

Immunisation Subcommittee of PTAC

Meeting held 18 February 2015

(minutes for web publishing)

Immunisation Subcommittee minutes are published in accordance with the *Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2008*.

Note that this document is not necessarily a complete record of the Immunisation Subcommittee meeting; only the relevant portions of the minutes relating to Immunisation Subcommittee discussions about an Application or PHARMAC staff proposal that contain a recommendation are generally published.

The Immunisation Subcommittee may:

- a) recommend that a pharmaceutical be listed by PHARMAC on the Pharmaceutical Schedule and the priority it gives to such a listing;
- b) defer a final recommendation, and give reasons for the deferral (such as the supply of further information) and what is required before further review; or
- c) recommend that PHARMAC decline to list a pharmaceutical on the Pharmaceutical Schedule.

These Subcommittee minutes were reviewed by PTAC at its meeting on 7 & 8 May 2015, a record of which will be available in July 2015.

1 Summary of recommendations

- 1.1 The Subcommittee **recommended** that HIV be removed from the recommended Special Authority criteria for hepatitis A vaccine, and requested evidence to review the incidence of hepatitis A in patients living with HIV before making further comment.

2 Record of Previous Subcommittee meeting

- 2.1 The Subcommittee noted PTAC's question in point 4.11 of the Subcommittee minutes regarding hepatitis A vaccine, and questioned whether vaccination should be for all patients living with HIV or patients at risk. The Subcommittee noted that PTAC considered that rather than having the broad description of patients with HIV the restriction should refer to people with HIV who are men having sex with men, patients with chronic liver disease, IV drug users and healthcare workers.
- 2.2 The Subcommittee noted that there was a suggestion of increased morbidity for patients with severe hepatitis A if they were also HIV positive. The Subcommittee also noted that hepatitis A infection was rare and considered the vaccine should not yet be funded for the general population who are HIV positive.
- 2.3 The Subcommittee considered that there were increased risks of patients contracting hepatitis A if they travelled to and from Pacific Islands. The Subcommittee also considered that some NZ based Pacific Island patients saw the islands as home rather than a visiting place, and hence may less often access pre-travel vaccination.
- 2.4 The Subcommittee noted that New Zealand's incidence of notified hepatitis A infection is lower than most other countries. The Subcommittee considered that it may be difficult to define and identify small patient populations that may be considered to be at greater risk of contracting hepatitis A or greater morbidity following contracting hepatitis A. The Subcommittee considered that the most effective vaccination is as part of rapid response by public health services if cases of hepatitis A occur in the community.
- 2.5 The Subcommittee **recommended** that HIV be removed from the recommended Special Authority criteria, and requested evidence to review the incidence of hepatitis A in patients living with HIV before making further comment.

3 Review of the National Immunisation Schedule

- 3.1 The Subcommittee noted that New Zealand's funded immunisation programme is similar to other international immunisation programmes and meets the World Health Organization (WHO) recommendations.
- 3.2 The Subcommittee noted that New Zealand regularly experiences outbreaks of measles imported from developing countries and then able to spread in New Zealand because of low immunisation coverage over preceding decades. While these New Zealand specific coverage issues have been corrected in infants and

young children by improved coverage, the adolescent and young adult cohorts remain vulnerable to wild type illness.

