An update on adult vaccination against pneumococcal disease - Proceedings of a Public Forum

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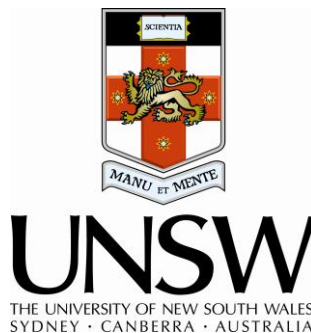Link to license to see what you are allowed to do with this resource.

An update on adult vaccination against pneumococcal disease

Proceedings of a Public Forum

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Executive summary

Forum highlights latest developments in managing adult pneumococcal disease

Researchers, policy makers, healthcare professionals, advisory groups and industry representatives reviewed the latest research and discussed future directions at a forum on adult vaccination against pneumococcal disease on 29-30th August, 2011 at UNSW in Sydney, Australia. The Forum was organized and chaired by Professor Raina MacIntyre with sponsorship from CSL Biotherapies.

Hosted by the School of Public Health and Community of Medicine at UNSW, the forum featured national and international speakers including Professor David Goldblatt, Professor Peter McIntyre, Professor Peter Richmond and Dr John Grabenstein. This report describes some of the key messages and issues discussed at the forum.

Diagnosis of pneumococcal disease remains challenging

It is well recognised that pneumococcal disease is an important issue for older people and those with comorbid conditions that place them at higher risk of disease. Although pneumococcal disease has been studied for many years, the diagnosis of non-invasive disease remains challenging. This is largely because there is no gold standard for diagnosis of non-invasive disease, with most diagnoses of presumptive pneumococcal pneumonia made by chest radiograph.

Much work is also required to improve therapeutics for pneumococcal disease. Early antibiotic use appears to positively affect outcomes. [1, 2, 3] Combination antibiotic therapy has also been shown to significantly reduce mortality in critically ill patients with pneumococcal pneumonia compared with single antibiotic therapy. [4]

Due to the challenges in diagnosis, the incidence of invasive pneumococcal disease (IPD) is often used to monitor the overall burden and trends in pneumococcal disease. Patterns of IPD incidence by age are similar internationally. The peaks of disease incidence are in the very young and in the elderly. The incidence of IPD in the general population in Australia is approximately 5–10 per 100,000. Rates of vaccine type IPD in non-Indigenous adults in Australia have declined since the funded national program for 23vPPV (in adults ≥ 65 years) and 7vPCV (in infants) commenced in 2005. [5]

The role of vaccination in managing adult pneumococcal disease

The national average for coverage for 23vPPV is approximately 53% in people aged ≥ 65 years. [6] Coverage is highest in people aged ≥ 75 years. In Indigenous adults, coverage is sub-optimal in all age groups. [7]

A study (Menzies, unpublished) used the indirect cohort and screening methods to evaluate whether 23vPPV is effective in the Australian setting. The indirect cohort method found that 23vPPV is highly effective in younger adults, and that effectiveness decreases with age. It also found that effectiveness is 15–40% lower in people with risk factors. The screening method found no decrease in vaccine effectiveness in elderly adults (≥ 75 years).

A 2008 Cochrane Review [8] found polysaccharide vaccines were effective in preventing IPD (any type). There was insufficient evidence to evaluate the role of vaccines in preventing pneumonia (all causes) and mortality (all causes).

Results differ between the two most applicable studies of clinical effectiveness over long intervals after the first dose of 23vPPV. One study shows effectiveness remains consistent over 9 years [9], while the other found effectiveness to decrease over time [10]. In most studies, antibody levels persisted above unvaccinated baseline levels for 5 to 10 years after administration of 23vPPV in adults. [11]

Revaccination with 23vPPV in adults after 5 to 10 years yields increases in antibody levels, with a consistent inverse association: if circulating antibody level at the time of revaccination is lower, then there is a greater antibody increase (and vice versa). [11]

The effectiveness of a vaccine may be dependent on an individual's ability to make an immune response. Ageing has been shown to reduce the functionality of anti-pneumococcal antibodies in unvaccinated individuals. In addition, phagocytes from the elderly (mean age 74 years) have a reduced capacity to kill pneumococci compared with phagocytes from the young (mean age 34 years). These immunological changes of ageing result in sub-optimal vaccine responses in the elderly. [12]

In young infants, PCV is highly effective. [13] The role of PCV in adults is less clear, as superior efficacy/effectiveness has not been demonstrated with PCV compared with PPV in adults. In addition, there is no conclusive evidence as yet of longer lasting protection in the elderly with PCV compared with PPV.

Populations with routine infant PCV immunisation have observed clear changes in pneumococcal epidemiology. [14] The replacement phenomenon has resulted in an increase in some of the serotypes not in 7vPCV in the elderly. A key issue to consider will be the cost-effectiveness of using 13vPCV in adults in conjunction with a mature infant PCV program that is likely to deliver herd protection in adults.

Correlates of protection for 7vPCV are essential in the licensure process of new formulations of vaccines. Data from studies evaluating protective pneumococcal antibody levels in different settings were amalgamated with serological data to produce a consensus value for a correlate of protection of 0.35 µg/mL for 7vPCV in infants. [15-19]

A study compared the immunogenicity of 23vPPV and 7vPCV for four serotypes (4, 6B, 18C and 19F) by frailty index in hospitalised elderly persons. [20] No significant differences were found between IgG responses to 7vPCV versus 23vPPV, with the vast majority of patients showing an acceptable response. Frailty was found to be as good a predictor of immune response to pneumococcal vaccines as age.

Another issue addressed at the forum was the adverse-event profile of 23vPPV. There is some evidence to suggest that an increase in injection site reactions (ISRs) can be expected in people revaccinated with 23vPPV, particularly in those revaccinated within 5 years of the prior dose. [21-24] In Australia in early 2011, there was a considerable increase in ISRs reported in people aged ≥ 65 years, particularly in NSW and ACT. [25] On 19 April 2011, the Therapeutic Goods Administration (TGA) advised health professionals not to administer a second or subsequent

dose of 23vPPV. [26] This advisory was pending the outcome of a review of an apparent increased rate of ISRs following administration of the second dose of vaccine.

[Subsequent to the meeting, in December 2011, TGA concluded its analysis and recommended that revaccination with 23vPPV should not be given routinely to immunocompetent individuals, but should be considered for patients at a high risk of serious pneumococcal disease, provided that at least five years has passed since the previous dose. [27] The Australian Technical Advisory Group on Immunisation (ATAGI) issued similar recommendations, specifying that for non-Indigenous adults aged ≥65 years, a second dose (a single revaccination) of 23vPPV, to be given ≥5 years after the first dose, is recommended for those who have a condition that predisposes them to an increased risk of invasive pneumococcal disease. [28]]

Future directions in the management of pneumococcal disease

'We all recognise that pneumococcal disease is an important issue for the elderly and those with comorbid conditions that put them at particular risk of disease,' said Professor Peter Richmond in a closing summation of the forum. 'We also still need to do more work in diagnostics and therapeutics.'

Evaluating the benefit of vaccines for different population groups and then implementing appropriate vaccination programs accordingly will be another important step. 'We need to think about what vaccines we do have, who they work in, and what is the most effective way of moving forward,' Professor Richmond said.

'If PPV in adults is recommended, then current coverage rates are vastly inadequate,' Professor Richmond added. According to many of the delegates at the forum, strategies for improving vaccine coverage, particularly in at-risk groups, need to be considered.

'Registers provide a major tool for improving coverage, as they eliminate the uncertainty about whether a person has been previously vaccinated,' Dr Menzies said. 'Also, healthcare providers are highly influential in advocating vaccination to their patients. We therefore need to explore ways to assist healthcare providers to prioritise vaccination.'

In the future, improved diagnostics, therapeutics, surveillance, vaccines and coverage will be important in advancing the management of pneumococcal disease.

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Day 1: 29 August 2011

Topic: Adult epidemiology
Chair: Prof Raina MacIntyre

Speakers (Day 1: 29 August 2011)

Professor Paul Torzillo

Professor Torzillo is an Executive Clinical Director, Head of Respiratory Medicine and a senior Intensive Care physician at Royal Prince Alfred Hospital and a Clinical Professor of Medicine at the University of Sydney, AU.

For more than 30 years he has had a major involvement in Aboriginal health. Professor Torzillo is Medical Director of the Nganampa Health Council in the north-west corner of South Australia and a member of the National Indigenous Health Equity Council.

Professor Peter McIntyre

Professor McIntyre, MBBS, PhD, FRACP, FAFPHM, is a Conjoint Professor in the Discipline of Paediatrics and Child Health and in the School of Public Health of the University of Sydney, AU. He is the Director of National Centre for Immunisation Research and Surveillance (NCIRS).

He is an authority, of national and international standing, on the epidemiology of pneumococcal disease and pertussis and in the role of vaccines in their prevention. Internationally, he is a member of Working Groups for the WHO Strategic Advisory Group of Experts on Pertussis and Pneumococcal vaccines.

Associate Professor Peter Richmond

Peter Richmond, MB BS (UWA) , MRCP(UK), FRACP, is Associate Professor at the School of Paediatrics and Child Health, University of Western Australia and the Head of Division, Vaccine Trials Group and the Head of Department of Clinical Research and Education, Child and Adolescent Health Services. He is the Deputy Chair of the Australian Technical Advisory Group on Immunisation (ATAGI).

1. Clinical perspective: Prof Paul Torzillo

Summary

- Diagnosis of pneumococcal disease remains difficult.
- Some evidence suggests that Serotypes associated with an increased risk for death are characterised by high carriage prevalence, low invasiveness, and are more heavily encapsulated.
- Early antibiotic use has an impact on outcomes.
- Combination therapy in severe disease improves outcome

Diagnosis

- Although pneumococcal disease has been studied for many years, precise diagnosis remains difficult.
- Difficulties with diagnosis are largely because:
    - there is no gold standard for diagnosis of non-invasive disease,
    - in developed countries, positive blood culture is uncommon
    - the proportion of non-bacteraemic pneumococcal pneumonia is unknown, with only weak and dated data currently available
    - there is currently no gold standard for diagnosis with which to compare newer diagnostic techniques.
- Many traditional study abstracts describe rates of pneumococcal disease in community-acquired pneumonia that are considerably higher than the rates of unequivocal, confirmed pneumococcal disease reported in the full details of the study. The true incidence of the disease is unknown.

Diagnostic tools

- Blood cultures are still a very important diagnostic tool; however, they are not positive very often.
- Sputum culture has uncertain sensitivity and specificity.
- Much work has been done with serum antibodies to pneumolysin and capsular polysaccharide. While this work has been interesting from an epidemiological perspective, it has limited use in the diagnosis of an individual patient. This is also the case with antibodies to pneumococcal choline binding protein A.
- The test probably used most commonly now in high income countries is the urinary antigen detection test. Approximately 20 studies have been conducted on the performance of urinary antigen tests in adults. The studies used a variety of microbiology techniques as the gold standard, including positive blood cultures, sputum cultures and gram stains. The sensitivity and specificity ranges reported are variable. As it is so difficult to establish a gold standard, it is not really possible to determine the sensitivity and specificity of the test, although the specificity appears to be higher than the sensitivity.

- One study [1] used real-time PCR tests to demonstrate an association between genomic bacterial load and the severity of pneumococcal pneumonia.

Serotypes

- A meta-analysis [2] of 7,322 adults and 903 children with pneumococcal pneumonia showed:
    - a decreased mortality rate associated with serotypes 1, 7F and 8
    - an increased mortality rate associated with serotypes 3, 6A, 6B, 9N
    - results were similar in children and adults
    - results were similar across Europe, the US and Africa, providing evidence that serotype is a factor in outcome for this condition.
- Some evidence suggests that serotypes associated with an increased risk for death are characterised by high carriage prevalence and low invasiveness, and are more heavily encapsulated.

Mortality

- Many reviews of mortality in pneumococcal pneumonia state that mortality has not changed significantly in the last 30 years. Although it is clear that mortality rates remain high, it is also important to note that there are many varying factors that determine the mortality results in different studies.
- Much mortality from community-acquired pneumonia appears to be associated with septic shock.
- Clinically, there are two types of mortality syndromes in people with pneumococcal pneumonia in intensive care units:
    - Those with septic shock – often young with no comorbidities.
    - Those with severe pneumonia – often elderly with comorbidities and a prolonged course of ICU illness often with developing multi-organ failure.

