Record of the Immunisation Subcommittee of PTAC Meeting held via videoconference on 02 September 2020

Immunisation Subcommittee records are published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2016.

Note that this document is not necessarily a complete record of the Immunisation Subcommittee meeting; only the relevant portions of the meeting record 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.

PTAC Subcommittees make recommendations, including priority, within their therapeutic groups of interest.

The record of this Subcommittee meeting will be reviewed by PTAC at its meeting of 12-13 November 2020, the record of which will be available in due course.

PTAC Subcommittees and PTAC may differ in the advice they provide to PHARMAC, including recommendations' priority, due to the committees' different, if complementary, roles, expertise, experience, and perspectives.

PHARMAC is not bound to follow the recommendations made below. Applications are prioritised by PHARMAC against other funding options and progressed accordingly. The relative priority of any one funding choice is dependent on a number of factors, including (but not limited to) the recommendation of PTAC and/or PTAC Subcommittees, the mix of other applications being assessed, the amount of funding available, the success of commercial negotiations and/or the availability of clinical data.

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Present from the Immunisation Subcommittee:
Sean Hanna
Chris Millar (Observer)
Elizabeth Wilson
Karen Hoare
Lance Jennings
Nikki Turner
Michael Tatley
Osman Mansoor (part of) joined in at 9.30am
Stephen Munn
Stuart Dalziel

Apologies:
Edwin Reynolds
Tony Walls

1. The role of PTAC Subcommittees and records of meetings

1.1. This meeting record of the Immunisation Subcommittee of PTAC is published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2016, available on the PHARMAC website at https://www.pharmac.govt.nz/assets/ptac-terms-of-reference.pdf.

1.2. The Terms of Reference describe, *inter alia*, the establishment, activities, considerations, advice, and the publication of such advice of PTAC Subcommittees and PTAC.

1.3. Conflicts of Interest are described and managed in accordance with section 7.2 of the PTAC Terms of Reference.

1.4. The Immunisation Subcommittee is a Subcommittee of PTAC. The Immunisation Subcommittee and PTAC and other PTAC Subcommittees have complementary roles, expertise, experience, and perspectives. The Immunisation Subcommittee and other PTAC Subcommittees may therefore, at times, make recommendations for vaccines and immunisation that differ from PTAC's, including the priority assigned to recommendations, when considering the same evidence. Likewise, PTAC may, at times, make recommendations for vaccines and immunisation that differ from the Immunisation Subcommittee's, or PTAC Subcommittees may make recommendations that differ from other PTAC Subcommittees'.

PHARMAC considers the recommendations provided by both the Immunisation Subcommittee and PTAC and any other relevant PTAC Subcommittees when assessing applications for vaccines and immunisation.

2. Record of Subcommittee meeting held Tuesday, October 15, 2019

The Subcommittee reviewed the minutes of the Immunisation Subcommittee meeting held on 15 October 2019 and agreed that the minutes be accepted.

3. Adjuvanted quadrivalent influenza vaccination for people aged 65 years and over Interests

Application

3.1. The Subcommittee reviewed the application from Seqirus (NZ) Ltd for adjuvanted inactivated quadrivalent influenza vaccine (aQIV) for use in people aged 65 years and over.

Recommendation

3.2. The Subcommittee **recommended**, within the context of vaccines and immunisation, that adjuvanted inactivated quadrivalent influenza vaccine (aQIV) for use in people aged 65 years and over be listed if cost neutral to unadjuvanted quadrivalent influenza vaccine (QIV).

3.2.1. The Subcommittee considered that the evidence of benefit for aQIV over QIV was low but that it is possible that aQIV may provide additional benefit, particularly in more severe influenza seasons when the AH3 strain dominates and QIV vaccine effectiveness is usually lower. The Subcommittee considered that aQIV was likely to be at least as effective as QIV.

Discussion

3.3. The Subcommittee noted that the same application from Seqirus (NZ) Ltd for aQIV was reviewed by PTAC at its August 2020 meeting. The Subcommittee noted that PTAC had recommended aQIV for those aged 65 years and over be declined due to low quality evidence and considerable uncertainty around the magnitude of benefit of an aQIV over QIV based on the indirect comparisons considered, with very wide confidence intervals for all estimates of effectiveness.

