11.05 Cost-effectiveness review of pneumococcal vaccines for the National Immunisation Program (NIP)

1 Purpose of Item

1.1 To request PBAC consideration of stakeholder input and additional Australian Technical Advisory Group on Immunisation's (ATAGI's) advice on a proposed vaccination schedule for those at high-risk of pneumococcal disease suitable for inclusion on the National Immunisation Program (NIP) schedule.

2 Background

2.1 In July 2016, the PBAC recommended Prevenar 13® (a 13-valent pneumococcal conjugate vaccine (13vPCV)) to replace the first dose of Pneumovax 23® (a 23-valent pneumococcal polysaccharide vaccine (23vPPV)) for older adults based on cost effectiveness over the 23vPPV. At that time, the PBAC noted that the cost-effectiveness of 23vPPV had not been previously reviewed and requested advice from the ATAGI on the clinical place and effectiveness of 23vPPV on the NIP with a view to potentially informing a review of the cost-effectiveness of 23vPPV. The PBAC noted that any outcomes of the review of 23vPPV may have implications for the 13vPCV listing.

2.2 In July 2017, the PBAC considered the advice of the ATAGI and recommended a cost effectiveness review (CER) of 23vPPV compared to no vaccine in the current NIP-funded indications for:

- Non-Aboriginal and Torres Strait Islander adults aged ≥65 years, with and without risk factors; and
- Aboriginal and Torres Strait Islander adults aged ≥50 years, with and without risk factors.
- Given the high and disproportionate burden of invasive pneumococcal disease (IPD) in Aboriginal and Torres Strait Islander adults, the PBAC also recommended a review of a stepped economic analysis and financial impact of providing 13vPCV, with or without 1 or 2 doses of 23vPPV, to Aboriginal and Torres Strait Islander adults ≥50yrs not previously vaccinated with 7vPCV or 13vPCV.

2.3 The PBAC first considered the CER report in December 2018 and sought further advice from the ATAGI on a proposed pneumococcal NIP schedule for individuals aged 12 months and older at high-risk of pneumococcal disease, where use of 13vPCV and 23vPPV could be considered cost-effective.

2.4 At its March 2019 meeting, the PBAC considered the ATAGI's advice (February 2019 ATAGI Advice). The PBAC accepted ATAGI's advice and considered it would be appropriate to fund one dose of 13vPCV followed by two doses of 23vPPV for those aged 12-59 months, newly diagnosed with medical conditions associated with very high risk of pneumococcal disease (a list of medical conditions was provided).

2.5 The PBAC also noted its consideration of the CER report in December 2018 and affirmed the findings, which supported routine vaccination with 13vPCV in older, healthy adults ≥75 years, based on acceptable cost-effectiveness. The PBAC also affirmed its view that one dose of the 13vPCV plus two subsequent doses of the 23vPPV in the Aboriginal and Torres Strait Islander population ≥50 years could be included on the NIP, based on high but acceptable cost-effectiveness in this population.

2.6 However, the PBAC considered the enhanced immunisation schedule for at-risk groups aged ≥ 5years as identified by the ATAGI in its advice, required further consideration. Therefore the PBAC requested the ATAGI provide further advice on additional at-risk conditions which may be appropriate for NIP- funding in those aged ≥ 5years, taking into consideration:

- conditions associated with a high incidence of IPD and small patient numbers, such as persistent nephrotic syndrome; and
- conditions where the risk of IPD is likely to be very high but difficult to accurately quantify because of small patient numbers.

2.7 The PBAC also noted the feedback from the sponsors of both vaccines and two other stakeholders requesting the opportunity for wider stakeholder consultation on the CER report.

For more detail on PBAC's view, see section 4 PBAC outcome

3 Consideration of the evidence

3.1 Targeted stakeholder consultation was conducted in May 2019 and ATAGI provided further advice on an enhanced immunisation schedule for additional at-risk groups in June 2019. Consumer comments were received via the consumer comments portal.