- **Treatment issues**

Antibiotics

- Antibiotic use makes a difference to outcome. Data from the Royal Prince Alfred Hospital in Sydney (1833–1952) show that with the introduction of antibiotics, mortality from lobar pneumonia more than halved.
- Early antibiotic use seems to be important. This is supported by two retrospective studies [3, 4] involving large patient numbers in community-acquired pneumonia, which showed an impact of early antibiotic therapy on hospital mortality. Another retrospective study [5] on septic shock showed that delivering antibiotic therapy within the first hour of hypotension resulted in an improved survival.
- The issue of penicillin resistance and its impact on mortality has generated much discussion in the literature. Overall, the data suggest that high-dose penicillin will be effective with an MIC less than 2. There is one recent systematic review that casts doubt on this; however, criticisms exist regarding the methodology used in the review.
- The role of combination versus single antibiotic therapy in pneumococcal disease has also been studied extensively. A prospective study [6] of 844 patients with blood-culture-positive pneumococcal pneumonia found combination versus single antibiotic therapy resulted in a significant difference in mortality in critically ill patients (14-day mortality: 23.4% versus

55.3%; p=0.0015). However, in non-critical patients, outcomes were not significantly different for combination or single drug therapy.

Activated protein C

- Activated protein C is a product that is reduced in cases of sepsis. It has also been demonstrated to have an important role in protecting against sepsis.
- A number of studies have examined the use of activated protein C in the treatment of sepsis. While there was initial early enthusiasm for its therapeutic use, concerns now exist regarding both adverse effects and lack of positive impact on outcomes. Currently, the latest data analyses suggest activated protein C has no overall beneficial effect in sepsis.

Corticosteroids

- The literature on the role of corticosteroids is still inconclusive. In cases of persistent hypotension or early ARDS, steroids are a reasonable option; however, there is no unequivocal evidence base for this approach.

Mode of respiratory support

- In cases of severe septic shock associated with pneumococcal disease in the intensive-care setting, a major challenge is maintaining oxygen delivery and reducing ventilator associated lung injury. Extracorporeal membrane oxygenation (ECMO) is one potential strategy for overcoming this problem.. Although there is no level I evidence to support its use in severe pneumonia there has been encouraging local experience utilizing ECMO for retrieval of patients with severe respiratory failure from peripheral centres to tertiary care centres. [7]

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2. Disease incidence in Australia: Prof Peter McIntyre

Summary

- The Australian 23vPPV coverage rate in people ≥ 65 years is 54.4%.
- 23vPPV coverage rates are considerably higher in people aged > 75 years, compared with those aged 60–74.
- Rates of IPD in non-Indigenous adults appear to change from the time when a funded national program for 23vPPV (in people aged ≥ 65 years) and 7vPCV in infants commenced (2005).

Australian pneumococcal vaccination schedule

- There are differences in the schedules for Indigenous and non-Indigenous people (both children and adults).
- Several changes have been made to the schedules over time. In 1998, Victoria decided to fund a polysaccharide pneumococcal vaccine program for adults aged ≥ 65 years. Fully funded national programs for older adults (≥ 65 years) and infants were simultaneously implemented in 2005.

Data sources

Pneumococcal vaccination coverage

- National Computer Assisted Telephone Interview (CATI)
    - Conducted every 2 to 3 years.
- New South Wales-based survey
    - Includes more detailed data about younger age groups.

IPD cases

- Only includes data from sterile-site isolates. All derived from the National Notifiable Diseases Surveillance System (NNDSS).

23vPPV coverage

- An Australian Institute of Health and Welfare (AIHW) survey provides data about those who report receiving pneumococcal vaccine within the previous 5 years [1]. The data show:
    - coverage rates of 54.4% in people ≥ 65 years
    - by age, coverage in those aged > 75 years is approximately double that of less elderly adults.
- The New South Wales survey [2] shows that:
    - in those aged < 65 years, coverage is low
    - coverage rates are considerably higher in people aged > 75 years, compared with those aged 60–74.

Rates of IPD in non-Indigenous adults

- The rates of IPD appear to change from the timepoint when a funded national program for 23vPPV (in people aged ≥ 65 years) and 7vPCV in infants commenced (2005).

Rates of IPD due to 7v serotypes in non-Indigenous adults

- Rates of IPD due to 7v serotypes have fallen in adults aged 50–64 years, and in those aged ≥ 65 years.

Analysis across serotypes

- We compared the first 2-year period from when the funded pneumococcal vaccine programs were introduced (2005–2006) and the following 3-year period (2007–2009) with the baseline period of 2002–2004. The analysis found:
    - significant reductions in IPD in the 2007–2009 and 2005–2006 periods, in people aged < 65 years, < 70 years and > 70 years
    - the most impressive reductions in disease were in the 7v serotypes. This may be attributed to the maturation of the conjugate vaccine program, leading to a disease reduction in these serotypes across other age groups.
- When examining the proportion of IPD cases accounted for by various serotypes, it appears that there has been an increase in those associated with 19A.
- There may be some kind of serotype-replacement-sparing effect associated with the 23v vaccine, especially with respect to serotype 19A, which is present in 23vPPV but not 7vPCV.

Conclusions

- It does not appear that 23vPPV has had an impact on invasive disease that is independent of what has been observed with 7vPCV. However, the available data surrounding this issue are coarse and limited.
- It is possible that a serotype-replacement-sparing effect is associated with 23vPPV.

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3. 23vPPV effectiveness: Dr Rob Menzies (*unpublished work*)

Summary

- The indirect cohort and screening methods were used to evaluate whether 23vPPV is effective in the Australian setting.
- The indirect cohort method found that 23vPPV is highly effective in younger adults, and that effectiveness decreases with increasing age.
- The screening method found no decrease in vaccine effectiveness in the group aged ≥ 75 years.

This talk contains unpublished work (pending publication). For this reason it is not included in this report.

4. Adults at high risk for pneumococcal disease: Prof Peter Richmond

Summary

- Comorbid medical conditions significantly increase the risk of IPD in adults of all ages.
- Indigenous adults have a significantly increased risk of IPD, even when accounting for risk-factor prevalence.
- Immunisation coverage in at-risk populations is poor.
- Evaluating risk factors based on the degree of compromised immune function may determine those most likely to benefit from PPV.

Recommendations for PPV

- The *Australian Immunisation Handbook* (9th edition) [1] recommends vaccination with 23vPPV for:
  - all aged ≥ 65 years
  - Aboriginal and Torres Strait Islanders aged ≥ 50 years
  - those with chronic illness leading to an increased risk of IPD:
    - chronic pulmonary and cardiac disease
    - chronic liver disease and alcoholism, diabetes
    - immunocompromised people (HIV, haematological malignancies, organ transplantation, immunosuppression)
    - functional or anatomic asplenia
    - chronic renal disease
    - CSF leak
  - tobacco smokers.
- It may be valuable to evaluate risk factors based on the degree of compromised immune function, in order to determine those most likely to benefit from PPV.
- Although the following categorisations are somewhat contentious, conditions involving a lesser degree of compromised immune function may include:
  - chronic pulmonary and cardiac disease
  - chronic liver disease and alcoholism, diabetes
  - CSF leak (including cochlear implants), anatomical asplenia
  - tobacco smokers.
- Conditions with a significant degree of compromised immune function may include:
  - HIV
  - haematological and generalised malignancies
  - organ transplantation and immunosuppression
  - functional asplenia
  - chronic renal disease.
- The current data indicate that the efficacy of PPV is reduced in the immunocompromised group, and that those with conditions involving a lesser degree of compromised immune function may benefit more from PPV. However, the immunocompromised group is actually at a higher risk of disease.

IPD rates according to risk factor

- The incidence of IPD in the general population is approximately 5–10 per 100,000.
- If effective vaccines are available, it is important to prevent cases and target at-risk populations with these vaccines. Historically, vaccination coverage in those with medically at-risk conditions has not been adequate.
- IPD rates in immunocompromised groups are particularly high:
    - HIV: 5.5–10/1000 person years
    - Haematological malignancy: up to 26/1000 person years
    - Splenectomy: 0.3/1000 person years (post-traumatic); 3.3/1000 person years (with haematological disorders).

Prevalence of risk factors in IPD cases in Australian adults (≥ 15 years)

- In Dr Menzies' analysis of 5,553 cases of IPD notified between 2001 and 2005:
    - risk factors were present in 43% of the population. However, further analysis shows that these figures are weighted towards the elderly, with 33.9% of those aged 15–64 reporting risk factors, compared with 54.3% of those aged ≥ 65 years. Therefore, it is important to drill down further when considering risk factors and vaccine policies
    - Indigenous adults represented 10% of the overall cohort. They were less represented in the group aged ≥ 65 years (14% aged 15–64 years; 1% ≥ 65 years), possibly due to shorter life expectancies. Risk factors were more prevalent in those aged ≥ 50 years (54%) compared with those aged 15–64 years (32%).

Tobacco smoking as a risk factor for IPD in adults

- Cigarette smoking accounts for approximately 50% of IPD in otherwise healthy adults [2, 3].
- The risk of developing IPD is 4.1 times greater (95% CI 2.4–7.3) for smokers than non-smokers aged 18–64 [4]. This increased risk is irrespective of any other risk factors present, so it creates an additive effect.
- Smoking also increases the risk of IPD among other at-risk groups, including immunocompromised persons.
- Smoking is a significant risk factor in Indigenous adults.
- Smoking prevention is an obviously important health strategy, as is pneumococcal vaccination in smokers.

IPD in Indigenous people

- The incidence of IPD in Indigenous people is significantly higher than in non-Indigenous people, even after accounting for the increased prevalence of risk factors. It is therefore important to consider that the risk of disease may depend on the particular community in which people live.
- The increased risk of IPD in Indigenous adults compared with non-Indigenous adults begins at approximately age 30, according to data from Western Australia [5].
- Data from Western Australia show that IPD rates have increased in young Indigenous adults, despite very successful reductions in vaccine-type disease in children and little replacement.

- Analysis of Indigenous serotype distribution by vaccine type and age group (Western Australian data, 2010) shows:
  - a decrease in 7V serotypes
  - perhaps some increase in non-vaccine serotypes
  - a significant increase in serotypes represented in 23vPPV, particularly serotypes 1 and 12F. Interestingly, 19A was not represented in people aged ≥ 5 years.
- It is important to consider whether the results for 23vPPV represent vaccination failures, or simply a failure to vaccinate. It is very difficult to accurately assess coverage, particularly in these populations.

Future directions for vaccines

- A vaccine with improved effectiveness in immunocompromised people would be an advantage.
- It is very difficult to make vaccine policy recommendations for specific groups, based on the current data available. We should be considering studies to address this issue.
- It is difficult to compare the differences between the pneumococcal polysaccharide vaccine and conjugate vaccine in high-risk populations.
- We will need to consider in the future if there is a role for a vaccine that can prevent NTHI carriage and/or disease.
- We need to consider how schedules for PCV and PPV can improve our ability to prevent disease, particularly in immunocompromised groups.
- It will be interesting to see the role of pneumococcal protein vaccines in the future.

Conclusions

- Comorbid medical conditions significantly increase the risk of IPD in adults of all ages.
- Indigenous adults have a significantly increased risk of IPD, even when accounting for risk-factor prevalence.
- Immunisation coverage in at-risk populations is poor. We need to develop strategies to ensure healthcare professionals are aware of the need to vaccinate these groups. A whole-of-life vaccination register may be a useful tool.
- Need to consider the role of new-generation 10v and 13vPCV for adults with chronic medical conditions.

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Panel and questions

Q. Australia is in a unique position in that we introduced adult and infant vaccination programs at the same time. This makes it difficult to evaluate the impact of the programs. When the programs were introduced, about 70% of disease in adults was caused by the seven serotypes in the conjugate vaccine. Therefore, numerically, the other serotypes will be causing much less disease. What is the significance of any fluctuations in the other serotypes?

Prof McIntyre: This raises the question as to whether part of the change in 7v types that are also contained in the 23v vaccine in older adults could be due to direct effects of the 23v vaccine. A major argument rejecting this idea is that the pattern of serotype distribution in older adults who are targeted for 23v has channelled infants, so we have observed considerable increases in 19A amongst older adults who are targeted for 23v as well as in infants.

In addition, we did not have a 'blank slate' to begin with – there was a low-level, staccato-type coverage occurring in the adult population prior to full vaccine funding. There was substantial coverage prior to 2005 in places such as Victoria, where there was already a funded program in non-Indigenous adults. It would be useful to build on the earlier work of Ross Andrews, which compared the impact of Victoria's program with New South Wales where there was no program in place (prior to 2005).

Q. Can you please comment on the situation with vaccination rates in the US?

Dr John Grabenstein: In people aged ≥ 65 years, vaccination rates for the 23v vaccine in the 1980s were approximately 30%. By 2000, vaccination rates had increased to approximately two-thirds of this population, and this rate has remained at a plateau ever since.

In the group aged < 65 years with risk factors, vaccination rates are currently at approximately 30%, which is where they have been for quite some time.

Q. How does surveillance vary across Australia? Does vaccination uptake vary across regions?

Dr Menzies: Coverage is fairly uniform across the country, with no great difference between urban and rural regions.

The Enhanced IPD Working Group has worked hard to standardise surveillance. From approximately 2002, the data are reasonably high quality. Notification by laboratory is now a fairly streamlined process, so we can be reasonably confident that data are complete.

