust estimates that could usefully contribute to cost effectiveness analyses for PCVs in older UK adults if outpatient community pneumonia that is treated in primary care be included.

6. Efficacy, effectiveness and duration of protection

Van Hoek and Miller used relevant published data available at the time (i.e. data that were available in 2015) to inform their assumptions regarding the efficacy and duration of protection provided by PCV-13 for immunocompetent adults aged ≥65-years [12]. Whilst this analysis did not specifically assess PPV23 Van Hoek and Miller concluded that PPV23 had only limited effectiveness and short duration of protection against PPV23 vaccine type IPD and a lack of protection against pneumococcal-attributed CAP, and overall had achieved little impact on pneumococcal disease in those aged ≥65-years in the UK [12]. This also reflected the conclusions drawn by the JCVI in October 2015 [11, 70]. However, since a single dose of PPV23 is currently routinely offered to all immunocompetent UK adults aged ≥65-years cost effectiveness assessments of routine use of next generation higher valency PCVs in older adults may need to include comparison with PPV23. The previous conclusions of Van Hoek and Miller of the effectiveness and duration of protection of PPV23 may therefore need to be reviewed and any relevant new data considered. In this context a more recent assessment of PPV23 effectiveness against IPD has been undertaken in UK adults aged ≥65-years in a large national study using all relevant IPD data to 2016/17. This analysis similarly concluded that PPV23 has only limited short term protection against PPV23 vaccine type IPD with no evidence of any impact at the population level [23]. Collectively relevant published studies to date investigating PPV23 protection against pneumonia show considerable variation in study design and

clinical outcome targeted, making it difficult to draw definitive conclusions. However, there is a lack of consistent evidence demonstrating the effectiveness of PPV23 against CAP in older adults [10, 71]. Whilst a recent systematic review [59] considered only data published 2016-2019 and concluded that PCV-13 and PPV23 were similarly effective against vaccine-type pneumonia and a recent review of data published from 2010–2020 suggested PPV23 may provide some benefit against vaccine type pneumococcal pneumonia for older adults[72], the issue of inconsistency nevertheless remains when the full wider body of effectiveness data for PPV23 against pneumonia are considered that includes more historical data. However, a new study now provides contemporary data on the vaccine effectiveness of PPV23 against hospitalised vaccine type pneumococcal CAP in UK adults specifically [73]. This was undertaken in a local population in the Greater Nottingham region using data collected between 2013 and 2018. It included adults aged ≥16-years but had only limited representation of older adults aged ≥65-years. The PPV23 vaccine effectiveness estimated in those aged ≥65-years and ≥75-years was 20% (95%CI -5%-40%) and 5% (95%CI -37-35%) respectively. The ability to draw robust conclusions in this context is compromised by the small number of adults aged ≥65-years included in the study and cannot therefore be considered to provide strong evidence that PPV23 provides some meaningful protection for older UK adults against pneumococcal pneumonia. This study also attempted to investigate duration of protection of PPV23 against CAP in UK adults. However, the relevant data are clearly problematic to interpret and similarly do not permit robust and confident conclusions to be made in this context. The authors conclusion that PPV23 provided UK adults aged ≥65-years with moderate long-term protection must therefore be viewed with caution. Overall, there are therefore no compelling new data to suggest the previous position taken by both the JCVI and Van Hoek and Miller that PPV23 provides UK adults aged ≥65-years with limited short-term protection against IPD and no protection against pneumococcal CAP should be changed [12, 70]. Any new assumption that PPV23 may protect older UK adults aged ≥65-years against CAP will need to be strongly supported by high-quality new data.

The previous assessment by Van Hoek and Miller considered that PCV-13 would be efficacious in immunocompetent UK adults aged ≥65-years [12]. This was based on data from a large randomized clinical trial (RCT) undertaken in adults aged ≥65-years in the Netherlands between 2008 and 2013 which showed efficacy of PCV-13 against vaccine-type IPD and CAP to be 75% and 45.6% respectively [60]. These continue to be the highest quality and most robust data available for assessing efficacy of PCV-13 against pneumococcal disease in older adults. Therefore, in the absence of any relevant new high-quality data, this RCT is expected to similarly form the basis for estimates of protection likely afforded by next generation higher valency PCVs against pneumococcal disease in older UK adults. Furthermore, data from a large observational study using a test negative design are also now available and support substantial PCV-13 effectiveness against CAP in adults aged ≥65-years (73%; 95%CI 13-92) [74]. These observational effectiveness data are unlikely to supersede the efficacy data presented by Bonten et al [60] but may be valuable to inform scenario analyses.