ATAGI Advice

3.2 In considering PBAC's March 2019 request for additional advice, ATAGI reviewed the epidemiology of IPD to identify further groups at similar high-risk to those groups already accepted by PBAC as cost-effective to vaccinate with both the 13vPCV and 23vPPV.

3.3 ATAGI advised that two additional groups to those considered by the PBAC in March 2019, also be funded through the NIP for one dose of 13vPCV at diagnosis and two subsequent doses of 23vPPV:

- individuals ≥ 5 years with relapsing or persistent nephrotic syndrome; and
- children 12 to 59 months of age who had experienced a previous episode of IPD.

3.4 ATAGI also requested the PBAC consider including all healthy Aboriginal and Torres Strait Islander children <5 years living in Western Australia, Northern Territory, South Australia and Queensland as being at very high risk of pneumococcal disease, allowing them to receive two additional doses of 23vPPV following the additional dose of 13PCV already currently funded, due to the high burden of IPD in these Aboriginal and Torres Strait Islander populations. ATAGI considered that aligning recommendations for all Aboriginal and Torres Strait Islander and medically at-risk children <5 years would greatly simplify implementation of the proposed new pneumococcal immunisation program.

3.5 ATAGI also requested the PBAC consider recommending the 13vPCV for healthy Australians ≥ 70 years of age, rather than the previously considered ≥75 years of age. The rationale for this request was based on the CER report (2018), which reported an acceptable, albeit slightly higher incremental cost-effectiveness ratio for the 70-year age group, as well as recognising that not all patients are likely to be vaccinated on their 70th birthday. The age threshold of ≥70 years aligns with the currently funded immunisation recommendations for Zostavax and therefore may also assist with implementation and uptake.

3.6 ATAGI therefore proposed a whole-of-life pneumococcal schedule, including both the populations considered cost-effective for the pneumococcal schedule by the PBAC in March 2019 and the additional populations outlined in the ATAGI 's June 2019 advice (refer to paragraphs 3.3-3.5). Refer to paragraphs 3.9 and 3.10 below for the whole-of-life pneumococcal schedule as well as a list of the high-risk conditions advised to be cost effective for vaccination with one dose of the 13vPCV and two doses of the 23vPPV.

3.7 ATAGI was of the view that if the 23vPPV is funded through the NIP for the high-risk populations at greatest risk of pneumococcal disease consistent with its advice (February & June 2019), it would negate the need to continue to subsidise the 23vPPV via the PBS.

3.8 ATAGI also noted that there are conjugate pneumococcal vaccines with expanded serotype coverage being developed and currently in phase II and III trials. Due to the potential availability of new vaccines and the changing epidemiology of

pneumococcal disease, ATAGI strongly advised that any updated pneumococcal NIP schedule be reviewed in three to five years.

3.9 The ATAGI-proposed whole-of-life NIP-funded pneumococcal vaccine schedule is outlined in Table 1 below.

Table 1 – ATAGI proposed whole of life NIP funded pneumococcal vaccine

Age group	Cohort	Proposed NIP-funded schedule
2 - 12 months	Healthy non-Indigenous children; and Healthy Aboriginal or Torres Strait Islander children living in Victoria, Tasmania, New South Wales or Australian Capital Territory	**13vPCV at 2, 4 and 12 months**
	Children diagnosed with any of the medical conditions associated with very high risk of pneumococcal disease (list A + B)*; and Healthy Aboriginal or Torres Strait Islander children living in Western Australia, Northern Territory, South Australia and Queensland	**13vPCV at 2, 4, 6 and 12 months** **23vPPV at 4-5 years** **23vPPV 5-10 years later**
12-59 months	Children newly diagnosed with any of the medical conditions associated with very high risk of pneumococcal disease (list A + B)*; and Healthy Aboriginal or Torres Strait Islander children living in Western Australia, Northern Territory, South Australia and Queensland	**13vPCV at diagnosis#** **23vPPV at 4-5 years** **23vPPV 5-10 years later**
≥ 5 years	Persons newly diagnosed with any of the medical conditions associated with very high risk of pneumococcal disease (list A)*	**13vPCV at diagnosis** **23vPPV at least 2 months later** **23vPPV 5-10 years later**
≥ 50 years	All Indigenous persons (regardless of risk factors)	**13vPCV followed by** **23vPPV at least 2 months later** **23vPPV 5-10 years later**
≥ 70 years	All non-Indigenous persons (regardless of risk factors)	**13vPCV**