Prof Richmond: When evaluating the quality of our surveillance, blood cultures are an important consideration, given that they represent the only reliable diagnostic method currently available. The availability of broader spectrum oral antibiotic agents in general practice should also be considered. Generally, physicians would not take a blood culture in general practice but they might in EDs. The use of antibiotic agents prior to taking a blood culture may affect the result.

Prof McIntyre: The quality of surveillance can also have an effect on the interpretation of data. If surveillance is significantly increased after the introduction of a vaccine and more

isolates are captured, this could be interpreted to say that the vaccine has not been effective. It is therefore very important to consider the quality of the surveillance when making evaluations.

Q. What has been the impact of immunisation programs on community-acquired pneumonia?

Dr Menzies: We have examined hospitalised pneumonia in children and older age groups. This analysis mainly focused on the impact of the conjugate vaccine, and we did see an impact on children in Australia. There was no impact visible on adults.

There has not really been a chance to determine if there has been any impact from the polysaccharide vaccine. This is because coverage with the polysaccharide vaccine has slowly increased, with the impact of the conjugate vaccine also in the background.

Q. From a clinical perspective, how big a problem is antibiotic resistance for pneumococcal disease?

Prof Torzillo: A 2007 Australian survey showed there were approximately 2,000 isolates and 17% of them were invasive. Overall, 2% of isolates had MICs > 2, which does not indicate a huge concern for intravenous treatment of pneumococcal pneumonia.

In terms of hospitalised patients, there are two key issues. Firstly, the lack of impact of penicillin resistance on outcome in the Spanish study depended on administering 12 million units of penicillin per day, and there are many places in Australia where doses would be lower. Secondly, most patients who are sick enough to be admitted to hospital will not be given penicillin alone; they will be administered empiric therapy. By the time it is determined if a patient has pneumococcal disease, the critical timeframe for delivering antibiotics may be already over. The debate around penicillin efficacy and the impact of resistance is not particularly relevant for people in developed countries with reasonable hospital access.

Prof McIntyre: Data primarily from NSW showed that serotype 19A was not really around prior to the use of 7v vaccine, and that while there were substantial levels of antibiotic resistance, this occurred mostly in serotype 9V. Since the introduction of 7v vaccine, 19A has increased while 9V has decreased; however, the 19A is highly antibiotic resistant at a level comparable to that of 9V pre-vaccine.

Q. What are the needs for surveillance and data collection in the future?

Dr Menzies: The NNDSS is over-burdened. We need increased resources to fund active follow-up, to clean data and to provide analysis.

Prof Richmond: eHealth software in general practice may provide a simple solution for data collection.

Prof McIntyre: Laboratory audits may be an option for improving surveillance and data collection.

Comment from floor: The electronic health record currently in development by the Australian Government may be a potential tool for capturing vaccination data. However, it may be difficult for researchers to gain access to this information.

Q. What is the relationship between influenza and pneumococcal disease? In the pandemic of 2009, what proportion of patients do you feel had an underlying bacterial infection, or was it mainly a primary viral infection?

Prof Torzillo: Our diagnostic tests are not good enough to confidently answer the question. Patients who were critically ill and admitted to intensive care had a syndrome of overwhelming primary respiratory failure without sepsis. I think the majority of these patients had a primary viral infection.

Day 2: 30 August 2011

Topic: Immunogenicity, efficacy and effectiveness
Chair: Prof Peter McIntyre

Speakers (Day 2: 30 August 2011)

Associate Professor Ross Andrews

A/Professor Ross Andrews is an epidemiologist with major research interests in vaccine preventable diseases and Indigenous health. He is the Head of the Child Health Division at Menzies and leads the Immunisation Team.

He played a major role in the establishment of enhanced surveillance for invasive pneumococcal disease in Victoria and has been invited to contribute to the revision of recommendations related to the use of polysaccharide pneumococcal vaccine for the 9th edition of the Australian Immunisation Handbook.

Professor David Goldblatt

David Goldblatt is Professor of Vaccinology and Immunology and Head of the Immunobiology Unit at the Institute of Child Health, University College London (UCL), UK.

Professor Goldblatt regularly advises the World Health Organization (WHO) on bacterial conjugate vaccines and is a Director of the WHO Reference Laboratory for Pneumococcal Serology at UCL. He was also a member of the UK Department of Health Joint Committee on Vaccines and Immunisations from 1997 to 2007.

Dr John Grabenstein

John Grabenstein, PhD, is Senior Medical Director for Adult Vaccines, Merck and Co. in Pennsylvania, US.

A pharmacist with over 30 years of experience, Dr Grabenstein has published extensively on topics including immunisation, public health and leadership. Currently, Dr Grabenstein provides scientific advice to Merck, with a particular focus on vaccination initiatives for pneumococcal disease and herpes zoster.

Speakers (Day 2: 30 August 2011) continued

Dr Iman Ridda

Dr Iman Ridda is a NHMRC Post-doctoral Research Fellow at the SPHCM, UNSW and Immunization research coordinator at NCIRS.

She has 7 years of experience in immunization research, mostly in clinical trials in older adults. She completed her doctoral work, supported by a University Postgraduate Award in 2009 at the University of Sydney in an NHMRC funded project 2005 on pneumococcal vaccination in frail elderly, which led to recommendations about pneumococcal immunisation in this group and 10 peer reviewed publications.

Dr Robert Menzies

Rob Menzies, BAppSc (Applied Bio), MPH, PhD, is an epidemiologist and leads the NCIRS surveillance unit.

He is an acknowledged expert in the field of vaccine preventable disease and vaccination policy for Aboriginal and Torres Strait Islander people. He is a technical member of the Pneumococcal Working Party of the Australian Technical Advisory Group on Immunisation, and his work has been used by working parties in their policy recommendations for pneumococcal, influenza and hepatitis A vaccination. He manages the preparation of regular surveillance reports on vaccine preventable diseases, adverse events following immunisation and vaccination coverage, and the application of advanced epidemiological methods to public health aspects of immunisation.

Associate Professor Kristine Macartney

A/Professor Kristine Macartney, MBBS, BMedSci, MD, FRACP, is the deputy director of Government Programs at NCIRS and a paediatric infectious diseases consultant at Children's Hospital Westmead.

She is a technical editor of the Australian Immunisation Handbook and a member of the Advisory Committee on the Safety of Medicines of the Therapeutic Goods Administration. She has a strong track record in all areas of vaccine preventable disease research, including vaccine safety and translation of evidence into policy and practice.

1. Cochrane Review – Vaccines for preventing pneumococcal infection in adults: A/Prof Ross Andrews

Summary

- The 2008 Cochrane Review found polysaccharide vaccines were effective in preventing IPD (any type), with vaccine efficacy of 74% (54%, 85%), but did not find evidence of benefit against pneumonia (all causes) and mortality (all causes).
- An updated analysis (yet-to-be published, containing three new trials) indicates the position on vaccine efficacy will not change significantly from the 2008 review.

Updated Cochrane Review (Moberly *et al.* 2011, unpublished)

- Utilised the same methodology as 2008 review (Moberley, 2008) [1] with an updated search strategy and incorporated the Cochrane Risk of Bias tool in the assessment.

Overview of methodology

- Intervention:
    - Randomised controlled trials of incorporating vaccination of adults aged 16 years or more with any pneumococcal polysaccharide vaccine. Excludes studies limited to HIV-positive participants.
- Three primary outcomes:
    - IPD (any type)
    - Pneumonia (all causes)
    - Mortality (all causes)
- Each assessed within population sub-groups:
    - Adults in low-income countries
    - Adults with chronic illness in high-income countries
    - Adults in high-income countries.
- Controversially, non-randomised studies were also included for the IPD endpoint. This was undertaken as a separate analysis.

Results

- Three new randomised controlled trials were identified since the last review:
    - Maruyama 2010 [2] (1,006 nursing-home residents): IPD, pneumonia
    - Kawakami 2010 [3] (786 participants with chronic illness): pneumonia
    - Furomoto 2008 [4] (191 participants with chronic illness): pneumonia, mortality.
- Like the 2008 review, the updated review found polysaccharide vaccines were effective in preventing IPD (any type). However, benefit against pneumonia (all causes) and mortality (all causes) was not demonstrated. Preliminary results from the pooled data from the randomised controlled trials showed:

- o IPD (any type): vaccine efficacy of 74% (95%CI: 55%, 86%, I^2 0%).
- o Pneumonia (all causes): vaccine efficacy of 28% (95%CI: 7%, 44%, I^2 85%)
- o Mortality (all causes): vaccine efficacy of 10% (95%CI: -9%, 26%, I^2 69%).
- There was a high level of heterogeneity for the all-cause pneumonia and all-cause mortality outcomes (I^2 85% and 69% respectively) with no overall benefit demonstrated against either. In contrast, the population sub-group that included four studies from low income countries (South African Gold Miners [5, 6] and Papua New Guinea Highlanders [7]) that were conducted in the 1970's showed a VE of 46% (95%CI: 33%,56%) and a low level of heterogeneity (I^2 10%).
- An update on vaccine effectiveness assessed from non-randomised studies was not presented. The 2008 review found VE against any IPD was 52% (39%, 63%).

The Huss meta-analysis

- A meta-analysis published by Huss *et al.* 2009 [8] found similar results for pneumonia and mortality as the 2008 Cochrane Review, but did not find polysaccharide vaccines to be effective in IPD. The Huss meta-analysis argued that this was a result of the quality of studies included in the review. The update of the Cochrane Review conducted in 2011, incorporated a risk of bias assessment but still found VE against IPD. The critical difference between the two meta-analyses remains the choice of studies included and omitted in the reviews.

Discussion

- In A/Prof Andrews' view, the position on vaccine efficacy will not be significantly different in the updated Cochrane Review in comparison with that published in 2008.
- All of the randomised controlled trials for IPD were re-assessed for risk bias, and only four trials received a rating of a low risk. A pooled analysis of these trials still gives evidence of vaccine efficacy against IPD.
- IPD sub-group analysis of vaccine efficacy:
  - o Adults in low-income countries: benefit demonstrated, however, it only included one study
  - o Adults in high-income countries with chronic illness: inconclusive
  - o Adults in high-income countries: benefit demonstrated.
- Pneumonia (all causes) sub-group analysis of vaccine efficacy:
  - o Adults in low-income countries: vaccine efficacy of 46% (33%, 56%). Benefit demonstrated
  - o Adults in high-income countries with chronic illness: vaccine efficacy of 7% (-19%, 27%). No benefit demonstrated from these data
  - o Adults in high-income countries: vaccine efficacy of 29% (-12%, 55%). No benefit demonstrated from these data
- Mortality (all causes) sub-group analysis of vaccine efficacy:
  - o Adults in low-income countries: benefit demonstrated, however, it only included one study
  - o Adults in high-income countries with chronic illness: no benefit demonstrated
  - o Adults in high-income countries: no benefit demonstrated.
- A number of caveats remain for both the update of the review and for the previous review. Not least among these is the number of different polysaccharide pneumococcal vaccines that are encompassed within this review. These include: the current the 23 valent vaccine,

which contains 25μg of purified capsular polysaccharide of each serotype; its predecessor, the 14 valent vaccine, which had 50μg of each serotype; and those used in the earlier studies which ranged from a 2 valent – 13 valent vaccine containing 50μg of the respective serotype.

Responses to questions

- It is a big ask to expect a pneumococcal vaccine to prevent all-cause pneumonia when the proportion of pneumonia that may be due to the pneumococcus, and particularly to the types contained within the vaccine, may vary widely. It is not surprising that the Cochrane Review could not demonstrate a benefit against all-cause pneumonia across such diverse settings.
- Previous reviews and much of the policy discussions around polysaccharide vaccine have stated that if the vaccine prevents death in areas with high mortality rates (such as Papua New Guinea), it will also be effective in others in high-risk groups (such as the elderly).
- It is difficult to ascertain from the Cochrane Review if there is age-related gradation for vaccine effectiveness. This is because the available data in terms of age of participants is mixed.
- An individual patient data meta-analysis would be extremely valuable in the area of pneumococcal vaccines.

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2. International perspectives on vaccine immunogenicity in adults: Prof David Goldblatt

Summary

- IPD rates are inversely proportional to the ability of blood to kill bacteria.
- Increasing age is a risk factor for pneumococcal disease.
- Superior immunogenicity has not been universally demonstrated for PCV compared with PPV in adults and results vary depending on serotype.
- Populations with routine infant PCV immunisation have observed clear changes in pneumococcal epidemiology. The replacement phenomenon has resulted in an increase in some of the serotypes not in 7vPCV in the elderly. A key issue to consider will be the cost-effectiveness of using 13vPCV in adults in conjunction with a mature infant PCV program that is likely to deliver herd protection.