- 3.3 The Subcommittee noted that Australia and the US immunise against Hepatitis B virus infection at birth and the UK is also considering introducing immunising against hepatitis B at birth. The Subcommittee noted that during the first year after birth the risk of acquiring hepatitis B is at its highest and that if the hepatitis B vaccination was given universally at birth it would protect against horizontal and vertical transmission. The Subcommittee also noted that vaccinating at birth does not negate the necessity of having the next three doses in the primary series.
- 3.4 The Subcommittee noted that there would be risks if there were to be a change in schedule timing to delivering a vaccination at birth, as lead maternity carers (LMCs) do not routinely administer childhood vaccines and there are both logistic and communication/education issues that would need to be addressed. The Subcommittee noted that babies born to mothers who are Hepatitis B positive are currently funded for vaccination at birth and that babies born to mothers who have had no antenatal serology testing are also vaccinated at birth. The Subcommittee noted that more evidence and data would be needed before consideration to a change in the vaccination schedule for hepatitis B was made.
- 3.5 The Subcommittee considered that starting the National Immunisation Schedule at six weeks remained appropriate and that some other countries are looking at bringing their vaccination schedule forward, in particular for better pertussis control. The Subcommittee noted that schedule age for the first infant dose (6-weeks) is less than in the United States (2 months) and several other countries.
- 3.6 The Subcommittee noted that the third dose of pertussis (currently administered as one of the antigens in the hexavalent vaccine) could be brought forward from 5 months to 4 months. However, the Subcommittee considered if this was done, there would need to be clarity as to whether an additional post 6 month booster dose would be necessary.
- 3.7 The Subcommittee noted that Australia is intending to re-introduce the toddler pertussis booster dose in the second year of life. The Subcommittee noted that New Zealand discontinued the fourth dose in 2006 shortly after Australia and considered that New Zealand should also consider re-introducing the fourth dose. The Subcommittee noted that the Ministry of Health has organised a one-day workshop on pertussis vaccination to be held in April and considered that the Subcommittee should review any recommendations that may come out of the meeting to determine what recommendations could be made for funding and with what priority.
- 3.8 The Subcommittee noted that overall it was satisfied with the current childhood immunisation schedule, except perhaps for the timing of the third dose of hepatitis B. The Subcommittee considered that any changes to the Schedule would require immunological evidence.
- 3.9 The Subcommittee considered the burden of pneumococcal disease in New Zealand and how it compared with other countries. New Zealand has an extra dose of pneumococcal vaccine in the primary course compared with the UK and

Australia schedules, and the Subcommittee discussed the possibility of reducing to 2 doses plus a booster, being either at 6 weeks and 5 months or 6 weeks and 3 months for the primary course. The timing of the booster dose would still remain in the second year of life. . The Subcommittee considered that it is most likely that New Zealand could go to a 2 plus 1 schedule and noted there is information from Scandinavia on pneumococcal vaccination outcomes that could be useful in forming that recommendation.

- 3.10 The Subcommittee noted that vaccination against meningococcal C was introduced in the UK and Australia as there was a high incidence of meningococcal C disease amongst toddlers and infants, whereas in the US it is the teenagers who are vaccinated against meningococcal disease as it is that age group that has the highest incidence. In New Zealand meningococcal B has a higher incidence than meningococcal C, however the Subcommittee **recommended** PHARMAC should assess the epidemiology of the incidence in New Zealand for similarities with patterns in the UK and Australia.
- 3.11 The Subcommittee considered that MMR at 15 months remained suitable for the schedule.
- 3.12 The Subcommittee discussed the continued need for a haemophilus influenzae B (Hib) vaccine to be given at age 15 months. The Subcommittee noted that invasive Hib disease is now in general very rare due to vaccination, although there had been concerns raised regarding breakthrough disease. The Subcommittee noted a review of HiB in New Zealand will shortly be published and it may offer answers to the number of vaccines required.
- 3.13 The Subcommittee noted that it will need to be decided when in the Immunisation Schedule varicella vaccination would be scheduled if it was funded. The Subcommittee noted that introduction of varicella may be complicated if there were a recommendation to re-introduce a fourth dose of pertussis vaccine. The Subcommittee considered New Zealand and Australia to be inconsistent with most of the rest of the Western world (except the UK) by not having the booster dose of pertussis in the second year of life. Pertussis vaccination will be discussed at the April 2015 workshop.
- 3.14 The Subcommittee noted that if varicella immunisation was introduced into the Schedule now it would most likely be scheduled as a monovalent for age 15 months, necessitating infants to have 4 injections in one visit. The Subcommittee considered that, generally, it was the vaccinators who were more concerned about giving multiple injections at one time than the parents of the infant but the child would remember vaccinations given three months earlier (if the 15 month schedule were to be divided between 12 months and 15 months) and would not be happy about receiving more injections. The Subcommittee noted that SAGE is to discuss multiple vaccinations at its April 2015 meeting.
- 3.15 The Subcommittee noted that in Australia and the UK, MMR and meningitis C vaccines are given at age 12 months along with the 3rd dose of pneumococcal vaccine (Australia) and HiB in the UK. The Subcommittee noted that MMR-V given to toddlers before age 18 months carries a small increased risk of febrile convulsions compared with giving MMR and varicella vaccines separately.

