

Immunisation Subcommittee of PTAC

Meeting held 28 October 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 11 & 12 February 2016, a record of which will be available in due course.

Record of the Immunisation Subcommittee of the Pharmacology and Therapeutics Committee (PTAC) meeting held at PHARMAC on 28 October 2015

1 Edmonston-Zagreb strain of measles vaccines

Application

- 1.1 The Subcommittee noted a submission from Te Arai for consideration of the inclusion of the Edmonston-Zagreb (EZ) strain of measles into the National Immunisation Schedule at ages 4.5 months and 9 months of age.
- 1.2 The Subcommittee noted that the product was not registered with Medsafe but noted that the submission had been brought to the Subcommittee primarily for consideration of the product suitability for use in an outbreak/epidemic situation.

Recommendation

- 1.3 The Subcommittee **recommended** that the submission for EZ strain of measles vaccine be declined for inclusion on the National Immunisation Schedule due to a lack of evidence showing the benefits of a monovalent vaccine over and above the currently funded MMR vaccine.

Discussion

- 1.4 The Subcommittee considered that the quality of the submission from Te Arai was of poor quality. The Subcommittee noted that the references provided did not substantiate the submission with no data being presented to validate vaccination at 4.5 months.
- 1.5 The Subcommittee noted a report from Strategic Advisory Group of Experts (SAGE) of Immunisation of the World Health Organisation for the Weekly Epidemiology Review (WER) paper due for publication in November 2015 stated, "A systematic review of the literature found that measles vaccination before 9 months of age is immunogenic, effective and safe. Vaccine effectiveness increases with the infant's age of vaccination and some evidence of a blunted response to the second measles containing vaccine (MCV)2 after the first MCV is given at <9 months of age was found with respect to geometric mean titre (GMTs) and avidity, but not for the proportion seropositive and cellular immunity."
- 1.6 The Subcommittee noted that the current WHO recommendation is, if the MMR vaccine is currently in use in the National Immunisation Schedule then the MMR vaccine should be used in the event of an outbreak or epidemic and that there was no information on any greater efficacy for the single antigen EZ strain of vaccine in these situations. The Subcommittee noted that ESR data shows the majority of measles cases notified in New Zealand are over the age of one year with the most cases being reported in ages 10 to 19 years of age and considered that there would be no added advantage in vaccinating at 4.5 months during an outbreak or epidemic.

- 1.7 The Subcommittee considered that reducing the age of vaccination for measles to add an extra dose at 4.5 months would not lower the rate of febrile convulsions and would have minimal effect on measles transmission based on NZ epidemiology. The Subcommittee noted that no data had been included in the submission to show a reduction in febrile convulsions with the single antigen measles vaccine versus the combination MMR vaccine currently being used. The Subcommittee noted that SAGE considers there is little benefit in vaccinating at 4 months.
- 1.8 The Subcommittee noted that WHO data suggests that at 4 months the seroconversion is ~40%, at 5 months it is ~60%, by 7 months it is ~70% and at 8 months it is ~90%. Furthermore, the Subcommittee noted that there is a possibility of early vaccination reducing the effectiveness of a further measles containing vaccine at a later age. The Subcommittee noted that there was no data available relevant to New Zealand to support measles vaccination under 6 months of age. The use of measles containing vaccine (MMR) in NZ in infants is currently recommended as an extra dose for infants from 6 months – 12 months in outbreak situations when appropriate.
- 1.9 The Subcommittee considered that the best strategy to reduce the likelihood of outbreaks and epidemics is to increase the current coverage. The Subcommittee considered that supplementary immunisation activities such as those carried out in the Americas (targeting special groups and a concerted effort to increase coverage) have a substantial impact of the incidence of measles.
- 1.10 In the event of an outbreak, the Subcommittee noted that there was no evidence provided in the submission to support switching from the currently funded MMR vaccine to a monovalent measles vaccine.

Ministry of Health Control Strategy

- 1.11 The Subcommittee noted information provided by MoH staff regarding progress made with their Measles Control Strategy. The Subcommittee noted that New Zealand intends to apply to the WHO for measles free status. For this to be granted there needs to be an absence of endemic measles virus transmission in a defined geographical area (e.g. region or country) for ≥ 12 months in the presence of a well- performing surveillance system. The Subcommittee noted that New Zealand should qualify as the outbreaks that have occurred in New Zealand have not been endemic but have been introduced by the return of travellers from overseas.
- 1.12 The Subcommittee considered that MMR coverage in New Zealand is currently at ~94% but there are lower rates of immunity particularly in the 10-25 years old age groups who went through the primary immunisation programme in a period when NZ had low immunisation coverage
- 1.13 The Subcommittee noted that the Ministry of Health Communicable Disease team were considering various strategies to increase measles immunity in the 10 to 25 year old age groups. Strategies under consideration included a school based program or a General Practitioner-lead programme.