- Patterns of IPD incidence by age are similar internationally. There are high rates of disease in the very young before rates decline, and then a marked increase in rates from approximately 65 years of age. This pattern is inversely proportional to the ability of blood to kill bacteria.
- The pneumococcus capsule has a critical effect on virulence. Unencapsulated pneumococci tend to be killed easily and to not cause disease. This is because the capsule protects the bacteria from binding complement – as soon as the capsule is lost, complement is able to bind and kill. However, the capsule is also the target for protective antibody. The antibody binds to capsule and has receptor-sites for complement. Phagocytic cells are also important for engulfing and killing pneumococci.
- ELISA is an assay that measures the antibody binding to the capsule. The opsonophagocytic assay (OPA) measures the ability of phagocytic cells to engulf and kill.
- In the very young, it is thought that their increased susceptibility to the disease is due to the absence of antibody.
- In the middle age groups, people have been exposed to pneumococci while growing up and developed immune memory to the pneumococcus. The presence of B cell memory (and possibly T cell immunity too), is the likely basis for protective immunity.
- It is still unclear why the elderly are so susceptible to disease.
- To prevent disease with a vaccine in susceptible individuals, we need to be confident their immune system can make a response.
- A recent study by Simell *et al.* 2011 [1] shows that ageing reduces the functionality of anti-pneumococcal antibodies in unvaccinated individuals. In addition, phagocytes from the elderly (mean age 74 years) have a reduced capacity to kill pneumococci compared with phagocytes from the young (mean age 34 years). Therefore, even if an individual has a good antibody response to a vaccine, a vaccine won't appear effective if the individual's neutrophils aren't working as well.
- A study by Romero-Steiner *et al.* 1999 [2] looked at vaccinating individuals of different ages with polysaccharide vaccine. ELISA and OPA were used to measure responses. ELISA showed that while older people might produce adequate levels of antibody for certain

serotypes, analysis with OPA showed that the killing ability of these antibodies was significantly lower than for younger people. There is therefore a disconnect between antibody measured by binding, and antibody measured by function. Controversy exists surrounding the respective roles of ELISA versus OPA.

- When compared with younger people, the elderly generally show the following responses to pneumococcal polysaccharide vaccines:
    - Binding IgG (ELISA): slightly lower
    - Functional antibody: lower
    - Avidity: lower
    - V region use (genes used by B cells to make antibodies): different and more restricted
    - Mutation rates: less mutated.
- The responses above suggest why the response to vaccine may be sub-optimal in the elderly. Therefore, when considering whether a vaccine is working, a lack of response may not indicate a problem with the vaccine – the problem may lay with the population.
- Prof Goldblatt's team has been trying to develop more specific assays to identify B cells circulating that are specific for pneumococci after immunisation. Interestingly, older individuals have higher numbers of cells. However, when these cells were taken into the lab to produce antibody, they uniformly all produced lower amounts of antibody if they were from older individuals. So while there were more cells circulating, they were less functional. Again, this presents a barrier to adequate immunisation.
- Although immune function deteriorates with age, there remains a huge imperative to prevent increased rates of disease in the elderly.

Purified polysaccharides: profile

- Purified polysaccharides are associated with the following characteristics:
    - T cell independent response
    - Poor B cell response below 2 years of age
    - Isotype restricted at any age (IgG2)
    - No memory induced at any age
    - Hyporesponsiveness with repeated doses.

Pneumococcal vaccination policies

- In spite of concerns regarding effectiveness, the recommendations around the world for the use of polysaccharide vaccine in people aged ≥ 65 years are almost universal. Almost every country in Europe has a vaccination policy for people aged ≥ 65 years (exceptions are France and the Netherlands). However, in spite of these recommendations, data show that the coverage is quite low (Eurosurveillance 2005) [3].
- Healthcare professionals working with patients 'in the field' may be skeptical about the efficacy of 23vPPV. In addition, confusion exists about the role of the conjugate vaccine.

7vPCV

- The conjugate vaccine has 7 serotypes. The amount of antigen is only 2μg for most of the serotypes, except for 6B (4 micrograms). The polysaccharide vaccine, in comparison, has 25μg for each of the 23 serotypes in the vaccines .
- Importantly, the conjugate vaccine has a protein carrier. Proteins can be taken up and presented by B cells to T cells, which provide help to the B cell. This results in cytokine

release and up-regulation of molecules. Isotype switching and affinity maturation occurs, inducing antibodies (at all ages). It is also thought that memory is induced at any age.

- A key feature of the conjugate vaccine is that it overcomes poor immunogenicity in young infants, and is therefore highly effective.
- A study (de Roux *et al.* 2008) [4] compared pneumococcal conjugate polysaccharide and free polysaccharide vaccines. After two doses of conjugate vaccine, there was no improvement in memory in adults. Therefore, the idea that the conjugate vaccine would be far superior in adults needs to be reconsidered.
- A study by Goldblatt (Goldblatt *et al.* 2009) [5] compared the immunogenicity of 7vPCV with 23vPPV in adults aged 50–80 years. Subjects were stratified further into three age groups (50–59 years, 60–69 years and 70–80 years) to look for any different effects of the vaccines within the sub-groups. The study found:
  o that the conjugate vaccine was not superior to the polysaccharide vaccine in every serotype, and that in 19F, the polysaccharide vaccine was actually superior. This challenges the notion that 7vPCV is superior to 23vPPV in every instance
  o that when considering persistence of antibody 12 months after a single dose of 7vPCV or 23vPPV, the only statistically significant serotype was 23F. Therefore, over a short period of time, the differential between polysaccharide and conjugate vaccines was lost
  o that after a second dose of 7vPCV or 23vPPV administered 6 months after an initial dose of conjugate, there was no significant difference in vaccine effect.
- A summary of head-to-head immunogenicity studies comparing the conjugate vaccine with polysaccharide does not conclusively show that the conjugate vaccine is superior in the elderly. In several studies responses to the vaccines are similar with some serotype responses (eg 19F) higher in polysaccharide recipients,
- Two studies of Baxendale *et al.,* 2010 [6, 7] could not find a difference in circulating or memory B cells when comparing polysaccharide and conjugate vaccines in elderly patients athough a recent study (Clutterbuck *et al.* 2012) has detected memory B cells in the circulation after PCV and not after PPV [8]
- There is currently only one study (French *et al.* 2010) that indicates the conjugate vaccine may be more effective than the polysaccharide in adults, and this study is in a specialised population – HIV +ve adults in Africa [9].
- Prof Goldblatt's evaluation of the use of pneumococcal conjugate vaccines compared with pneumococcal polysaccharide vaccines in adults showed:
  o better immunogenicity has not been universally demonstrated for PCV
  o there is no real evidence of enhanced immune memory in adults for PCV
  o there is no evidence as yet of better/longer lasting protection in the elderly for PCV
  o there is the ability to use repeated doses of PCV (no hyporesponsiveness following second dose)
  o superior efficacy with PCV has been demonstrated in a population with HIV.

The impacts of the conjugate vaccine

- There clearly are changes in pneumococcal epidemiology in populations with routine infant PCV immunisation.
- A key issue to consider will be the cost-effectiveness of using 13vPCV in adults in conjunction with a mature infant PCV program that is likely to deliver herd protection.
- PCV can prevent you from acquiring the pneumococcus from other individuals. Effectively, this provides indirect protection. In high-income countries, the major pool of pneumococci in

the nasopharynx exists in the very young (< 5 years). Adults in high-income countries tend to have rates of carriage < 10%. Reducing pneumococci transmission has a profound effect on IPD rates in adults.

The UK experience

- The UK analysed the effect of 7vPCV in the US before beginning its own infant vaccination program in 2006. The result has been a significant reduction in IPD in the 7vPCV serotypes in children < 2 years. There has also been an indirect effect to reduce IPD in the 7vPCV serotypes in the elderly (> 65 years) since the introduction of the infant vaccination program. Overall, there has been approximately a 20% reduction in IPD in the elderly.
- The replacement phenomenon has resulted in an increase in some of the serotypes not in 7vPCV in the elderly.
- 13vPCV was introduced in October 2010. In children < 2, there has already been a reduction in the amount of disease for the serotypes that are in 13v but not in 7v. 13vPCV is already having an impact on replacement disease in children. In the elderly, there also appears to be early evidence of an indirect effects reducing disease.

Recent vaccination policy discussions in the UK

- In March 2011, a letter was distributed from the UK Department of Health stating that the committee was considering removing the aged-based recommendation for polysaccharide vaccine in the elderly. The committee felt there was an absence of polysaccharide efficacy at the population level. Possible explanations for this situation include the following:
  - o Coverage only increased modestly when the recommendation to provide the vaccine to all ≥ 65 years was initially made. Therefore, any potential impact of the vaccine was possibly already there, because the vaccine had already been given to the high-risk elderly
  - o Not all IPD cases at the time of vaccine introduction were due to 23v serotypes.
- After some consideration, the committee decided that:
  - o revised figures show efficacy for up to 5 years in those with no risk
  - o a revised cost-effectiveness analysis showed an age-based vaccination program was probably more cost-effective than one that was risk-based.
- There was therefore no change to the recommendation. The committee noted that it will be important to keep changing epidemiology under close review to assess the indirect effect of 13vPCV.

The future for pneumococcal conjugate vaccines in the elderly

- A study from the Netherlands (Hak *et al.* 2008) [10] will analyse the efficacy of 13vPCV in elderly adults. The study will use a new, highly sensitive serotype-specific urine assay to make the diagnosis of serotype-specific pneumococcal disease in pneumonia. Given the current difficulties with accurate diagnosis, the prospect of the assay is intriguing and exciting.
- It is important to recognise that we are currently using a paediatric formulation of the conjugate vaccine. We need to consider whether the amount of antigen in the current 7v, 10v or 13v formulations is ideal for adults.

The role of non-capsule-based vaccines

- Non-capsule-based vaccines may represent the 'holy grail'.
- An ideal protein vaccine for pneumococci may:
    o be a ubiquitous protein that all pneumococci express
    o be expressed stably
    o be expressed on the surface
    o induce a protective immune response.

Conclusions

- Increasing age is a risk factor for pneumococcal disease.
- Improved vaccines are required to prevent pneumococcal pneumonia in adults.
- Widespread PCV is impacting on the epidemiology of disease in adults
    o This may lead to the need for new strategies/vaccines to prevent disease.

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3. 23-valent Pneumococcal Polysaccharide Vaccine (23vPPV) – evidence after repeat dosing in adults: Dr John Grabenstein

Summary

- Results differ between the two most applicable studies of clinical effectiveness over long intervals after the first dose of 23vPPV.
- 23vPPV antibodies in adults persist above unvaccinated baseline for 5 to 10 years in most studies.
- Revaccination after 5 to 10 years consistently yields increases in antibodies.
- Adverse events after 23vPPV revaccination are more frequent than after primary vaccination in most studies, yet typically self-limited.

23vPPV adult revaccination policies worldwide, August 2011

- A global review of selected 23vPPV adult revaccination policies shows:
  - the majority of countries recommend selective revaccination, particularly in people with risk factors. The most common interval recommended for revaccination is 5 years after the initial dose
  - notable exceptions include calls for routine revaccination in Norway, Slovakia, Sweden, and Switzerland, and by the European Geriatric Medical Society (EUGMS)
  - until recently, Australia recommended routine revaccination after 5 years. This recommendation was suspended by the TGA in April 2011
- Routine revaccination practices are common in most countries for tetanus-diphtheria toxoids, yellow fever vaccine, and other vaccines to sustain antibody levels

Clinical protection against pneumococcal disease by 23vPPV

- The two studies most commonly discussed reached diametrically opposite conclusions:
  - Shapiro *et al.* 1991 [1]:
    - Case-control study reported overall vaccine effectiveness of 56% (42%, 67%)
    - Vaccine effectiveness for immunocompetent people: 61% (47%, 72%; n=808)
    - Vaccine effectiveness for 65–74-year-olds: 71% (30%, 88%; n=213)
    - Vaccine effectiveness declined across five age strata, and as time elapsed (especially beyond 5 years)
    - Authors comment about waning immunity ("quite small for period studied") and cumulative probability of exposure to additional serotypes.
  - Butler *et al.* 1993 [2]:
    - Indirect cohort study reported overall vaccine effectiveness of 57% (45%, 66%; n=2837)
    - Vaccine effectiveness for immunocompetent people ≥ 65 years: 75% (57%, 85%; n=156)

- Vaccine effectiveness did not decline with increasing interval after vaccination:
  - 5 to 8 years after vaccination: 71% (24%, 89%)
  - ≥ 9 years after vaccination: 80% (16%, 95%).

Pneumococcal disease and pneumococcal vaccination

- Pneumococcal disease is difficult to diagnose. It is also difficult to know how much antibody is sufficient to provide protection against disease. No correlate of immunity has been established for pneumococcal vaccines in adults.
- Protection against disease has been linked to circulating antibody levels.
- Following pneumococcal vaccination, serotype-specific antibody levels decline after 5–10 years. A more rapid decline in antibody levels may occur in some groups.