Some uncertainty persists regarding the duration of protection afforded by PCV-13, with only limited relevant data available. The RCT undertaken by Bonten et al concluded that PCV-13 efficacy occurred soon after vaccination and persisted throughout the duration of the clinical trial (almost 4 years) with no obvious decline in protection [60]. These data were used in the assessment by Van Hoek and Miller [12] but given the limited duration of follow up, lifelong protection following vaccination with PCV-13 was not assumed. Instead a waning scenario was employed which was considered to

reflect a conservative approach. This assumed a constant protection for the first nine years post vaccination after which it would drop every 5 years until 20 years post vaccination when subsequent onward levels of protection remain constant [12]. A subsequent post-hoc analysis of the RCT described by Bonten et al is also now available that provides some new data on this aspect [75]. This included one additional year of follow up and found PCV13 was protective against both IPD and CAP in adults aged ≥65-years over the 5-year period with no waning of efficacy observed during the additional year of observation included. Unless any new relevant data subsequently become manifest it is likely these data will be used to inform assumptions regarding duration of protection for assessments of cost-effectiveness for next generation higher valency PCVs. These suggest it may not be unreasonable to assume that protection afforded by higher valency next generation PCVs is unlikely to wane rapidly and will be relatively long lasting with no substantial decline for the first decade. However, at present this remains an important area of uncertainty.

7. Cost and quality of life

In their assessment of the cost-effectiveness of PCV-13 in immunocompetent UK adults aged ≥65 years Van Hoek and Miller [12] stated that costs and QALY loss remained uncertain parameters. Those used were based on the analysis of Rozenbaum et al [76] and were derived from NHS reference costs. Van Hoek and Miller made adjustment for inflation, with £715 and £4,800 estimated as the cost of hospital admission with CAP and IPD respectively. Whilst there is currently no new evidence indicating the cost of hospital admission with IPD should be reviewed, UK government guidance now available on payment by results in the NHS suggests £715 may underestimate the cost of hospital admission with CAP, possibly substantially [77]. Tariff information for a case of lobar, atypical or viral pneumonia with and without complications is listed at £4,165 and £1,675 per day respectively for an ordinary elective spell. For a non-elective spell, the tariff is £3,214 and £936 per day for cases with and without complications. Complications of pneumonia are more common in the elderly and those with long-term health conditions [78]. This suggests that pneumonia cases with complications will be more frequent in adults aged ≥65-years and this should be taken into consideration when estimating the cost of hospitalisation, and that the higher cost estimates associated with complications may be more appropriate in this age group. However, further research is needed to confirm the cost of a hospital admission for CAP for UK adults aged ≥65-years. Until new data become available the estimate of £715 previously used in the cost effectiveness assessment of PCV-13 should be considered with caution since the cost of hospitalisation for UK adults aged ≥65-years with CAP could be substantially higher.

Van Hoek and Miller used an overall QALY loss for IPD that declined with increasing age (ranging from 0.14 for those aged 65 years to 0.01 for those aged 100 years) and used an assumption that the QALY loss for CAP in adults aged ≥65 years was 0.006 [12]. This estimate of the impact of IPD on patients' health related quality of life (HRQoL) has been used in many other economic evaluations of adult pneumococcal conjugate vaccination[76, 79, 80, 81]. However, it is based on an assessment of parents views of the impact of IPD on their children's HRQoL rather than being measured in adult patients themselves[82]. Findings of a recent systematic review of the literature suggest the impact of pneumococcal sepsis and bacteremia on adults' HRQoL may be much larger than previously estimated, with adult IPD being associated with negative utility values (i.e. worse than death health states)[83]. Moreover, two new studies both estimate the one-year excess QALY loss due to CAP to be much higher for adults aged ≥65-years at 0.13 [84, 85] and assessments of the cost effectiveness

of higher valency next generation PCVs should now consider using this value as a baseline figure. Previously economic evaluations of PCV-13 also assumed that patients surviving IPD or CAP would return to a health state reflecting similarly aged healthy individuals. There is growing evidence from both UK and wider global data that adult patients who survive IPD or CAP experience increased morbidity and mortality [86, 87, 88, 89, 90, 91, 92, 93, 94]. Future analyses of the cost effectiveness of higher valency next generation PCVs may therefore need to consider ways to capture the reduced health state subsequently experienced by individuals following an episode of pneumococcal disease to reflect the full value these pneumococcal conjugate vaccines can potentially provide.