However, the Subcommittee noted there are a number of options available for introducing varicella and/or the 4th dose of pertussis in the future. The Subcommittee noted that PHARMAC is open to options and intends to include the ability for suppliers to submit responses for supply of multivalent vaccines in the upcoming RFP. The Subcommittee **recommended** that PHARMAC source data on vaccinating with MMR at the earlier age of 12 months and its risks.

- 3.16 The Subcommittee noted that there is better immunisation coverage in 1 to 3 year olds than in 4 year olds. The Subcommittee questioned whether it remained necessary to vaccinate against polio at 4 years and **recommended** the evidence be reviewed at a future meeting to assess whether we could reduce to three doses. If the evidence is favourable the quadrivalent DTaP-IPV could be replaced with dTap at age 4 years.
- 3.17 The Subcommittee noted that a varicella catch up could possibly be given at 11 to 12 years of age. The Subcommittee noted that currently 11 to 12 year olds were affected by measles outbreaks therefore a MMR catch up for those people without two documented vaccinations could also be looked at with the possibility of using a combination MMR-V vaccine. The Subcommittee noted that the concept of school vaccinations is embedded at intermediate level as a result of the Tdap and HPV vaccination being standard practice and an MMR or MMR-V vaccine could be introduced into the school programme for children with no documented history of two MMR vaccinations and/or no history of varicella vaccine.
- 3.18 The Subcommittee considered that any possible introduction of meningococcal C and B vaccines was for a separate discussion. The Subcommittee surmised that, if an adolescent vaccination programme was to be considered, then the Ministry of Education would prefer not to have a high school-based vaccination programme.
- 3.19 The Subcommittee noted the options suggested by the Ministry of Health for catch up vaccination of the young adult population at risk of contracting measles, which were to retain arrangements as is, or have GP vaccinations and/or a school based programme. The Subcommittee noted that there was an age-related cohort group (those aged 11 to 29 years) where many had not received the MMR vaccination when they were younger, mainly due to lower immunisation coverage in New Zealand in earlier decades. This exposed age range (11-29) covers child-bearing age groups where rubella is also a concern. The Subcommittee noted that the issue of MMR in adolescents was being considered by the Ministry at present and information on modelling and strategies would be brought to the next meeting.
- 3.20 The Subcommittee noted that there were no suggested changes to the current recommendations for vaccination of pregnant women.
- 3.21 The Subcommittee noted that the age 45 and 65 tetanus (Td) booster vaccinations were fully funded but that general practices charged the patient for the non-vaccine cost of immunisation as this was not funded by the Ministry. The Subcommittee noted that the Ministry of Health was to review all funding of immunisations in this age group.
- 3.22 The Subcommittee noted that the uptake of Td vaccination at ages 45 and 65 years is unknown. The Subcommittee questioned the need for continuing with the

recommendation for vaccination at these age groups as the recommendations for boosting are historic, previously having been every 10 years, now every 20 years. The Subcommittee noted that a third of young adults have had no primary course of tetanus and therefore would not be boosted with tetanus at a later date. The Subcommittee noted that this vaccine is funded for boosting for tetanus-prone wounds and should be considered the focus at wound care time when patients should be asked if they have had a primary course, rather than routinely giving a 'booster', and this question should also be asked of patients at age 45.