This dose is additional to the funded doses of 13vPCV for healthy infants, or the 13vPCV dose required for catch-up as for healthy children aged <5 years who have not completed their primary vaccination series of 13vPCV in infancy

3.10 The list of medical conditions associated with very high-risk of pneumococcal disease, advised to be cost effective for vaccination with one dose of the 13vPCV and two doses of the 23vPPV includes:

***List A: Individuals newly diagnosed with the following medical risk conditions:**

1. Functional or anatomical asplenia including:
    a. sickle cell disease or other haemoglobinopathies,
    b. congenital or acquired asplenia (e.g. splenectomy) or hyposplenia
2. Immunocompromising conditions including:
    a. congenital or acquired immune deficiency including symptomatic IgG subclass or isolated IgA deficiency
    b. haematological malignancies
    c. solid organ transplant haematopoietic stem cell transplant (HSCT)
    d. HIV infection
3. Chronic respiratory disease including:
    a. suppurative lung disease, bronchiectasis and cystic fibrosis
    b. chronic lung disease of prematurity
4. Chronic renal disease including:
    a. end stage renal disease – eGFR <15mL/min
    b. relapsing or persistent nephrotic syndrome
5. Proven or presumptive cerebrospinal fluid (CSF) leak
6. Cochlear implants
7. Intracranial shunts
8. Previous episode of invasive pneumococcal disease (IPD)

List B: In addition, children <5 years with the following conditions:

9. Born less than 28 weeks gestation
10. Trisomy 21
11. Chronic heart disease including cyanotic heart disease and heart failure

Sponsor and Consumer comments

3.11 The PBAC considered the comments provided by three health professionals and the following organisation: The Lung Foundation, Asthma Australia, National Seniors, Royal Australian College of General Practitioners, and COTA Australia.

3.12 These submission all contained similar concerns relating to the proposal to increase the age of initial vaccination in healthy adults from 65 to 75 years of age and replacement of the 23vPPV with the 13vPCV in this elderly non- Aboriginal and Torres Strait Islander healthy population. Concerns regarding the change from 23vPPV to 13vPCV included:

- the large population aged between 65 and 75 years that would have increased risk of exposure to pneumococcal pneumonia
- the changing prevalence of pneumococcal serotypes due to the effects of the infant 13vPCV program
- ATAGI underestimating the vaccine efficacy (VE) of 23vPPV against community acquired pneumococcal disease; and the growing prevalence of serotype 3.

3.13 Seqirus, sponsor of the 23vPPV, provided a pre-PBAC response supporting the views and concerns expressed by the organisations above. In particular, concerns raised about reduced access or no access to the 23vPPV for individuals with chronic lung diseases such as COPD, asthma, interstitial lung disease and bronchiectasis.

3.14 Seqirus reiterated their view that the effectiveness rate of 5.6% for non-invasive pneumococcal pneumonia applied in the cost-effectiveness evaluation was an underestimate and disputed the ATAGI advice on this matter.

3.15 Seqirus noted that there is currently no surveillance program to accurately capture non-invasive pneumococcal disease in Australia, and that this information could better inform cost-effectiveness evaluations of the current program on non-invasive disease. [redacted]

3.17 Seqirus requested that a full public summary document of the CER report be published, including a thorough description of the economic model and rationale for pivotal assumptions underlying the recommendation, to enable public scrutiny.

[redacted]

For more detail on PBAC's view, see section 4 PBAC outcome

4 PBAC Outcome

4.1 The PBAC recommended the implementation of a whole-of-life NIP-funded pneumococcal vaccine schedule, in line with ATAGI's June 2019 advice. The PBAC

considered the proposed pneumococcal schedule was cost-effective, targeting those at highest-risk of pneumococcal disease across all age groups.