Antibody persistence and response to revaccination: literature review

- Dr Grabenstein presented a literature review of antibody persistence after pneumococcal polysaccharide vaccination (now published in *Vaccine* 2012) [3]. For the purposes of the presentation, the review focused only on:
  - general populations of adults
  - studies with ≥ 3-year intervals between vaccinations
  - 25 µg per antigen formulation
  - contemporary assay methods for immunogenicity methods.
- The literature review yielded 10 articles addressing antibody persistence, seven addressing antibody response to revaccination, and 19 addressing safety of revaccination.
- Summary of <u>antibody persistence</u> after 23vPPV in adults (both IgG and OPA):
  - At study entry, 5/5 revaccinee cohorts had significantly higher antibody concentrations in comparison to vaccine-naïve adults
  - Antibody levels declined progressively as time after vaccination elapsed
  - In 5/10 studies, antibodies persisted 5 to 10 years above baseline level or the level of vaccine-naïve adults
  - In 4/10 studies, antibody levels were less persistent
    - Involve populations of non-ambulatory adults or with host-factor issues
    - 2/4 studies affected by small sample size
  - Covariates: no apparent age or gender effect.
- Summary of <u>response to revaccination</u> with 23vPPV:
  - In 7/7 studies, revaccination after ≥ 5 years yielded significant increases in antibody levels (IgG and OPA)
  - In two studies, peak antibody levels after revaccination were statistically lower than after primary vaccination, although revaccination peaks were still ≥ 2 µg/mL in those studies
    - Involve populations of non-ambulatory adults or with host-factor issues
  - 5/5 studies assessing antibody level at revaccination found it to be inversely associated with response. That is, individuals with low baseline levels were more likely to achieve a higher revaccination peak, and vice versa
  - 2/5 studies found increasing age inversely affected response to revaccination, but 3/5 did not.
- The issue of hyporesponsiveness with revaccination of 23vPPV is dependent on factors such as the time period elapsed between primary vaccination and revaccination (and hence

circulating antibody level at time of revaccination). Health status and capacity to respond to vaccine may also play a role. Hyporesponsiveness is not an all-or-nothing phenomenon.

Safety with repeat dosing of 14vPPV or 23vPPV

- Since the late 1970s, there has been an increased frequency of injection-site reactions (ISRs) reported after revaccination, compared with primary vaccination.
- Several modern studies (with larger subject numbers and longer intervals between doses) also found a higher rate of ISRs among revaccinees, compared with primary vaccinees. However, other modern studies found no difference in the rate of ISRs based on the number of prior doses.
- Three large, linked databases have been used to assess many thousands of vaccinees:
  - Shih (2002) [4]: those revaccinated < 5 years of prior dose were 1.17 times as likely to visit ED and 1.13 times as likely to visit a doctor, compared to primary vaccinees
  - Jackson (2006) [5]: no difference in rate of medical encounters < 2 weeks after third vaccination (0.5%), compared to doses 1 or 2 (0.3% and 0.7%)
  - Snow (1995) [6]: no meaningful difference in hospitalisation rates within 30 days for revaccinees and primary vaccinees.
- Regardless of frequency or relative risk, adverse events after revaccination are typically reported as transient, lasting several days, and resolving with symptom treatment.
- The rate of adverse events is related to the circulating antibody level at the time of revaccination in 7/8 studies.

Conclusions: persistence of effect and repeat dosing with 23vPPV in adults

- Results differ between the two most applicable studies of clinical effectiveness over long intervals after the first dose of 23vPPV:
  - Butler: effectiveness remains consistent over 9 years
  - Shapiro: effectiveness decreases over time.
- Antibody persistence after 23vPPV in adults (both IgG and OPA):
  - Literature indicates that antibody levels persist above unvaccinated baseline for 5 to 10 years in most studies.
  - Exceptions involve populations of non-ambulatory adults or with host-factor issues.
- Response to revaccination – immunogenicity:
  - Revaccination after 5 to 10 years yields increases in antibody levels (IgG and OPA).
  - A consistent inverse association has been demonstrated: if circulating antibody level at time of revaccination is lower, then there is a greater antibody increase (and vice versa)
    - Longer intervals between doses results in lower circulating antibody levels.
- Response to revaccination – safety:
  - Adverse events after 23vPPV revaccination are more frequent than after primary vaccination in most studies.

Table 1. Persistence of Circulating Antibody 3 or More Years after Pneumococcal Polysaccharide 23-valent Vaccination

Lead Author, Year	Reference	N	Age (y) Range, Means	Initial Population (vis-à-vis PPV)	Serologic Observation Point, in Y after Previous Vaccination	Authors' Description of Antibody Level at Study's Serologic Observation Point, in Years After Previous Pneumococcal Vaccination [a]							
						3	4	5	6	7	8	9	10
Musher, 2010	[7]	1,008	50-91 58, 73	Primary vaccinees or vaccinated 3-5 y ago	5			IgG: Both cohorts 2-3-fold > naïve for 7/8 types. Revaccinee level ≈ primary for 8/8 types					
Manoff, 2010	[8]	120	65-88 71	Primary vaccinees or vaccinated 3-5 y ago	5			IgG and OPA: Both cohorts > naïve for 3/3 types. Revaccinee level ≈ primary for 3/3 types					
Musher, 2011	[9]	143	60-93 76	Primary vaccinees or vaccinated 3-5 y ago	10								IgG: Both cohorts > naïve for 7/8 types. Revaccinee level ≈ primary for 8/8 types
Hammitt, 2011	[10]	315	NS 60,63,67	Primary vaccinees or vaccine doses 2, 3, or 4	6-22 (medians 7 and 8)			IgG: Both revaccination cohorts > naïve for 5/5 types. OPA: Both revaccination cohorts > naïve for 3/5 types. IgG and OPA: Revaccinee level > primary for 5/5 types					
Hedlund, 2000	[11]	150	50-85 71	Pneumonia patients given primary vaccination	3	IgG: Near baseline for 6/6 types							
Jackson 1999	[12]	142	50-74 NS	Primary vaccinees or vaccinated ≥5 y ago	5			IgG: Revaccinee baseline > naïve for 2/3 types					
Sankilampi, 1997	[13]	62	65-88 72	Primary vaccinees	3	IgG: 4/6 types > baseline							
Törling, 2003	[14]	61	56-88 75	Pneumonia patients given primary vaccination	3 and 4-7 (mean 5.3)	IgG: 1.5 x baseline value		IgG: Levels < baseline for 6/6 types (yet >2 mcg/ml for 6 of 6 types and >5 mcg/ml for 2 of 6 types)					
Santosham, 2001	[15]	24	~18-40 NS	Primary vaccinees	3-3.5	IgG: 3/3 types did not differ from baseline [a]							
Waites, 2008	[16]	23	25-56 41	Primary vaccinees with spinal-cord injury	5			IgG: For 5 types, 39%-100% ≥ 0.35 mcg/ml					
Konradsen, 1995	[17]	15	50-67 63	Primary vaccinees	5			IgG: 6/6 returned to baseline					

IgG – immunoglobulin G, NS – not specified, OPA – opsonophagocytic activity

a – All three levels at month-37 point > 2.4 mcg/ml and higher than unvaccinated control groups

Table 2. Response to Revaccination with Pneumococcal Polysaccharide 23-valent Vaccine, Where Revaccination Occurred 3 or More Years after Earlier Vaccination

Lead Author, Year	Ref-er-ence	N	Age (y) Range, Means	Initial Population (vis-à-vis PPV)	Interval (y) Between Primary and Revaccination	Authors' Description of Antibody Level after Revaccination at Serology Point, in Years After Previous Pneumococcal Vaccination							
						3	4	5	6	7	8	9	10
Musher, 2010	[7]	1,008	50-91 58, 73	Primary or vaccinated 3-5 y ago	3-5 (median 3.9)	IgG: 8/8 types ↑ in both primary and revaccinees. Peaks [a] comparable for 7/8 (50-64 y/o) and 6/8 (65+ y/o) types [b]							
Manoff, 2010	[8]	120	65-88 71	Primary or vaccinated 3-5 y ago	3-5	OPA: 3/3 types ↑ in both primary and revaccinees. Peaks comparable for 2/3 types							
Musher, 2011	[9]	143	60-93 76	Primary or vaccinated 3-5 y ago	10								IgG: 8/8 types ↑ in both primary and revaccinees. Peaks comparable for 8/8 types
Hammitt, 2011	[10]	315	NS 60,63,67	Primary vaccinees or vaccine doses 2, 3, or 4	6-22 (medians 7 and 8)				IgG and OPA: 5/5 types ↑ in both primary and revaccinees. IgG: Peaks comparable for 4/5 types. OPA: Peaks comparable for 5/5 types				
Jackson, 1999	[11]	142	50-74 NS	Primary vaccinees or vaccinated ≥5 y ago	5-13 (median 6)			IgG: 3/3 types ↑ in both primary & revaccinees. Peaks comparable for 2/3 types					
Lackner, 2003	[18]	67	68-100 86	Vaccinated ≥5 y ago	mean 7.2 ± 2.4			IgG: 7/7 types ↑ at day 30, but 2/7 types 1 year later (with 5/7 types > 2 mcg/ml at year-1 point)					
Törling, 2003	[14]	61	56-88 75	Pneumonia patients given primary vaccination	4-7 (mean 5.3)			IgG: 6/6 types ↑. But 6/6 revaccination peaks lower than primary vaccination peaks (yet 6/6 types >2 mcg/ml before revaccination)					
Waites, 2008	[16]	23	25-56 41	Primary vaccinees with spinal-cord injury	5			IgG: For 5 types, 70%-100% ≥ 0.35 mcg/ml. OPA: 3/3 types ↑	IgG: 1 y later, 57-100% ≥ 0.35 mcg/ml for 5 types. OPA: 2/3 types ↑				

IgG – immunoglobulin G, NS – not specified, OPA – opsonophagocytic activity

a – Peak comparisons refer to serotype-specific comparisons of initial post-vaccination time point (i.e., 1 month after vaccination) for primary vaccinees compared to revaccinees.

b – Serotype-specific peaks were comparable for 7/8 serotypes in 50-64 year-old cohorts, compared to 6/8 in the 65+ year-old cohorts.

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4. Pathways to licensure for extended pneumococcal conjugates – the role of correlates of protection: Prof David Goldblatt

Summary

- Correlates of protection for 7vPCV are essential in the licensure process of new formulations of vaccines. Correlates of protection also potentially address the issue of how much antibody is necessary for protection.
- A consensus value for a correlate of protection for 7vPCV in infants was calculated at 0.35 µg/mL.
- Although correlates of protection for 7vPCV are currently imperfect, they have formed the basis for the licensure of new conjugate formulations, and thus have been essential for moving the field forward.

Defining protective antibody levels

- Strategies for defining protective antibody levels include:
  - Seroepidemiology linked to disease epidemiology
  - Passive infusion of antibody in animals or humans
  - Observations from efficacy trials.

Immune correlate of protection

- The definition of a correlate is the phenomenon that accompanies another phenomenon, is usually parallel to it, and is related in some way.
- The relationship between vaccine efficacy for IPD (% protected) and the distribution of serum antibody concentrations in the vaccinated population can be used to derive the serum antibody protective threshold.
- Determining vaccine efficacy involves looking at the rate of disease in a vaccinated group versus the rate of disease in the control group.
- A reverse cumulative distribution for antibody levels in a population can be used to determine the correlate of protection.

7vPCV

- A pivotal trial from Northern California [1] evaluated the efficacy, safety and immunogenicity of 7vPCV in children.
- The Black trial included a per-protocol analysis for the cases and the controls. The breakdown was 39 cases in the control group and only one case in the vaccine group, leading to a vaccine efficacy result of 97.4%. The fact that there was only one case in the vaccinated group made calculating a correlate of protection problematic.
- When 7vPCV was licensed, there were not efficacy data for all 7 serotypes available. The vaccine was licensed based on aggregate efficacy. Therefore, all the antibody level data were aggregated into a single curve for calculating the projected correlate of protection. The correlate of protection was determined to be 0.2 µg/mL in a US setting. This result was supported by antibody OPA and seroepidemiology data [2].

- However, other studies were investigating the efficacy of PCV in vastly different settings worldwide. It was therefore important to consider whether the correlate of 0.2 µg/mL determined in Californian children would still be applicable in other populations. The levels of pneumococcal antibody required for protection were found to be considerably higher in South African, Gambian, and American Indian populations [3, 4, 5].
- Factors such as very different housing conditions and environments may contribute to the different correlates of protection observed across the world. Different forces of infection are present depending on where people live.
- Data from studies looking at protective pneumococcal antibody levels in different settings were amalgamated with serological data to produce a consensus value for a correlate of protection of 0.35 µg/mL. A consensus value is necessary, as vaccines need to be licensed for universal use.
- Important caveats/assumptions surrounding the correlate of protection for PCV include:
    - The data used looked at IgG after the third infant dose – it did not account for booster doses. This is because almost all cases occurred before the booster, and because the period before the booster carries higher risk
    - Protection is a step function
    - All populations are similar
    - All serotypes are similar
    - Correlate is based on IPD only
    - Correlate does not consider adults.
- A WHO recommendation stated that to achieve licensure, new PCV formulations must undergo a head-to-head study against 7vPCV and demonstrate non-inferiority at the correlate of 0.35 µg/mL.