8. Conclusions

The previous cost effectiveness analysis for PCV-13 undertaken by Van Hoek and Miller was a robust assessment using all relevant data that were available at the time. Wherever possible, local UK data were utilised to ensure the analysis was as bespoke as possible to the UK adult population aged ≥65-years. However, for some parameters relevant insight and data inputs were limited. During the five years since this analysis was undertaken substantial new local and global data have emerged, which supersede those previously used, helping to address some of the areas of uncertainty that previously existed. These new data also provide critical insight into new epidemiological trends for pneumococcal disease in older UK adults that have emerged since 2013/14 and enable the accuracy of previous predictions to be assessed. Some areas of uncertainty continue to persist, particularly regarding the duration of protection afforded by PCVs when older immunocompetent adults are directly vaccinated. Appropriate use of these new, more contemporary data will therefore be critical for supporting any cost effectiveness assessments of vaccinating immunocompetent ≥65year olds in the UK with new generation higher valency PCVs.

The body of relevant data that now exists suggests the UK is well placed to make robust and informed assessments regarding the cost effectiveness of vaccinating immunocompetent ≥65-year olds with the new generation higher valency PCVs that are expected to shortly become available. These new, more contemporary data that are available provide important inputs for key parameters for cost effectiveness models and provide key insight into new emerging trends and the accuracy of previous predictions. Making informed and robust decisions about use of these new higher valency PCVs for routine use in older adults will be important for public health in the UK.

9. Expert Opinion

In addition to the fifteen and twenty valent PCVs that are now in late development, two twenty-four valent PCVs have entered human trials with a thirty valent product also at a preclinical stage [95]. These have the potential to protect individuals against an increasing range of pneumococcal serotypes and suggests the need to make robust and timely assessments of PCVs for potential routine use in older UK adults will continue for both the medium- and longer-term future as development of these new higher valency candidates progresses. Research initiatives into adult pneumococcal disease will therefore need to be continued in the UK over the coming decade with ongoing surveillance critical for timely insight into the latest epidemiological trends and the adult pneumococcal disease burden. Whilst a high quality national routine surveillance system is well established in the UK for IPD, surveillance of adult CAP should be expanded beyond the current small local geographical area. Stratification of these surveillance data by individual pneumococcal serotype

will also continue to be very important, particularly for assessing new PCVs that include broader ranges of serotypes. Current methodology used in the UK enables all individual serotypes causing IPD to be identified but this is not yet the case for pneumococcal CAP [7, 15]. This suggests there is a need to develop new assays that can detect more than the 24 pneumococcal serotypes in urine specimens from patients with CAP that the current generation of multiplex urinary antigen detection assays are capable of [32, 96].

The body of relevant data that can now be used to support cost effective analyses of PCVs in immunocompetent UK adults aged ≥65 years has increased considerably in the last 5 years. These new data address some of the uncertainty that previously existed when the assessment of PCV-13 was undertaken and will help make subsequent cost-effectiveness analyses for use of new higher valent PCVs in older UK adults much more robust, but data gaps still exist. For example, whilst the UK has a high-quality routine national surveillance system for IPD further studies are needed into the burden of hospitalised CAP in the UK population of older adults, particularly to provide more robust incidence estimates and the proportion that is specifically being caused by the pneumococcus (and specific pneumococcal serotypes). A knowledge gap that remains in the UK is the burden of pneumococcal pneumonia in immunocompetent older adults that is treated in primary care. Whilst this may not be a key factor that influences cost effectiveness assessments of PCVs it may contribute substantially to the burden of disease currently handled by the primary care health service in the UK, suggesting that vaccinating UK adults aged ≥65-years with higher valency PCVs could potentially relieve some of the continuing pressure the NHS finds itself under, in particular during the winter months. Future research initiatives should therefore consider further investigating this topic in the UK. Additional research is also needed to accurately define the current cost of treating a case of hospitalised adult CAP in the UK with the £715 previously used possibly a substantial underestimate.