4.2 The PBAC reaffirmed its July 2016 recommendation that, on the basis of cost-effectiveness compared with 23vPPV, a single dose of 13vPCV should replace the single dose (or the first dose for those adults with risk factors) of 23vPPV that is currently provided to the older adult populations through the NIP (≥65 years non-Aboriginal and Torres Strait Islander, ≥50 years Aboriginal and Torres Strait Islander).

4.3 The PBAC reaffirmed its view following its consideration of the CER report in December 2018, that that even at zero vaccine cost, the 23vPPV compared to no vaccine did not appear to be cost-effective in healthy, non-Aboriginal and Torres Strait Islander adults aged ≥65 years. The PBAC also reaffirmed that it considered the 13vPCV appeared to be most cost-effective in the non-Aboriginal and Torres Strait Islander population when administered at 75 years of age, at the price accepted by the Committee in July 2016.

4.4 The PBAC reaffirmed that it considered the cost-effectiveness of vaccinating Aboriginal and Torres Strait Islander adults ≥50 years with one dose of 13vPCV followed by two doses of 23vPPV was acceptable, given the high and disproportionate burden of IPD amongst Aboriginal and Torres Strait Islander adults.

4.5 The PBAC recalled its March 2019 advice, that vaccination with 13vPCV was not only considered to be most cost-effective when given to non- Aboriginal and Torres Strait Islander adults without risk factors at age ≥75 years, but that vaccination at this age coincided with the highest IPD rates observed amongst older Australians. Subsequently, vaccination at ≥75 years resulted in the quality adjusted life years (QALY) gained almost doubling when compared to vaccination at ≥65 years. Therefore, given the likely waning of VE over time, vaccination at ≥65 years compared to ≥75 years resulted in the population most at-risk of IPD not achieving maximum protective effect from pneumococcal vaccination, at the age where incidence of IPD is highest.

4.6 The PBAC further recalled that in March 2019, it recommended the enhanced immunisation schedule for at-risk groups aged 12 months and older as identified by the ATAGI in its February 2019 advice, required further consideration. The PBAC also considered targeted stakeholder consultation was appropriate in order to consolidate the at-risk groups aged 12 months and older who would be eligible for vaccination with both the 13vPCV and the 23vPPV.

4.7 The PBAC noted the comments received from the targeted stakeholder consultation, Seqirus and Pfizer. In particular, the PBAC noted the concern that the cost-effectiveness of 13vPCV in otherwise healthy adults ≥65 years is sensitive to

assumptions about immunogenicity in older people, rates of waning and VE against residual 13vPCV serotypes.

4.8 The PBAC identified a recently published cohort study, reporting on the VE of the 23vPPV and the changing incidence of IPD between 2002 and 2017 in England and Wales (Djennad et al. 2018). The Study reported moderate estimates of VE against IPD that declined over 5 years. The incidence of IPD due to 23vPPV-exclusive serotypes, not included in the 7 and 13-valent conjugate vaccines (PCVs), did not decrease after routine 23vPPV vaccination. The PBAC considered this finding was consistent with the Australian setting, where 23vPPV serotypes remain prevalent, despite the availability of the 23vPPV on the NIP for the last several years.

4.9 The PBAC noted that ATAGI strongly supported the proposed changes to the pneumococcal immunisation program discussed at the March 2019 PBAC meeting. The PBAC also accepted further ATAGI advice (June 2019), detailing a proposed whole-of-life NIP-funded pneumococcal vaccine schedule. This included ATAGI's updated recommendations to revise age of vaccination for non-Aboriginal and Torres Strait Islander adults with 13vPCV from ≥ 75 to ≥ 70 years, to align vaccination age with the Zostavax schedule and to facilitate implementation and uptake of the pneumococcal program.

4.10 The PBAC also noted the ATAGI's advice (June 2019), to extend the pneumococcal NIP schedule to include additional high-risk groups to those recommended in its February 2019 advice (refer to paragraphs 3.3-3.5) and considered these groups should also be eligible for funding one dose of 13vPCV and two subsequent doses of 23vPPV, under the NIP.