ELISA and OPA

- Controversy exists regarding the value of ELISA versus OPA. However, in the post-vaccine setting, OPA and ELISA are very well correlated both in adults and children.

Is the correlate relevant to all serotypes?

- Finnish data [6] show that the level of protection from the vaccine differs by serotype.

Is the correlate relevant to other pneumococcal diseases syndromes?

- Due to the huge burden of disease in adults, pneumonia is of particular interest.
- An analysis of PCV efficacy against various endpoints suggests that efficacy is highest for IPD, followed by pneumonia, otitis media and nasopharyngeal carriage. When considering correlates of protection, it seems the level of antibody required for protection is highest for nasopharyngeal carriage, followed by otitis media, pneumonia and IPD.

Is the correlate dependent on the assay used to evaluate a new vaccine?

- The assay used to obtain licensure for Synflorix (GlaxoSmithKline [GSK]) was technically different, which meant that 0.35 µg/mL in the WHO ELISA (non-22F) appeared equivalent to 0.2 µg/mL in the GSK ELISA.

Is the paediatric correlate relevant to adult disease, and is the PCV correlate relevant post-PPV?

- Generally, antibody levels appear to be much lower after three primary doses of PCV in infants compared with a single dose of PPV in adults. After a booster conjugate dose in infants, responses for some of the serotypes appear to be higher for PPV, and some appear to be higher for conjugate.
- Antibodies induced by the polysaccharide vaccine are not necessarily biologically identical to those induced by the conjugate.

Conclusions

- Correlates of protection for PCV are currently imperfect
  - They are not the same for each serotype or for different populations
  - Concentrations after priming may not predict long-term protection
  - The impact of the booster dose was not accounted for when developing correlates
  - The relevance to syndromes other than IPD is not clear
  - The relevance to adults is not clear
  - The relevance to antibodies induced by PPV is not clear.
- However, correlates for PCV have formed the basis for the licensure of new conjugate formulations, and thus have been essential for moving the field forward.

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5. Immunogenicity of pneumococcal vaccine in frail, older people: Dr Iman Ridda

Summary

- A study compared the immunogenicity of 23vPPV and 7vPCV for four serotypes (4, 6B, 18C and 19F) by frailty index in hospitalised elderly persons.
- No significant differences were found between IgG responses to 7vPCV versus 23vPPV.
- The vast majority of patients showed an acceptable response.
- Age was shown to have no significant impact on immunological response to vaccination, except for serotype 18C. However, frailty had a significant effect on immunological response for serotypes 4, 18C and 19F.
- Frailty is a better predictor of immune response to pneumococcal vaccines than age alone.

Background

The proportion of older people in the population is rising. [1]
- An increasing number of frail, older patients are admitted to hospitals. The health system is required to manage problems associated with chronic conditions, in addition to frailty.
- Despite the growing proportion of older people in the population, older adults are often excluded from randomised controlled trials. This is due to exclusion criteria and practical problems in recruitment.
- An increased focus on health issues experienced by older adults is required.
- In developed countries, the annual incidence of IPD has been estimated at > 50 per 100,000 for adults aged ≥ 65 years. [2, 3]
- The increased frequency and severity of pneumonia in the elderly can be largely attributed to ageing organ systems. However, age may not be the only measure of overall susceptibility to disease in the elderly.
- We hypothesised that frailty may be a predictor of a decline in immune function. A study was developed to evaluate this hypothesis within the specific context of response to pneumococcal vaccines.

Study aim

1. To compare the immunogenicity of 23vPPV and 7vPCV for four serotypes (4, 6B, 18C and 19F) by frailty index in hospitalised elderly persons. [4]

Methods

Design

- A randomised, clinical trial of 7vPCV + 23vPPV compared to 23vPPV alone in hospitalised elderly patients. The 7vPCV arm received a dose of PPV at 6 months.

Eligibility

- Any patient ≥ 60 years of age admitted under the geriatric, orthopaedic, cardiology, rheumatology or stroke units at Westmead Hospital, who has not received pneumococcal vaccine.
- Life expectancy of at least 12 months to provide opportunity for follow-up.

Tests

- Patients were tested at baseline and 6 months post-vaccination for serological immunity (IgG levels by ELISA) for serotypes 4, 6B, 18C and 19F.
- Patients were also evaluated for the Barthel Index (BI), Mini Mental State Examination (MMSE) and the Frailty Index (FI).
- The FI aims to detect comorbidity, disability and frailty. It consists of 40 items for scoring. The total score is calculated to provide a frailty measure. The minimum possible score is a 0 (least frail), and the maximum is 40 (most frail).

Measurement of pneumococcal antibody

- Antibody were studied using ELISA.
- Serotypes 4, 6B, 18C and 19F were tested.
- There are no guidelines for the interpretation of results generated with the serotype-specific assay, and no international standard. There is also no agreed-upon threshold for geriatrics. In the absence of this threshold, we used the ratio of pre- and post-serotype specific IgG antibody levels as the measure of response:
  - Poor response: ratio < 2.0-fold
  - Acceptable response: ratio ≥ 2.0–3.99-fold
  - Strong response: ratio ≥ 4.0-fold.

Recruitment

- 5,534 patients were assessed for eligibility. Of those:
  - 4,730 were excluded based on their vaccination status or life expectancy
  - 489 patients did not participate
  - 315 were randomised to receive either the conjugate (trial intervention; n=161) or polysaccharide (control intervention; n=154).
- To date, 119 patients have been analysed in the polysaccharide group and 122 patients in the conjugate group.
- The study period was from May 2005 to February 2007.

Results

- Serology tested for 241 (23vPPV=119; 7vPCV=122).
- Female: 136; male: 105.
- Age range: 60–100 years.
- Medical, social and demographic data were collected.
- Patient characteristics between the two treatment groups were evenly distributed, except for the MMSE, where there were more patients within the normal than the impaired group. The FI showed that all patients recorded scores of ≥ 1, with a wide spread of scores from 1–24 (low: 1–10; moderate: 11–15; severe: 16–24).
- The total pre- and post-vaccination IgG antibody concentration results (as measured by ELISA) showed that all patients demonstrated an increase from baseline to 6 months of follow-up, post-vaccination. However, 7vPCV did not induce a higher antibody response than 23vPPV for the serotypes examined.

- Age was shown to have no significant impact on immunological response to vaccination, except for serotype 18C. However, frailty had a significant effect on immunological response for serotypes 4, 18C and 19F. Gender was not shown to be significantly related to the immunological response in the four serotypes studied.
- An analysis of antibody responses by treatment groups (poor, acceptable and strong responders to individual serotypes at 6 months) showed:
    - Serotype 4: in 7vPCV arm, 28.7% showed a strong response, compared with 18.5% in 23vPPV arm
    - 29–57% of patients met the definition of acceptable or strong response for individual serotypes.

Discussion

- Pneumococcal disease presents a serious risk of morbidity and mortality due to declining immune response with increasing age. [5, 6]
- This limits the efficacy of vaccines; however, our study showed that 29–57% of patients met the definition of acceptable or strong response for individual serotypes. This result is encouraging and provides evidence to counter negative perceptions surrounding the pneumococcal vaccine.
- Results were limited to only four serotypes primarily due to limited funding. The four serotypes studied were chosen because they are included in both study vaccines, and represent a spread of serotypes to which the vaccines are highly and poorly immunogenic.
- Frailty is a good predictor of immune response to pneumococcal vaccines. It has also been shown that the FI predicts mortality better than chronological age alone.
- Older patients are less likely to be vaccinated as a result of their age. If FI were used to assess such patients, providers may be less likely to overlook them for vaccination.
- Our results suggest that even in frail patients there is some benefit of vaccination.

Conclusions

- No significant differences were found between IgG responses to 7vPCV versus 23vPPV.
- Functional antibody responses need to be studied to determine if there is a difference between vaccine types.
- The vast majority of patients showed an acceptable response.
- Frailty is a better predictor of immune response to pneumococcal vaccines than age alone.
- We recommend the use of the FI in future randomised controlled trials.

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Panel and questions

Q. Can you please comment on the use of OPA versus ELISA?

Prof Goldblatt: The key message regarding OPA versus ELISA is that in the context of a post-vaccine study, generally there is a very good correlation between the antibody measured by ELISA and the antibody measured by OPA. Studies of people in elderly age groups also show a good correlation between ELISA and OPA. In addition, OPA is now better controlled than it was in the past.

Q. The Ortqvist (1998) trial selected people that had an episode of pneumonia. These people were then vaccinated by placebo or active product and followed up for a second episode. Is it valid to include the Ortqvist trial in the Cochrane Review, given that the selection criteria differed from the other trials?

A/Prof Ross Andrews: The Ortqvist trial is a valid inclusion because by selecting people with an initial episode of pneumonia, you are selecting those at high risk of a second event.

Q. What is your view on the use of both conjugate and polysaccharide vaccines? :

Prof Goldblatt: When conjugate vaccine is given to young children, they lay down immune memory. The concern about the polysaccharide vaccine is that it draws on the memory pool but does not replenish it. The polysaccharide provides circulating antibody but it may (theoretically) interfere with subsequent responses. However, in elderly populations it may be more important to provide people with circulating antibody, which can be done very effectively by first administering conjugate and then polysaccharide vaccine. This accounts for a spread of serotypes and provides good responses.

Q. Is there any difference between polysaccharide following conjugate vaccine in children versus adults?

Prof Goldblatt: The concern is that nice memory is laid down in children given conjugate vaccine and when they are then given a dose of polysaccharide vaccine, memory B cells become stimulated, then become plasma cells and die. Thus memory is depleted.

In a study by Kim Mulholland and colleagues performed in Fiji, conjugate vaccine was given to infants for priming, followed by a small dose of polysaccharide in some of the infants at approximately 9 months of age. A dose of polysaccharide was then given to all at 18 months of age. The study showed that responses were compromised in children that had had polysaccharide vaccine at 9 months of age. It appears that the dose at 9 months had interfered with the memory that had been laid down through the conjugate vaccine.

It is also important to consider that there is probably some sort of threshold as to how much antibody can be produced. This is why we do not have extremely high levels of pneumococcal antibody, even though we are probably exposed fairly regularly.

Comment from floor: In Kim's study, the antibody levels that were reached after the challenge were essentially the same. The argument for hyporesponsiveness

associated with the additional dose of polysaccharide vaccine was that the increase was less. However, a lower baseline level will elicit a higher response.

Q. When trying to make policy decisions about revaccination, we want to match the antibody persistence for different serotypes over time such that it might reflect the local epidemiology. Do you have any comments on differential antibody persistence?

Dr Grabenstein: All of the studies in my review had to provide a serotype-specific antibody level. Some studies reported a cumulative antibody level, and these studies were disregarded. It is crucial to assess all serotypes.

Q. It appears that in the group at the highest risk of pneumococcal disease, the evidence for benefit from the vaccine is the weakest. Therefore, are we targeting vaccines effectively? Are we focusing too much on the group where benefit is least, and should we redirect our efforts?

Dr Ridda: In our study, we found a very high vaccination rate in the group that we targeted. Originally, we planned to recruit people ≥ 65 years, but we needed to reduce the minimum age to 60 because we could not find enough people that were not already vaccinated due to the vaccination program. We found people aged ≥ 75 years were less likely to be vaccinated. The frailty index may have a role in helping to determine vaccination strategies in older age groups.

Dr Grabenstein: A big issue is the potential for long intervals with no intervention. For example, a child diagnosed with diabetes at age 8 may not be vaccinated again until they reach 65. We need to consider whether that one dose is considered sufficient for such an extended length of time.

Prof Torzillo: In response to Dr Grabenstein's concern: the situation across Australia is highly variable. There is no good process for follow-up. Some at-risk people will regularly be revaccinated every 5 years, while others will go for many years without revaccination. Commonly, it seems many people are vaccinated when they are hospitalised, and then never again.

In response to the issue that people who have the highest rates of disease may also be those that do not respond as well to the vaccine: the difficulty with the 23vPPV in developed countries is that there has been lots of investment in people at highest risk, without much evidence in outcomes. If there is an effect from this vaccine, it is small.

Q. Can you please comment further on the issue of vaccine use in chronic disease/high-risk groups?

A/Prof Andrews: The Australian Indigenous population is a high-risk group of particular concern.