4 Two dose HPV vaccination

- 4.1 The Subcommittee noted that since the introduction of the HPV vaccination internationally a number of studies have been completed comparing a two-dose schedule with the three-dose schedule using both Gardasil (the vaccine currently in New Zealand), and Cervarix (a bivalent HPV vaccine containing type 16 and 18, registered but not currently available in New Zealand).
- 4.2 The Subcommittee reviewed reports of several clinical trials and reviews assessing the use of a two dose HPV vaccination regimen versus a three dose: Dobson et al (JAMA 2013;309 (17):1793-1802), Safaeian et al (Cancer Prev Res 2013;6(11):1242-1250), the April 2014 recommendation from the World Health Organization's Strategic Advisory Group of Experts (WHO SAGE), Jit et al (BMJ 2014;350:g7584 doi: 10.1136/bmj.g7584), and Stanley et al (Expert Rev. Vaccines 2014;13(8):1027-38.)
- 4.3 The Subcommittee noted the evidence from clinical trials for the two dose schedules in 9-14 year olds is restricted to immunogenicity, which indicates that a two-dose schedule is non-inferior to a three-dose schedule when assessed against immune response. The Subcommittee noted that at present there is no evidence from these trials demonstrating the duration of protection and there is no robust evidence from any randomised trial in 15-26 year old women that shows clinical efficacy against the diseases for a two dose schedule in this age group.
- 4.4 The Subcommittee noted that Gardasil has been registered for a two-dose vaccination schedule in a number of markets internationally including the UK, and the European Union and that the UK, Switzerland, the Netherlands, Mexico and Quebec have changed from the three dose schedule to a two dose schedule.
- 4.5 The Subcommittee noted that the adoption of a two-dose vaccination schedule poses a potential risk to the strength and longevity of the immune response and it is recommended that cohorts vaccinated with a two dose schedule be monitored to ensure there is no breakthrough disease. The Subcommittee also noted that Stanley et al report follow up studies of the cohorts vaccinated with the quadrivalent vaccine are ongoing and have extended up to 9 years thus far, with no breakthrough cases of cervical intraepithelial neoplasia.
- 4.6 The Subcommittee noted that 58% of 12 year old girls in New Zealand have received three doses of HPV vaccine whereas other countries have 70-80% coverage. The Subcommittee noted that immunisation rates may improve with a two-dose regime compared to the current three-dose regime. The Subcommittee

noted advice from the Ministry of Health that up to an additional 1,500 women may be vaccinated if the vaccine were given as two-doses. The Subcommittee also noted that the fact that three doses would be required after the 15th birthday should be strong encouragement for girls to get vaccinated before their 15th birthday. The Subcommittee noted it is not compulsory for schools to participate in the vaccination programme and that only approximately 20% of patients are being vaccinated in primary care settings if their school does not offer a programme. The Subcommittee noted that there is no active recall system in primary care for HPV immunisation.

- 4.7 The Subcommittee **recommended** funding the two-dose HPV vaccination for girls up to 15 years of age, with a high priority. The Subcommittee noted that the three-dose HPV vaccination would remain funded for girls over 15 years of age.
- 4.8 The Subcommittee noted that Gardasil is currently registered with Medsafe for use as a three dose regimen and for the number of doses to be reduced to two, the supplier would need to apply to Medsafe for a change to the registration status. The Subcommittee noted that if a change to a two dose vaccination schedule is made prior to the registration change, the product would be given off-label requiring additional consent from the parents/caregivers which some may not be comfortable giving. The Subcommittee **recommended** PHARMAC discuss with the supplier the possibility of a change in the registration status.
- 4.9 The Subcommittee noted that the Ministry of Health does not have a targeted surveillance programme for HPV. The Subcommittee considered that as part of an immunisation programme, in order to measure efficacy and efficiency, it is best international practice to have active surveillance programmes; all other antigens on the national immunisation schedule are notifiable diseases under the Health Act, apart from HPV related disease; a key primary indication for HPV vaccination are the cervical, anal and oral cancers linked to HPV infection; while these cancers are reported in New Zealand's cancer reporting systems, long latencies (up to decades) between the introduction of the vaccine, or changes to the vaccine schedule, and these diseases of interest mean that the effects of a change to the HPV schedule, or HPV programme, cannot be timely assessed.
- 4.10 The Subcommittee noted that the most sensitive early indicator would be a change in the incidence of genital and/or laryngeal warts, where these are a surrogate for the HPV related cancers, being the causal link between HPV infection and HPV related cancers; with the introduction of HPV immunisation programmes internationally there have been good reports of decreased incidence of warts in youth and young adult populations, occurring quickly and far more timely after introduction of the vaccine, and strengthening the case for surveillance strategies for the early identification of changes in the epidemiology of HPV sequelae; an appropriate active surveillance system would be notification under the Health Act of these early sequelae, as occurs with all other diseases/antigens on the national immunisation schedule, to have a robust surveillance system for what is a not inconsiderable health investment.
- 4.11 The Subcommittee however questioned if there was sufficient baseline data to be able to identify differences in trends in future, and noted that a trigger point would need to be determined to identify appreciable changes in incidences. The