- 1.14 The Subcommittee noted that the MoH carried out a cost benefit analysis with Massey University looking at the 25% of the population who were not immunised and concluded that the cost for immunising each child was between \$74 and \$1800 depending on the method/strategy used.
- 1.15 The Subcommittee noted that the MoH was developing a National Verification Committee in response to a request from the World Health Organisation (WHO) for all countries to develop a committee with a minimum of 5 independent members covering a range of specialties including paediatrics and adult medicine, similar to the makeup of the Immunisation Subcommittee. The purpose of the National Verification Committee would be to provide advice on elimination strategies and assistance in the writing of reports.
- 1.16 The Subcommittee noted that it would be difficult to merge the National Verification Committee and the Immunisation Subcommittee due to possibly conflicting terms of reference (ToR) and the likely workload involved. However, the Members considered that it would be appropriate for the MoH to invite members of the Subcommittee to join the National Verification Committee and those with the capacity to be on both could do so.

2 Diphtheria, tetanus and acellular pertussis (DTaP) vaccines

Recommendation

- 2.1 The Subcommittee **recommended** that international advice is sought on this topic.

Discussion

- 2.2 The Subcommittee noted a discussion document submitted by GlaxoSmithKline (GSK) discussing the various vaccination options using its diphtheria, tetanus and pertussis containing vaccines.
- 2.3 The Subcommittee noted that GSK's hexavalent has been listed as sole supply in the National Immunisation Schedule since 2008, the Infanrix-IPV since 2002, and Tdap since 2008. The Members considered that these were well established products in New Zealand and internationally.
- 2.4 The Subcommittee noted that a 2+1 primary vaccination schedule is in place in nine European countries. The Subcommittee noted that a 2 + 1 Schedule has the potential to give a degree of flexibility with the third dose being given at either 12 months or 15 months.
- 2.5 The Subcommittee considered that there was sufficient evidence to show that a 2+1 vaccine schedule would likely be sufficient for diphtheria, tetanus, and polio coverage as the incidence of these diseases is very low in New Zealand. Members also considered that a 2+1 schedule was unlikely to make a difference in hepatitis B cases in infants.

- 2.6 The Subcommittee noted that other countries using the 2+1 schedule had good control with Hib and that data suggested that a total of 3 doses worked and it did not matter greatly when those 3 doses were administered. The Subcommittee noted that ESR has reported 2 deaths from Hib in the last 10 years and 5 cases of the disease were reported in 2014 (one of whom was not vaccinated). The Subcommittee considered that there is a low incidence of invasive Hib but that most Hib disease occurs in the first year of life prior to vaccination.
- 2.7 The Subcommittee considered that moving to a 2 + 1 schedule may lead to a gap in the level of protective antibodies between the 2nd and 3rd doses of the vaccine and discussed the possibility that this would be covered by herd immunity as per the international evidence. The Subcommittee considered that Hib would most likely not be a problem as it is currently well controlled internationally which indicates that three doses are effective.
- 2.8 The Subcommittee noted that there was little clear evidence for or against moving to a 2+1 schedule for the coverage of pertussis. The Members noted that potential issues caused by moving to a 2+1 schedule with pertussis could be offset by targeting pregnant women for immunisation due to the severity of the disease in the first year of life.
- 2.9 The Report on the Effectiveness of Pertussis Immunisation in Children (EPIC) Study, Auckland University, unpublished, showed a small difference between the 2nd and 3rd doses with the difference in VE between the two groups being minor.
- 2.10 The Subcommittee considered that a schedule which involved fewer injections and few antigens being introduced would be preferable to the caregivers of the infants. The Members noted that while the number of injections would decrease, the number of GP visits would still remain the same but be redistributed over the first 18 months of the child's life.
- 2.11 The Subcommittee noted that a move to a 2 + 1 schedule would be unlikely to make any difference in mortality due to pertussis as there are very few deaths from pertussis with 8 having been reported between 2000 and 2012, all but one of which were in the first 3 months of life. The Subcommittee noted the incidence rate is 468/100,000 under the age of 3 months; 145/100,000 in 3-5 month olds; 26/100,000 in 6 to 11 month olds and 2.7/100,000 in 1 to 4 year olds. The Subcommittee noted that Māori and Pacifica children are 3 times more likely to be hospitalised than European for pertussis.
- 2.12 The Subcommittee noted that New Zealand mothers tend to go back to work earlier than Scandinavian mothers and therefore New Zealand children are in child care at an earlier age. The Subcommittee considered that for this reason, among others, if there was a move to a 2 + 1 schedule considerable effort would need to be put in to get the 2nd dose on time and to increase the vaccination rate in pregnant women.
- 2.13 The Subcommittee noted that the infant immunisation levels were currently the best they had ever been in NZ and that now was a good time to implement any changes. The Members considered that a weighted pros and cons list for moving from 3+1 to 2+1 could be of use.