In Australia, we have provided polysaccharide vaccine to infants on a first-principles basis, rather than a strong evidence base. Largely, it seems the impact on high-disease-burden settings has been disappointing. We've published data from the Northern Territory to show that although vaccination coverage rates have increased, there has been no change in overall disease rates. Upon distilling the data, we found that in pockets of high coverage there were higher levels of vaccine impact.

However, vaccine uptake was very different across different areas. Ecological aspects are also an important consideration.

Prof MacIntyre: Studies have consistently shown that older people are less likely to be vaccinated against influenza or pneumococcus, despite generally high coverage levels in the community. Indeed, people aged over 80 years were statistically significantly less likely to be vaccinated. However, if elderly people were considered on an individual basis, many were not particularly frail. There is a perception among clinicians that there is no point in bothering with vaccination in the very old. However, when older people contract pneumonia they are sent to hospital for extended periods. This is an issue that needs to be addressed.

Comment from floor: In North Queensland, we were able to demonstrate that 23v vaccine is very effective against serotype 19A replacement disease. In non-Indigenous adults aged ≥ 65, there was no increase in replacement disease. In adults < 65 years, there was almost a 200% increase in replacement disease, the vast majority of which was 19A. This observation indicates that the 23v vaccine was preventing 19A replacement disease in those ≥ 65 years who were receiving the vaccine for free. It seems the 23v vaccine was having an impact on an adverse effect of the conjugate vaccine in young children.

Topic: Adult pneumococcal immunisation
Chairs: A/Prof Ross Andrews and Prof Paul Torzillo

1. 23vPPV coverage in adults: Dr Rob Menzies

Summary

- Computer Assisted Telephone Interviews (CATIs) and face-to-face interviews were used to determine 23vPPV coverage in adults in Australia.
- Coverage data reflect the introduction of 23vPPV recommendations and programs in Australia over time.
- The national average for coverage is approximately 53% in people aged ≥ 65 years. Coverage is highest in people aged ≥ 75 years.
- Coverage in Indigenous adults is sub-optimal in all age groups, but especially in ages where it is funded only for them.
- Coverage estimates for Indigenous adults are not frequent enough – from ABS surveys every 6 years.

Sources of data on 23vPPV coverage

CATIs

- Used random digit dialling.
- After questions were asked regarding influenza vaccination, participants were asked 'have you been vaccinated with pneumococcal (or pneumonia vaccine) in the previous 5 years?'
- Importantly, there was no validation of data (self-reporting only).
- Risk factors were collected
    - o There were insufficient numbers to report on Indigenous status.
- CATIs included:
    - o National Influenza Survey [1]
        - ▪ 2000 (≥ 65 years). A one-off survey
    - o NSW Population Health Surveys
        - ▪ 2002+ (≥ 50 years). This is a rolling CATI program that has provided data annually from 2002 [2]
    - o Adult Vaccination Surveys
        - ▪ 2004 (≥ 40 years) [3], 2006 (≥ 40 years), 2009 (≥ 18 years). [4] These years were the only ones to include pneumococcal data
    - o CATI with validation by immunisation provider
        - ▪ Ross Andrews, Victoria, 2000–2001 (≥ 65 years). This was the only data source to provide validation by immunisation provider. [5]

Face-to-face surveys

- Particularly useful for Indigenous people.
- Involved census sampling.
- There was no validation of data.
- Face-to-face surveys included:
    - o National Health Survey
        - ▪ 2001, 2004/2005 (≥ 18 years)

- o National Aboriginal and Torres Strait Islander Health Survey
  - ▪ 2001, 2004/2005, 2010/2011 (≥ 18 years). [6,7]

23vPPV: history of vaccination programs

- Use of the vaccine has progressively increased over time as vaccine recommendations and programs have been introduced. The NHMRC first recommended 23vPPV in high-risk groups in 1991. The vaccine was funded publicly in Victoria for people ≥ 65 years from 1998. Nationally, it was publicly funded for Indigenous people ≥ 50 years and high-risk people aged 15–49 from 1999. In 2005, the vaccine was publicly funded nationally for all people ≥ 65 years.

23vPPV coverage in people ≥ 65 years

- Coverage data reflect the patterns in the vaccination programs described above.
- There was a considerable increase in coverage in Victoria in 1998/1999 when the state's funded program commenced. Coverage in Victoria then reached a plateau.
- In the other states, there has been more of an incremental increase in coverage over time.
- The national average for coverage is approximately 53%. There is not a substantial difference in coverage between the individual states and territories.

23vPPV coverage by age group, Australia 2009

- An incremental increase in coverage can be seen in the age group where vaccine funding commences (from 65 years). The increase then plateaus from approximately 80 years of age.

Indigenous adults [8]

Pneumococcal vaccination < 5 years (data from 2004/2005)

- The reported coverage in younger Indigenous adults (18–49) with risk factors is low and similar to that in younger Indigenous adults without risk factors.
- Coverage is sub-optimal in all age groups. This may be a reason why the vaccine does not appear effective.

23vPPV coverage by remoteness (data from 2005/2005)

- Coverage is lower in urban areas compared with remote areas.

Conclusions

- General population:
  - o Coverage is not high enough
  - o There appears to have been an incremental increase in coverage in people aged ≥ 65 years from 2000 (and possibly earlier) to 2006
  - o Coverage rate has plateaued at approximately 55%
  - o Coverage is highest in people aged ≥ 75 years
  - o Coverage may be approximately 20% in 18–64-year-olds with risk factors
  - o There appears to be little geographic variation in coverage
  - o Future needs:
    - ▪ Annual surveys

- ▪ Validation of vaccination status.
- Indigenous adults:
  - o Coverage is too low. The most likely cause of this is that in mainstream health systems, Indigenous people are not recognised as such and are not offered targeted programs
  - o Coverage is similar to non-Indigenous people at ≥ 65 years
  - o Coverage is lower in people aged 50–64 years
  - o Coverage is only 10–15% in young adults with risk factors
  - o Geographic variation has an effect, with higher coverage in remote areas
  - o Future needs:
    - ▪ More frequent surveys
    - ▪ Validation of vaccination status.

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2. Adverse events following 23vPPV in Australia: A/Prof Kristine Macartney

Summary

- In people aged ≥ 65 years in early 2011, there was a considerable increase in ISRs reported, particularly in NSW and ACT.
- As a result of the increased reporting of reactions, the TGA recalled batch N3336 of 23vPPV in March 2011. Initially, reported reactions seemed to be associated with this batch.
- After the recall of the N3336 batch of 23vPPV, there was an increase in reports of ISRs before a decline. It is possible that healthcare providers were stimulated to report by the recall.
- On 19 April 2011, the TGA advised health professionals not to administer a second or subsequent dose of 23vPPV. This advisory was pending the outcome of a review of the increased reporting rate of ISRs following administration of the second dose of vaccine that did not appear batch related.
- The literature suggests that we can expect higher ISR rates in revaccinated people, particularly in people that are revaccinated within 5 years of the prior dose.

23vPPV in Australia

- NIP funded for:
  - adults ≥ 65 years
  - Indigenous adults ≥ 50 years
  - Indigenous adults 15–49 years with risk factors
  - Indigenous children in 4 jurisdictions: booster at 18–24 months.
- PBS for:
  - medical 'at risk'
  - 'splenectomised persons over 2 years of age; Hodgkin's disease; persons at high risk of pneumococcal infections'
  - or *Australian Immunisation Handbook* (9th edition) definitions [1]
    - booster following PCV.

Revaccination recommendations

- Recommendations in the *Handbook* are complex.
- If the recommendations are followed, a person could be eligible for up to 3 doses of 23vPPV.
- Compared with the international context, Australia has extensive recommendations in the *Handbook* for revaccination, particularly in regards to the focus on people aged ≥ 65 years receiving a second dose 5 years after the first.

ISRs following 23vPPV immunisation

- 23vPPV is often administered at the same time as the influenza vaccine, ahead of winter.
- In people aged ≥ 65 years:

- o In 2002–2010, in all jurisdictions, reports of adverse events to 23vPPV increased around late summer/autumn
- o By week 12 of 2011, NSW and ACT were beginning to see a considerable increase in the reporting of ISRs. Some of these reactions were reasonably severe, with extensive redness and swelling. Some people sought medical care and were hospitalised.
- As a result of the increased reporting of reactions, the TGA recalled batch N3336 of 23vPPV in March 2011 [2]. Many of the reactions reported seemed to be associated with this batch.
- This recall prompted a review of our AEFI data for 23vPPV from 2010 and prior years (Mahajan, 2011) [3]:
  - o AEFI reporting rate was 39.7 per 100,000 doses for ISR
    - ▪ The 2010 rate was higher than for 2009: 13.3 per 100,000 doses
  - o 155 AEFI reports for older adults with 23vPPV
    - ▪ 9% coded as serious
    - ▪ 81% were reports of ISR
    - ▪ 21% reported fever
  - o 42% reported conjoint administration with influenza vaccine, compared with 24% in 2009.
- The National Centre for Immunisation Research and Surveillance (NCIRS) reviewed the reporting rates for ISRs following 23vPPV in people aged ≥ 65 years (data source: TGA database, 2002 to 2010, by year of vaccination. Reporting rates calculated per 100,000 population). Our analysis found [3]:
  - o rates were reasonably low across jurisdictions in 2009
  - o in Queensland and South Australia, reporting rates increased in 2010. It is important to consider that under the NIP funding for vaccination that began in 2005, many of the patients that were vaccinated when the program commenced would have been due for revaccination in 2010/2011.
- The NCIRS also reviewed the reporting rates for ISRs following 23vPPV in people aged < 65 years (data source: TGA database, 2002 to 2010, by year of vaccination. Reporting rates calculated per 100,000 population). Our analysis found [3]:
  - o reporting rates fluctuated in South Australia
  - o generally, there were no substantial changes in reporting rates across this timeframe in this age group.
- It is important to recognise that adverse-event-reporting data have many limitations.
- After the recall of the N3336 batch of 23vPPV, there was an increase in reports of ISRs before a decline. Reports increased particularly in New South Wales, although an increase was also seen in other jurisdictions. It is possible that healthcare providers were stimulated to report by the recall.
- The TGA received more data from jurisdictions besides New South Wales, and that the issues were potentially not just confined to the N3336 batch. On 19 April 2011, the TGA advised health professionals not to administer a second or subsequent dose of 23vPPV. [4] This advisory was pending the outcome of a review of an apparent increased rate of ISRs following administration of the second dose of vaccine, the results of which were due out shortly after this presentation.
- 2011 AEFI reports to 19 April 2011 showed [2]:
  - o 173 adverse reactions reported, with 168 ISRs
  - o 84 ISRs were severe:

- cellulitis
- extensive swelling from shoulder to elbow
- and/or abscess.
  - o Preponderance of second dose (revaccination) reactions
    - Severe reactions: 55% were second dose
    - 26% were first dose, 17% were unknown.
  - o Batch testing revealed no anomalies
        Although 33% of reactions were associated with batch N3335 many other batches were implicated.

Literature review: 23vPPV safety in adults

- We identified > 27 studies on adverse events after revaccination with PPV.
- Factors associated with local ISRs:
  - o Subcutaneous versus intramuscular route (OR 3.20; 1.13–9.13)
  - o Higher pre-vaccination antibody level
  - o Younger age
  - o Re-vaccination, particularly within 5 years
  - o Possibly concurrent influenza vaccine administration (findings were inconsistent).

Safety of repeated doses of PPV in adults

- Features of early studies/case reports:
  - o Small number of subjects (may have been underpowered)
  - o Lower valency PPV
  - o Higher polysaccharide content per serotype
  - o Dose intervals were 1 to 4 years.
- Features of more recent studies:
  - o Cohort based
  - o Include healthcare database studies.
- Two studies utilised the USA Medicare population database for adults aged ≥ 65 years:
  - o Burwen *et al.* 2007 [5]:
    - Identified ICD-coded hospitalisations: cellulitis/abscess in upper arm
    - Reactions peaked mostly in 3 days following 23vPPV
    - Hospitalisation rate was 2.5 (1.8–3.3) per 100,000
    - There was a higher reaction rate for revaccination with 23vPPV within < 5 years: RR 2.6 (1.3–5.0; p=0.004)
    - Revaccination after ≥ 5 years did not indicate a significant risk difference.
  - o Shih *et al.* 2002 [6]:
    - Investigated any healthcare service use within 14 days after a repeat 23vPPV dose:
      - 1.3 times as likely for ED visit (1.2–1.5)
      - 1.2 times as likely to be hospitalised (1.1–1.4)
      - 1.13 times as likely to visit a GP (1.1–1.2)
      - Higher RR of health service utilisation in people revaccinated within 5 years.
- Jackson *et al.* 1999 [7]:
  - o Prospective study investigating AEFI for 13 days after 23vPPV
    - 901 subjects received first 23vPPV dose

- 513 subjects received repeat 23vPPV dose, 5–13 years after prior dose (median 6 years)
- Systemic reactions were similar between first-dose vaccinees and revaccinees
- ISRs: most in first 2 days following vaccination
  - Arm soreness: 74% of revaccinees versus 57% of primary revaccinees
  - Relative risk: 1.3 (1.2–1.4).
- Sizeable local reactions were more commonly observed in healthier, younger revaccinees.
- Hammitt *et al.* 2011 [8]:
  - Prospective study of adults aged 55–74 years in Alaska, within 4 days after 23vPPV
    - 188 subjects were revaccinees (second, third or fourth dose)
    - Revaccinees reported more joint pain, fatigue, headache, ISRs and decreased arm movement compared to first-time vaccinees (n=121)
    - AEFI was not associated with age or chronic illness; however, the study was probably underpowered to detect a substantial difference with age or chronic illness.
- Musher *et al.* 2010 [9]:
  - Prospective study of adults receiving second dose of 23vPPV within 3–5 years of first dose
    - Those receiving the first dose at ≥ 65 years were less likely to have an ISR than revaccinees ≥ 65 years or younger primary vaccinees (53% versus 75%; p<0.001)
    - Revaccinees were more likely to experience erythema (35%) and induration (40%) compared with primary vaccinees (erythema: 15%; induration: 20%; p<0.001)
    - There was a higher proportion of severe ISRs in people aged ≥ 50 years following revaccination than in the primary vaccination group (17% versus 4%).