An important issue highlighted by new data that are now available is the unpredictable epidemiological nature of pneumococcal disease and the difficulty with confidently projecting longer term trends, particularly when certain individual serotypes are considered [38]. Accurately projecting future trends for pneumococcal disease in older UK adults and the extent to which this is influenced by indirect protection induced by routine paediatric PCV programmes therefore remains a challenge and needs to be approached with caution in future cost effectiveness analyses. Whilst great value is often given to the ability of PCVs to induce indirect protection in adult populations, assumptions that indirect protection alone induced by a paediatric PCV programme will rapidly reduce the vaccine type adult disease burden to negligible levels within a few years may be overly optimistic with more consideration for the public health value of directly protecting older adults warranted. This also suggests that new carriage studies will continue to be valuable in the UK to monitor carriage trends in younger age groups over time for individual pneumococcal serotypes, particularly for those that have recently emerged as important causes of disease in older adults but have rarely been detected in carriage studies to date. This may help to better understand the extent to which new generation higher valency PCVs may impact paediatric carriage of the pneumococcus and induce indirect protection once they become available for use in routine paediatric programmes.

Future cost effectiveness assessments of new generation higher valency PCVs in immunocompetent UK adults aged ≥65-years may choose to replicate the methodology used previously by Van Hoek and Miller and just update this by incorporating those relevant new data now available [12].

However, data are now emerging that highlight various additional aspects and approaches that subsequent cost effectiveness assessments of PCVs may want to consider incorporating to more accurately reflect the full value of these vaccines. For example, there is growing evidence that older adults who recover from pneumococcal disease do not return to their previous health state and subsequently experience an increased risk of morbidity and mortality, with implications that may influence the cost effectiveness of routine adult PCV programmes when a longer term perspective is considered [89, 90, 91, 92, 93, 94]. Future assessments should also consider including the broader socioeconomic consequences that routine vaccination of the elderly with higher valency PCVs could have and the potential additional value they offer in this context [97]. There is also the growing problem of antimicrobial resistance (AMR) and the extent to which routinely vaccinating UK adults with higher valency PCVs could help in reducing use of antimicrobials that would otherwise be used to treat adults with pneumococcal disease [98, 99, 100]. Lastly there is compelling evidence now becoming manifest that vaccinating older adults with PCVs is associated with a significant risk reduction of all cause pneumonia and that approaches incorporating this aspect may be needed to estimate the full public health impact PCVs can have on this disease burden in the older adult population and this topic has recently been reviewed in detail. [101, 102, 103, 104]. Given the importance of including the broader public health impact of vaccines when making public health policy decisions, cost effectiveness analyses of higher valency PCVs that incorporate this approach may provide an important new perspective and insights into the full value of these vaccines.

Historically dynamic transmission models have not been used in cost effectiveness assessments of PCVs in older adults as relevant data have suggested pneumococcal carriage is very rare in older adults with those aged ≥65-years contributing very little to pneumococcal transmission. This has been supported by the body of UK carriage data available to date which has consistently found that carriage in UK adults was only rarely detected using standard methodology [45, 46, 47, 105]. However, recent research using new methodological approaches is now suggesting that respiratory carriage of *Streptococcus pneumoniae* may have been substantially underestimated in older age groups and is highlighting evidence of a possible transmission reservoir among adults [49, 50, 51]. This research is currently at an early stage, but should similar data continue to emerge suggesting a role of older adults in pneumococcal transmission the use of dynamic transmission models in cost effectiveness assessments of PCVs in older adults may need to be considered. Furthermore, this may strengthen the case for vaccinating older age groups with pneumococcal conjugate vaccines specifically given their ability to impact carriage and interrupt transmission [9, 21, 106, 107, 108].

The devastating morbidity and mortality caused by the COVID-19 pandemic has increased public awareness and understanding of the importance of adult vaccination more broadly, particularly for those that can help protect the elderly against important causes of respiratory disease. There is also speculation emerging regarding a potential direct benefit of pneumococcal vaccines on the prevention of COVID-19. Possible SARS-CoV-2-pneumococcus associations with plausible immunological mechanisms are being hypothesised by which pneumococcal vaccines may potentially improve the immune response to SARS-CoV-2 [16, 109, 110, 111]. This will require careful research before any firm conclusions can be drawn, but some supportive data are available from a study of a nine-valent PCV in South African children and a study of PCV-13 in US adults aged 65+ years [17, 112]. These data suggest that the pneumococcus may have a role in the development of pneumonia associated with COVID-19 and that PCVs may help prevent COVID-19 associated pneumonia in both paediatric and older adults, particularly severe COVID-19 outcomes. However,