Subcommittee noted that it may be a number of years before an appreciable change in the incidence of genital warts cases may be identified. The Subcommittee considered that should New Zealand change to a two dose regimen, data from overseas countries that have already changed to a two dose system should be monitored as this would act as an early warning system should these countries experience an increase in genital warts.

- 4.12 The Subcommittee noted the Health (Protection) Amendment Bill, amending inter alia the notifiable disease provisions of the Health Act, is currently under review and **recommended** a submission be made to include genital and laryngeal papillomatous warts notifiable by medical practitioners as non-identifying STI notifications.

5 Zoster Vaccine CUA

- 5.1 The Subcommittee noted that in May 2014 PHARMAC received an application for funding zoster vaccination, which was reviewed by PTAC at its August 2014 meeting. The Subcommittee noted that PTAC recommended funding zoster vaccination with a medium priority.
- 5.2 The Subcommittee noted that PTAC requested PHARMAC prepare CUAs covering a range of assumptions including age-related disease burden scenarios that incorporated remaining life expectancy for specific demographic groups for PTAC to review. The Subcommittee also noted that PTAC requested that assumptions include a waning of vaccine efficacy over time as per currently available data, and that sensitivity analysis include a possible booster at 10 years (although members did recognise that the 10-year boosted scenario has no current evidence base).
- 5.3 The Subcommittee noted the number and age of patients who were dispensed 35 x 800 mg aciclovir tabs and considered this to be a good indication of the incidence of herpes zoster in New Zealand. The Subcommittee also noted the number and age of patients being treated with capsaicin cream 0.075% without any diabetic products being concomitantly prescribed.
- 5.4 The Subcommittee did not identify any literature on the severity of recurrent episodes compared with the initial presentation therefore had no evidence that subsequent cases differed in severity
- 5.5 The Subcommittee noted that it is reasonable to use the number of patients treated with 800mg aciclovir 5 times daily as a base for the incidence rate in New Zealand and it compared well to other estimates of incidence, eg. the Australia BEACH estimate of 15.2 per 1000 for those aged over 60 years (Stein et al. Vaccine 2009;27:520-529). The Subcommittee also noted that these patients dispensed acyclovir with only partially represent all patients with symptomatic shingles presenting for medical care in general practice, being approximately only 80% of all presenting patients in the Wallis et al Dunedin study (J Prim Health Care 2014;6(2):108-113).