- 2.14 The Subcommittee **recommended** that international advice is sought on this topic also; a SAGE Subcommittee has completed some modelling in this area which showed that the 2+1 schedule is expected to be effective provided the patients received all of their doses on time. This report was presented to the WHO SAGE meeting and background papers will be available on line.

3 Hexaxim - hexavalent

Application

- 3.1 The Subcommittee reviewed an application from Sanofi-Pasteur for Hexaxim, a multi-antigen vaccine that contained 2-components of pertussis, in June 2013. Members noted that at the November 2013 meeting, PTAC had reviewed a paper from PHARMAC regarding the inclusion of Hexaxim into the National Immunisation Schedule. Hexaxim was not registered for use in New Zealand at the time; however, the product had since become registered with Medsafe in March 2014.

Recommendation

- 3.2 The Subcommittee **recommended** that PHARMAC seek international advice on whether changing from a 15 month Hib vaccine to a hexavalent vaccine including a 2-component pertussis vaccination would be appropriate.
- 3.3 The Subcommittee **recommended** that Hexaxim is a suitable product for listing on the National Immunisation Schedule for vaccination at 6 weeks, 3 months and 5 months.

Discussion

- 3.4 The Subcommittee noted that at that time, PTAC recommended PHARMAC not change to a 2 component acellular pertussis vaccine and that PHARMAC should seek the advice of the Immunisation Subcommittee as to the appropriateness of the current pertussis vaccination schedule, including whether an additional dose at 12-15 months would be appropriate. The Committee requested advice from the Immunisation Subcommittee on whether a 2-component aP vaccine would be acceptable for funding on the Immunisation Schedule.
- 3.5 The Subcommittee noted that the application for Hexaxim was to replace Infanrix-hexa (a GSK product) on the National Immunisation Schedule for doses at 6 weeks, 3 months, and 5 months of life. The Members noted that this application was not for a toddler booster dose.
- 3.6 The Subcommittee considered that the primary differences between Hexaxim and Infanrix-Hexa were:

- Hexaxim was available as a liquid suspension in a ready to use pre-filled syringe while Infanrix-Hexa was available as a lyophilized powder (Hib component) and liquid suspension (DTPa-HBV-IPV component) which required reconstitution prior to use.
 - Hexaxim had a lower diphtheria toxoid content compared to Infanrix-Hexa (>20 versus >30 IU), and the diphtheria toxoid levels in Hexaxim were lower than current international standards (>30 IU).
 - Hexaxim included two pertussis antigens (pertussis toxoid, filamentous haemagglutinin) versus Infanrix-Hexa which included three pertussis antigens (pertussis toxoid, filamentous haemagglutinin, pertactin).
 - Hexaxim includes a novel hepatitis B surface antigen while Infanrix-Hexa included a previously well-established antigen.
 - Hexaxim had a higher Hib polysaccharide content compared to Infanrix-Hexa (12mcg versus 10mcg).
- 3.7 The Subcommittee noted that the evidence provided by the supplier included four large randomised controlled trials, all conducted by the supplier, which demonstrated non-inferiority of Hexaxim to Infanrix-Hexa for primary series in terms of immunogenicity.
- 3.8 The Subcommittee considered that patients and vaccine administrators would likely prefer the ready to use liquid formulation of Hexaxim to the powder and liquid suspension which required reconstitution. Members noted that using the pre-filled syringes would reduce the number of clinical errors and save time; however, they also noted that having a vaccine which required reconstitution was established practice for those who administered vaccines.
- 3.9 The Subcommittee noted that there was weak evidence comparing the efficacy of 2 versus 3 pertussis components. Members noted that the supplier stated in their application that a SAGE report indicated that the 2 pertussis components was as effective at pertussis control than products with more pertussis components; however, members were unable to find this statement in the SAGE report.
- 3.10 The Subcommittee considered the Cochrane review conducted by Zhang et al (Acellular vaccines for preventing whooping cough in children (Zhang et al Cochrane Database Syst Rev 2012 Mar 14;3:CD001478) of double blind randomised efficacy and safety trials of acellular vaccines in children under 6 years concluded that one and two component vaccine were less effective than those with 3 or more components. The Subcommittee noted that Sanofi-Pasteur consider these results not to be a true reflection of all 2 component vaccines as bias was introduced by an experimental vaccine that was never commercialised as the efficacy was considered to be too low.
- 3.11 The Subcommittee noted that the submission included four large clinical trials conducted by Sanofi demonstrating non-inferiority of Hexaxim to Infanrix-Hexa. The Subcommittee also noted a randomised trial by Tichmann et al conducted in 45 centres in Germany and funded by GSK (Vaccine 2005;23:3272-3279) which showed higher antibody levels for hepatitis B, diphtheria and polio from vaccination with the GSK vaccine, Infanrix-Hexa brand, and similar results for tetanus, Hib and pertussis between the Sanofi and GSK vaccines. The Subcommittee noted that countries that have shown good control with the 2