the importance of vaccination against SARS-CoV-2 for all eligible individuals remains paramount to controlling the COVID-19 pandemic. Regardless of any possible direct benefit of pneumococcal vaccines for the prevention of COVID-19, a higher valency PCV nevertheless has the potential to help reduce pressure on the NHS, especially in the context of the COVID-19 pandemic and the disease burden this is causing, by decreasing the burden of pneumococcal disease in older UK adults,. Furthermore, data are now emerging from the UK showing that co-infection with the pneumococcus and SARS-CoV-2 is associated with a very high case fatality rate, particularly in older adults[113]. This suggests a possible synergistic effect between SARS-CoV-2 and the pneumococcus, with prior pneumococcal infection increasing the risk of infection and severe illness associated with SARS-CoV-2 infection [18]. These data are currently limited to just IPD where such co-infections have so far been infrequent, with further research also needed to investigate SARS-CoV-2 co-infection and mortality in those with non-invasive pneumococcal disease to provide full insight into the public health implications of this observation. However, to date co-infection with the SARS-CoV-2 virus and the pneumococcus has been rarely identified [ref Lansbury 2020; Russel 2021].

How the COVID-19 pandemic evolves in the UK and how successfully and rapidly it can be brought under control through widespread vaccination, with vaccination of the elderly considered critical [114], may have important implications for adult vaccines in the future and the priority given to new higher valent adult PCVs when they become available. Various COVID-19 vaccines are in development with three now authorised for temporary supply under Regulation 174 in the UK [115, 116]. Widespread vaccination with COVID-19 vaccines in the UK has therefore now begun in earnest with immunisation of the elderly prioritised [114]. This unprecedented roll out of an adult vaccine in the UK may influence thinking about the future public health role and need to invest in vaccines that protect the health of older adults specifically. However, there is evidence emerging that the COVID-19 pandemic and subsequent social distancing measures and national lockdowns imposed in the UK have been associated with a reduction in transmission of common respiratory infections, including the pneumococcus [ref Brueggeman 2021]. A large decline in IPD across all age groups has occurred, with the assumption that non-invasive pneumococcal disease has been similarly impacted [113]. Whilst the burden of adult pneumococcal disease has declined this may only prove to be temporary once relaxation of social distancing measures are permitted, allowing transmission of the pneumococcus to return to pre pandemic levels. How common respiratory pathogens may re-emerge in the post COVID-19 era remains very uncertain with a recent modelling study is predicting that large outbreaks of respiratory disease could occur in the years following the removal of social distancing measures as a result of a build-up of susceptible individuals [117]. Whilst this study primarily focused on influenza and RSV it illustrated the potential for social distancing measures to impact the dynamics and persistence of a much wider range of infections, including the pneumococcus.. Finally, it is also becoming evident that circulation of the SARS-CoV-2 virus may persist in the longer term with new strains emerging [ref Tang 2021; Planas 2021]. This suggests co-infections of SARS-CoV-2 virus with the pneumococcus could become more frequent if normal transmission of common respiratory infections resumes once social distancing restrictions are eased. Given there is some evidence suggesting co-infection with the pneumococcus and SARS-CoV-2 virus is associated with more severe illness and outcomes, vaccinating older UK adults with higher valent PCVs could potentially become additionally important in the post COVID era [113].

In conclusion, the global COVID-19 pandemic has added a potential new perspective to decision making for adult vaccines that target causes of respiratory disease. At the time of writing there is

much uncertainty about how the epidemiology of the pneumococcus may re-emerge in the UK in the post COVID era and the extent to which strains of the SARS-CoV-2 virus will continue to circulate. Ongoing high-quality surveillance and research will be important to answer these questions and will help inform the public health need and role of higher valency adult PCVs in the UK.

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	4	6B	9V	14	18C	19F	23F	1	5	7F	3	6A	19A	22F	33F	10A	15B	8	11A	12F
PCV-7																				
PCV-13																				
PCV-15																				
PCV-20																				

Table 1. The individual pneumococcal serotypes included in PCVs previously (PCV-7) and currently (PCV-13) used in the UK and the two next generation higher valency PCVs (PCV-15 and PCV-20)