- 5.6 The Subcommittee noted that it is unclear why the incidence of zoster is increasing but this has been noted overseas and hence the incidence may continue to rise.
- 5.7 The Subcommittee noted that the zoster vaccination provided good protection for at least 5 years but ongoing immunity is not clear. The Subcommittee noted there was no evidence or information on the need for booster vaccinations. .
- 5.8 The Subcommittee noted that zoster vaccine efficacy does vary by age with vaccine efficacy for herpes zoster, at approximately 64% in the 60-69 year age group, 41% in the 70-79 year age group and 18% in the over 80 year age group (Oxman et al. N Eng J Med 2005;352:2271.).
- 5.9 The Subcommittee noted that implementation costs could be reduced if zoster vaccination was given concurrently with the influenza vaccine funded for all aged 65 years and over although the Subcommittee also noted that it may not be easy to incorporate the zoster vaccination into the annual influenza vaccination due to the primary care workload in the pre-flu season
- 5.10 The Subcommittee noted that the incidence of secondary cases of herpes zoster is uncertain but reported as 2-5%. The Subcommittee also noted that a prior attack of herpes zoster will usually confer substantial protection against subsequent attacks for some years and the safety of the zoster vaccine has been demonstrated in such situations.
- 5.11 The Subcommittee noted that the van Hoek paper highly influenced the UK funding the zoster vaccination at age 70. The Subcommittee also noted that the US and Australia recommend zoster vaccination be given at age 60.
- 5.12 The Subcommittee **recommended** funding zoster vaccination for patients at 65 year of age with a catch-up.
- 5.13 The Subcommittee noted that further analysis and research should be undertaken to ensure that Maori and Pacific Island patients receive equal benefits from funded Zoster vaccination at age 65 considering their age of death is lower than the rest of the population.

6 Pneumococcal vaccine for over 65's

- 6.1 The Subcommittee noted that at its' February 2014 meeting, PTAC reviewed an application from the supplier for funding pneumococcal polysaccharide 23 vaccine (PPV23) for all people 65 years and older. The Subcommittee noted PTAC recommended the application be declined due to low quality evidence. The Subcommittee noted that PTACs' minutes were reviewed by Immunisation Subcommittee at its September 2014 meeting and recommended that the Subcommittee further discuss PPV23 and PCV13 vaccines for adults at its next meeting.
- 6.2 The Subcommittee noted they were supplied with PTACs minutes, the supplier's application, the original PTAC cover paper and the relevant references for review. The references included the Moberley et al 2008 Cochrane Review of Vaccines for

preventing pneumococcal infections in adults, Vila-Corcoles et al BMC Infectious Diseases 2010;10:73, Dominguez et al Eur Respir J 2010;36:608-14, and Maruyama et al BMJ 2010;340:c1004, but that no further information on PCV13 had been received.

- 6.3 The Subcommittee considered the cost effectiveness modelling for PPV23 by the supplier was not robust on assumptions and, as the model was locked, the assumptions could not be tested. The Subcommittee noted that the Cochrane review was inconclusive that the studies provided no new evidence of benefit except for the Japanese study by Maruyama et al. The Subcommittee noted that Maruyama et al reported that all causes of pneumonia and pneumococcal pneumonia were significantly higher in the placebo group than in the vaccine group and that the death rate from pneumococcal pneumonia was also significantly higher in the placebo group than the vaccinated group. The Subcommittee noted that the Japanese population may not be comparable to the New Zealand population.
- 6.4 The Subcommittee noted that the ESR pneumococcal 23 report on 65 year olds suggests that there may be some herd effect starting to occur as a result of the vaccination of the younger population with the conjugate vaccine. However, the Subcommittee noted that a change in surveillance in 2009 makes it difficult to assess any changes that may have occurred and the ambivalence of the data would make it difficult to assess any benefits if pneumococcal 23 vaccinations were to be introduced. The Subcommittee noted that in 2011, the UK Joint Committee on Vaccination and Immunisation (JCVI) recommended that universal vaccination with PPV23 for all people over the age of 65 years be discontinued, with the vaccine continuing to be offered to those considered to be at risk. Following release of this statement the JCVI received views from interested parties and reassessed the evidence. The Subcommittee noted that the JCVI concluded that vaccination of this group may be effective and cost saving and have elected to continue universal vaccination of all people over the age of 65 years.
- 6.5 The Subcommittee noted that currently funded PCV13 and PPV23 vaccination is only available for under 18 year olds who are considered at high risk. The Subcommittee noted that at its February 2014 meeting the Subcommittee had recommended that the restriction of 18 years old be removed, allowing funded access to all patients considered to be a high risk regardless of age.
- 6.6 The Subcommittee **recommended** investigating funding pneumococcal vaccination further and in particular assessing vaccination with PCV 13 followed by PPV23 either for universal vaccination of all people over the age of 65 or for patients considered to be at high risk of pneumococcal infection.