4.11 The PBAC considered a revised whole-of-life NIP-funded pneumococcal vaccine schedule, consistent with ATAGI's June 2019 advice- including those at highest risk of IPD of all ages, to be cost-effective and recommended the NIP schedule be updated accordingly (refer to paragraphs 3.9 and 3.10).

4.12 The PBAC noted ATAGI's advice that the revised pneumococcal vaccination schedule will ensure that all very high risk populations are eligible for vaccination with both the 13vPCV and the 23vPPV on the NIP. Therefore, the PBAC agreed with the ATAGI and considered the PBS listing of the 23vPPV for those at high risk of pneumococcal infection was no longer required and recommended delisting the vaccine from the PBS.

4.13 The PBAC accepted ATAGI's advice, that due to the changing epidemiology of the serotypes causing pneumococcal disease, and potential availability of new and more effective vaccines, that the NIP-funded pneumococcal schedule could be reviewed in 3-5 years if considered necessary by the ATAGI.

4.14 The PBAC recommended implementation of the following whole-of-life pneumococcal vaccine schedule, including both the 13vPCV and the 23vPPV, as having acceptable cost-effectiveness for inclusion on the National Immunisation Program (NIP):

- All healthy non–Aboriginal and Torres Strait Islander adults ≥ 70 years: 13vPCV (single dose)
- All Aboriginal and Torres Strait Islander adults ≥50 years: 13vPCV (single dose) and 23vPPV (two subsequent doses approximately five years apart)
- In all persons ≥ 5 years of age newly diagnosed with a condition putting them at very high risk of pneumococcal infection: 13vPCV (single dose) and 23vPPV (two subsequent doses approximately five years apart).

4.15 Based on ATAGI's advice on the high pneumococcal disease rates in certain high-risk infant populations, the following additions were also recommended to the infant pneumococcal program for children under five years of age:

- Non-Aboriginal and Torres Strait Islander children 2-12 months with very high risk of pneumococcal infection: an additional dose of 13vPCV (single dose) at 6 months (already funded for Aboriginal and Torres Strait Islander children) and 23vPPV (two subsequent doses approximately five years apart).
- Aboriginal and Torres Strait Islander children < 5 years living in Western Australia, Queensland, South Australia and Northern Territory (areas of high incidence): Two additional doses of 23vPPV following the currently funded additional dose of 13vPCV at 6 months.
- Children 12 – 59 months newly diagnosed with a condition putting them at very high risk of pneumococcal infection: 13vPCV (single dose) and 23vPPV (two subsequent doses approximately 5 years apart).

Outcome:
Recommended

Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

Sponsor's Comment

Seqirus is disappointed that these PBAC recommendations will limit access to 23vPPV for the Australian population. Many Australians who are currently eligible for NIP-funded or PBS-subsidised 23vPPV vaccination will no longer be offered protection against disease attributable to the 11 unique serotypes contained in this broad spectrum vaccine. Seqirus therefore urges that the impact of the proposed changes to the NIP be closely monitored through enhanced surveillance of invasive and non-invasive pneumococcal disease.

Seqirus supports the recommendation to fund access to both 13vPCV and 23vPPV for Australians at very high risk of pneumococcal disease.

Seqirus further notes that paragraph 4.8 describes results of the Djennad et al, 2018 study. The authors of the study note that: "The recent increase in IPD due to some of the PPV23 serotypes in England and Wales would support continuation of the elderly PPV23 programme, especially given the significant positive effectiveness against the major replacing serotypes causing IPD in this vulnerable age group. Extending the age at with PPV23 is offered and/or offering additional PPV23 doses at regular intervals might help prevent more cases of IPD". The results of the Djennad et al, 2018 study are consistent with findings in Australia, where, despite suboptimal coverage, 23vPPV has helped to minimise the serotype replacement impact of the infant 13vPCV program in older adults eligible for the current NIP program. This is evidenced by IPD notifications attributable to non-vaccine serotypes increasing to a far greater extent than those attributable to the 11 unique serotypes contained in 23vPPV.

Pfizer had no comment.