component vaccine (Sweden, Denmark and Japan) have high vaccination rates - ~100%. The Subcommittee considered that New Zealand now has a vaccination rate not dissimilar but continues to have high rate of pertussis.

- 3.12 The Subcommittee considered that the data available shows that Hexaxim is non-inferior to Infanrix-Hexa with the only question being Hepatitis B. The Subcommittee noted that the Hexaxim gives lower geometric mean titres which may relate to longevity of response but it is known that people with low hepatitis B antibodies get a very good anamnestic response to a booster. The Subcommittee noted that the Australian Technical Advisory Group on Immunisation (ATAGI) had approved Hexaxim as suitable for inclusion on the Australian Immunisation Schedule providing that an 18 month Hepatitis B booster is introduced.
- 3.13 The Subcommittee considered that Hexaxim could be used in the 2+1 vaccine schedule proposed by GSK (described in minute 7); however, members did not recommend changing both the dosing schedule and the pertussis components at the same time.
- 3.14 In summary, the Subcommittee considered that there the immunogenicity data shows the GSK and Sanofi products are comparable, although there may be a possible concerns regarding the pertussis and Hepatitis B components and considered that these would need to be monitored closely if Hexaxim was listed in the National Immunisation schedule.

4 Pneumococcal vaccines – Synflorix and Prevenar 13

- 4.1 The Subcommittee noted that PHARMAC had received two submissions for pneumococcal vaccines; a 10-valent vaccine (PCV10), Synflorix, from GSK and a 13-valent vaccine (PCV13), Prevenar13, from Pfizer.
- 4.2 The Subcommittee noted that universal pneumococcal vaccination was introduced in New Zealand in 2008 with a 7 valent vaccine from Wyeth, now a Pfizer product. Synflorix, a 10 valent vaccine from GSK was listed following the tender in 2011 and this product was in turn replaced by Pfizer's 13 valent Prevenar 13 in 2014.
- 4.3 The Subcommittee considered that both of the submissions were of good quality, providing solid data which showed that the vaccines were efficacious.
- 4.4 The Subcommittee noted that the main difference between the two vaccines was the inclusion of the antigens 3, 6A and 19A in PCV13. The Subcommittee noted that there has been a significant reduction in invasive pneumococcal disease caused by the vaccine serotypes since the introduction of pneumococcal vaccines although there had been an increase in the disease caused by 19A in 2014 with 11 cases being identified versus 6 the previous year.
- 4.5 The Subcommittee considered that an important issue is whether there is cross protection for 19A from the 19F contained in both PCV10 and PCV7. The Subcommittee noted that the Domingues et al (Lancet Respir Med 2014;2:464-71) reported vaccine effectiveness of 83.8% (95% CI 65.9 - 92.3) against vaccine

serotypes and 77.9% (CI 41.0 – 91.7) against vaccine related serotypes and 82.2% (CI 10.7 - 96.4) against serotype 19A. The Subcommittee noted that in July 2015, the European Medicines Agency approved a type II variation for Synflorix and the vaccine label now includes effectiveness data on 19A and acquired otitis media.