AEFI notifications since suspension of 23vPPV revaccination

- It is unclear whether healthcare providers have stopped revaccinating, or if they have just stopped vaccinating altogether.
- Reports for ISRs in people ≥ 65 years following 23vPPV vaccination have declined.

Revaccination recommendations from selected overseas countries

USA (2008)

- 23vPPV at age 65 years (at least 5 years after previous dose), and in other risk conditions.
- No routine 23vPPV revaccination without underlying conditions.

Canada

- No routine 23vPPV revaccination without underlying conditions.

Germany (2009)

- Rescinded recommendation for routine revaccination of older adults (without risk conditions) due to:
  - o lack of evidence for any major benefit from a revaccination dose in most other groups
  - o concerns regarding immune hyporesponsiveness
  - o lack of immune memory and thus long-term protection following revaccination; and
  - o concern about increasing local reactions following revaccination.

UK (June 2011)

- No routine 23vPPV revaccination without underlying conditions.
- Initially advised discontinuation of routine 23vPPV for people aged ≥ 65 years – this advice has been re-evaluated and recommendation currently stands.

Conclusions

- We have observed higher rates of ISRs following 23vPPV in 2011. Higher rates of ISRs were potentially also occurring in 2010, but were perhaps not recognised.
- The literature suggests that we can expect higher ISR rates in revaccinated people, particularly in people that are revaccinated within 5 years of the prior dose.
- To make recommendations, it is important to compare the risk-benefit of revaccination in various populations. There is currently a lack of data in this area to comprehensively compare benefits versus risks of re-vaccination across different populations.
- In the future, it will be important to compare the safety of 23vPPV with 13vPCV in adults.

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Panel and questions

Q. Why is a whole-of-life register unattainable?

Dr Menzies: Various groups have been advocating for such a register for many years, and it appears that opportunities to implement a register have already passed. Funding a register is also an issue. Realistically, a register probably will not be implemented in the near future.

The National Immunisation Strategy has provided opportunities to consider how adult vaccination records are managed. However, no firm decisions regarding adult records have been made. If no changes are made to improve adult records, then the use of surveys needs to increase.

Q. What strategies should be implemented to improve vaccine coverage?

Dr Menzies: Registers provide a major tool for improving coverage, as they eliminate the uncertainty about whether a person has been previously vaccinated. In addition, studies show that healthcare providers are the most influential source for advocating vaccination to their patients. We therefore need improved data on the vaccination status of patients, and to motivate healthcare providers to prioritise vaccination.

One of the limitations of the Australian health system is that a claim submitted for vaccination reimbursement does not necessarily state that it is for a vaccination. This means we are unable to collect demographic data based on vaccination claims.

There are data on vaccines purchased under the PBS; however, the vaccine becomes publicly funded as people age and so this source of data declines over time.

Comment from floor: The inclusion of vaccination records in the personal electronic health record may be a way to address issues surrounding uptake and data collection.

Another simple option that could be rapidly implemented is to lobby for a Medicare item number for the pneumococcal vaccine itself. Medicare data could then be searched to determine if an individual has had the vaccine.

Prof Torzillo: Immunisation coverage is a population health problem. In Australia, we try to address coverage through our private practice delivery system; however, accessibility to GPs varies enormously across the country. No improvement in coverage will be seen unless a population health approach is adopted.

Comment from floor: Healthcare providers are the most important gatekeepers in deciding who is administered the vaccine. Given the current evidence and burdens already placed on GPs, it would be difficult to reassure GPs that the pneumococcal vaccine is important for our elderly, frail and at-risk populations.

Prof Richmond: If we are recommending use of the vaccine, then current coverage rates are vastly inadequate. A pop-up reminder service in GP patient software may be a tool for prompting GPs to vaccinate. It may also be possible to source better coverage data from GPs using such software.

Comment from floor: A survey has shown that patients will accept vaccination when offered it by GPs, and that GPs claim to offer vaccines whenever they have the

opportunity. It was found that GPs in clinics with practice nurses were more likely to offer the vaccine than if they did not have this resource.

A/Prof Andrews: The Northern Territory and Queensland have state-based immunisation registers, and we should endeavour to pool together data by region in these areas routinely. This may apply pressure nationally and embarrass other states into action to produce data.

Topic: What does the future hold for pneumococcal vaccines?
Chair: Prof Peter Richmond

Open panel discussion: Prof Goldblatt, Prof Torzillo, Prof McIntyre and A/Prof Andrews

Prof Richmond: It is well recognised that pneumococcal disease is an important issue for older people and those with comorbid conditions that place them at higher risk of disease. Much work is still required in the areas of diagnostics and therapeutics for pneumococcal disease.

Currently there is one licensed pneumococcal vaccine for use in the adult population. There is fairly strong evidence that the vaccine is highly effective in non-immunocompromised young adults. The vaccine also appears to be reasonably effective in healthy older adults; however, it seems less effective in those that are immunocompromised.

There is some evidence to suggest that ISRs are an issue, particularly if people are revaccinated within 5 years of receiving a prior dose.

We would expect in the future that there will be another licence for the older population with the pneumococcal conjugate vaccine (13v). We will need to consider how this vaccine should be used, particularly in conjunction with a population-based program with an infant pneumococcal conjugate vaccine that is likely to deliver herd protection.

Another issue to consider is how to improve coverage.

Prof McIntyre: The evidence that we have seen seems to indicate that younger and healthier people are more likely to benefit from PPV. Therefore, it is not surprising that the UK found that although risk-factor-based programs may seem attractive, they can be difficult to implement.

It appears that the focus should be on increasing PPV rates in the 65–74 years age group, rather than in those aged ≥ 75. Instead of being concerned with issues of revaccination, we should instead ensure those in the 65–74 years age group receive at least one dose.

It will be interesting to see the results of the CAPITA study, particularly in relation to the additional benefits of 13vPCV in community-acquired pneumonia in adults.

Dr Grabenstein: It would be useful to have more information around the delivery of vaccines by healthcare providers. This may help industry provide better support to improve vaccine uptake.

It would also be valuable to explore the linkage between the vaccination data and the disease data from North Queensland and the Northern Territory, in order to perform effectiveness analyses.

Comment from floor (CSL representative): Confusion exists among some general practice clinics as to which patients are due for vaccination.

Pneumococcal vaccinations have traditionally 'piggy-backed' on influenza vaccinations, which probably accounts for getting the coverage rate to where it is currently.

Comment from floor: The 2-dose routine for PPV may be creating an issue. It would be simpler for GPs to know that they need to just give one dose at age 65, rather than trying to remember if the patient is due for a second dose.

At age 75, people are eligible for a full-health assessment and will be offered vaccination if they have not had it already. This may explain why there is an increase in coverage at age 75.

Although more practice nurses will be introduced into general practice clinics next year, a specific immunisation-based payment for nurses will be removed. This may reduce the number of people vaccinated in clinics.

Prof Torzillo: In the region in which I work, coverage in children under 5 years is 100% every year. We employ highly organised, conventional population health strategies to ensure that this is the case. Regions in Australia that do not have adequate private-practice services should probably also employ similar approaches.

In regards to the use of 23vPPV in Indigenous adults in Central Australia, the vaccine does not seem to have had a significant effect on disease. This may be due to existing comorbidities. Another vaccine in this population would be preferable.

A/Prof Andrews: Cold-chain issues for pneumococcal vaccine need to be addressed, particularly in remote Australia. These issues relate more to freezing the vaccine, rather than an inability to keep it cold. As a result, the vaccine supplied may not be viable.

Discussions with other countries indicate that policies for revaccination worldwide are not drawn from a strong evidence base.

Prof Goldblatt: In the context of a high-income setting with a mature conjugate vaccine program in children, a key issue is the potential impact of 13v vaccine in adults. It is important to consider whether we could have an indirect impact on IPD in adults, but not on pneumonia. The impact on pneumonia seems to be difficult to measure. However, if the mechanism is reduced carriage, then we may be able to assume that if IPD is reduced, pneumonia will be also.

It will also be important to consider the value of using 13v vaccine in adults in the context of a mature program with high coverage in infants and therefore very little disease caused by the 13 serotypes in the vaccine. In addition, if the ongoing epidemiology changes so that most of the serotypes in 13v are no longer a problem, it may not be cost-effective to first give 13v vaccine and then 23v vaccine.

Prof Goldblatt: We have no gold standard for diagnosing pneumococcal pneumonia in the absence of a positive culture. We have considered whether bacteraemic pneumonia is a different entity to non-bacteraemic pneumonia. The problem with non-bacteraemic pneumonia is our ability to detect what proportion of that is pneumococcal is severely compromised by the absence of the gold standard assays. It is therefore currently impossible to determine whether the conditions exist on a spectrum of the same disease or if they are fundamentally different.

Prof Richmond: Aetiological studies in adult pneumonia using new diagnostics would be useful.

Comment from floor (Pfizer representative): It is unknown whether the diagnostic test that is being used in the CAPITA study will become a marketed test in the future.

Comment from floor: The statement about revaccination recommendations for 23vPPV has not yet been finalised. We have worked with the company to provide extra clarity regarding the risks of vaccination in the PI. We are also liaising with the ATAGI working group. It is difficult to conduct a risk–benefit analysis when the benefit of revaccination is unclear.

Dr Grabenstein: Antibody levels will continue to decline in people vaccinated with 23vPPV long ago. In regards to splenectomy, a Scandinavian group established algorithms for a flexible period for revaccination that was based on a person's current pneumococcal antibody level. That is, the interval for revaccination was customised according to the person's response. It is important to recognise that when antibody level has dropped to baseline, a person is back to their original risk of disease.

A/Prof Andrews: It appears that the current TGA warning regarding revaccination with 23vPPV has become as much about the benefit of revaccination as it is about the adverse events that occurred.

Comment from floor: The TGA is focused on the resolution of the adverse events issue associated with 23vPPV; however, whenever an increase in adverse events is reported, the overall risk-benefit needs to be evaluated. ATAGI have been asked if it wishes to continue with its recommendations for the vaccine.

Prof Richmond: There could be a recommendation made to increase the length of time between boosters to 10 years, to reduce the likelihood of an adverse event to the vaccine.

A/Prof Macartney: We should continually re-evaluate the benefit of our vaccination programs.

Comment from floor: Considerable replacement disease has been observed in the non-Indigenous group aged 50–64 years. Some of this disease has been severe and life-threatening. This group does not tend to have a complex of comorbidities. It may be worth considering lowering the age for routine PPV, particularly in the context of the events surrounding the introduction of the conjugate vaccine.

A/Prof Andrews: A study showed that lowering the age for routine PPV to 50–64 years was cost-effective. However, the dilemma still remains that if the vaccine is introduced at 50 years, it is unclear how long people should wait for another dose.

Prof Richmond: The message to GPs regarding pneumococcal vaccines should be that coverage is extremely poor in at-risk groups. GPs should ensure that at-risk patients receive at least one dose of pneumococcal vaccine.

Comment from floor: If evidence of benefit could be demonstrated, it may be valuable to incorporate routine pneumococcal vaccination in the mid-life health check (at age 45–50 years). This approach may help achieve higher coverage.

Prof Goldblatt : When the UK Department of Health stated that it was re-evaluating its recommendations for PPV, various groups were invited to give comment. The view of GPs seemed to be that they would find it easier to deliver vaccine based on age requirements, rather than through a risk-based program. Many groups were surprised that the Department of Health was moving in this direction, given that it is quite unusual to take vaccines out of programs.

The epidemiology of disease changes in the context of an immunisation program, which can then have an impact on the program's cost-effectiveness.