- 4.6 The Subcommittee noted that studies in the US (Lancet Infect Dis 2015;15(3):301-9) and the UK (Lancet Infect Dis.2014;14(9):839-46) have reported high levels of vaccine efficacy against all invasive pneumococcal disease, PCV13 specific type invasive pneumococcal disease and 19F both after a 3 + 1 regimen (US) and a 2 + 1 regimen (UK).
- 4.7 The Subcommittee noted that there are a number of international studies that show efficacy for both vaccines against vaccine serotype.
- 4.8 The Subcommittee noted that there is accumulating data to show that a 2 + 1 regimen is equivalent to a 3 + 1 for both Synflorix and Prevenar 13 and considered that vaccination at 6 weeks and 3 months would be appropriate. The Subcommittee noted that overall invasive pneumococcal disease has dropped dramatically and now would be a good time to introduce a 2 + 1 regimen.
- 4.9 The Subcommittee considered that both PCV10 and PCV13 are suitable for inclusion on the National Immunisation Schedule but that if PCV10 were listed for universal vaccination it may be necessary to continue to list PCV13 for vaccination of high risk groups.

5 TdaP booster

- 5.1 The Subcommittee noted an application from BioCSL (now Seqirus) for a monovalent acellular pertussis TdaP-Booster vaccine to be considered as an alternative for inclusion in the National Immunisation Schedule.
- 5.2 The Subcommittee noted that acellular pertussis vaccines contain from 1 to 5 antigens including varying amounts of filamentous haemagglutinin (FHA), pertactin (PRN) and/or fimbriae (FIM) types 2 and 3 and consider that the role of these additional antigens is subject for debate.
- 5.3 The Subcommittee noted the Cochrane Review (Zhang et al Cochrane Review 2014;Issue 9) summarised six efficacy trials of acellular vaccines containing various numbers of components for preventing whooping cough in children under the age of 6 and concluded that multicomponent vaccines had higher efficacy than the mono or two component vaccines. However, the Subcommittee noted that this review has been challenged for the following reasons:
 - Only 6 trials were used, of which only 2 specifically used mono component aP- one published in 1988 the other in 1995 and all were looking at primary immunisation course not booster.
 - Bias occurs when paired FHA serology is used for lab confirmation of pertussis- the presence of anti- FHA induced by vaccine results in missed diagnosis and hence inflates the efficacy estimates of multi component

vaccines. If recalculated by excluding pertussis cases confirmed solely by paired FHA serology this gives efficacy of mono vaccines as 78%. In a review by Granstrom in 1996 (Vaccine 1996;14:17-18) the corrected efficacy in the 3 double blind randomised controlled efficacy trials for mono, three and five component aP vaccines were all approximately 80% i.e no difference.

- 5.4 The Subcommittee noted that the applicant presented two more recent randomised controlled trials which considered safety and immunogenicity: Thierry-Carstensen et al 2012 (Vaccine 2012;30:5464-71) and Carlsson et al 2015 (Vaccine 2015;33:3717-25).
- 5.5 The Subcommittee noted the Thierry-Carstensen study was a randomised double blind controlled study in adults over 18 years of age, comparing mono Tdap with Td. Immunogenicity was measured by levels of anti-T, anti-d and anti-PT. Results indicated a similar booster response rate for anti-T and anti-d and 92% response rate for PT. Unfortunately, the study did not directly compare mono with multi-component vaccines. The authors do however refer to a paper by Blatter et al (Vaccine 2009;27:765-72) using the same method of measurement with corresponding anti-PT booster responses of 77.2% for Boostrix and 47.1% for Adacel.
- 5.6 The Subcommittee noted the authors explain the higher response on the higher dose of pertussis toxoid in the mono vaccine (20 mcg compared with 8 mcg) and the fact that the tetanus toxoid is inactivated by hydrogen peroxide rather than formaldehyde and/or glutaraldehyde resulting in a lower degree of epitope impairment and a better antigen.
- 5.7 The Carlsson et al study (Vaccine 2015;33:3717-25) looked at 230 adolescents who had primary multicomponent aP (5) and who were randomised to receive either multi (5) or mono aP booster. Safety results were similar. There was a higher anti-PT response in the mono aP vaccine. The authors stated that whether or not this correlates to a clinical effect is not known.
- 5.8 The Subcommittee considered that the vaccines do appear to be equivalent in terms of safety profile; however, there is some debate about their equivalence in terms of efficacy. The Subcommittee noted that the vaccine is working really well in Denmark which indicates it may be a better vaccine because the toxoid is less denatured.
- 5.9 However, the Subcommittee considered that due to the issues in New Zealand with regular pertussis epidemics, there was insufficient evidence to demonstrate any benefit to changing to a mono vaccine and potentially run risks if the vaccine proved less effective and therefore did not consider this product suitable as an alternative for listing on the National Immunisation Schedule.
- 5.10 The Subcommittee noted there was a lack of evidence regarding the use of the Tdap-Booster vaccine in pregnant women which is a group which should be targeted for immunisations.