3.4. The Subcommittee noted that the burden of disease with regard to hospitalisations from influenza and influenza-like-illness (ILI) is highest in people aged less than one year and those aged 65 and over, and that rates are highest in Māori and Pacific people. The Subcommittee also noted that those living in more deprived areas have a higher influenza attributable death rate than those in less deprived areas.

3.5. The Subcommittee noted that the elderly generally respond less to vaccines, including the currently funded non-adjuvanted quadrivalent influenza vaccine, due to immunosenescence. Members noted that adjuvants are used to improve the response to vaccines, to offset the effects of immunosenescence.

3.6. The Subcommittee noted that hospitalisation rates can vary considerably from year to year and are usually highest when A subtype (H3N2) viruses dominate a season.

3.7. The Subcommittee noted two studies by Khieu et al. investigating hospitalisation and mortality incidence rates in New Zealand attributable to influenza from 1994 to 2008 (Khieu et al. Vaccine 2015;33:4087-92, Khieu et al. J Infect 2017;75:225-33). The Subcommittee noted that the highest proportion of hospitalisations and deaths attributable to influenza were in adults aged 65 and over, and that influenza attributable death rates are higher for more deprived areas of New Zealand (NZDep2013 quintiles 9 and 10; RR (NZDep 9 and 10 compared with quintiles 1 and 2) 1.8, 95% CI 1.3 to 2.4).

3.8. The Subcommittee noted that the influenza attributable mortality rates reported by the Ministry of Health (MoH) provide a lower estimate than that reported in the Khieu et al. 2017 study. The Subcommittee noted that reported rates from different datasets and studies vary significantly, which makes it difficult to calculate cost-effectiveness. The Subcommittee considered that this should be taken into account when using the data for analysis, and that outcomes using the available data should be used as general guidance only.

3.9. The Subcommittee noted that for the 2019 influenza season, MoH reported that influenza vaccine coverage was 66% in adults aged 65 and over, 57% in Māori people aged 65 and over, and 70% in Pacific people aged 65 and over. The Subcommittee noted that vaccination coverage has been static for a number of years, remaining around 60%, and that coverage needs to be improved for high risk elderly people.

3.10. The Subcommittee noted that adjuvanted vaccines are associated with more adverse events than non-adjuvanted vaccines (such as local tenderness at the injection site, swelling or bruising), but considered that any potential concerns of increased adverse events with aQIV would be allayed by the fact that adjuvanted vaccines have been used for many years.

3.11. The Subcommittee noted that the appropriate comparator for aQIV in New Zealand is QIV, but because there are no head-to-head trials of aQIV comparing with a QIV, the supplier had instead provided an indirect comparison using Fluad aTIV as the common comparator, providing indirect signals of nominal superiority over TIVs and non-inferiority with aQIV. The Subcommittee considered that the absence of a head-to-head comparison of QIV with aQIV was a substantial limitation with the application.

3.12. The Subcommittee noted a phase III multi-centre, double-blind, randomised clinical trial that compared aTIV to aQIV using haemagglutination inhibition (HI) as a surrogate endpoint (Essink et al. Vaccine. 2020;38(2):242-50). The Subcommittee noted that the trial demonstrated non-inferiority of aQIV compared with aTIV for geometric mean titre and seroconversion rates, and that reactogenicity profiles were generally comparable. The Subcommittee noted that aQIV demonstrated immunogenicity against two B lineages, compared with aTIV which only includes one B lineage. However, the Subcommittee noted that the evidence presented in the study was only for immunogenicity, and that the data was primarily for immunogenicity rather than vaccine effectiveness, so considered that the evidence for clinical benefit of aQIV over aTIV was limited.

3.13. The Subcommittee noted a prospective, non-experimental cohort study (n=107,661, 170,988 person-years) in a community setting (excluding residents of aged-care facilities) comparing aTIV with unadjuvanted TIV in northern Italy (Mannino et al. Am J Epidemiol. 2012; 176(6):527-33). The Subcommittee noted that the primary endpoint was the incidence of hospitalisation for influenza or pneumonia across

three consecutive influenza seasons, which were assessed over three time periods around peak influenza incidence (narrow, ie. those weeks adjacent to peak influenza occurrence with > 1 case per 1000 person-weeks; intermediate, ie. those weeks adjacent to peak influenza occurrence with > 0.5 cases per 1000 person-weeks; broad, the entire influenza season). The Subcommittee noted that there was uncertainty around the vaccine effectiveness estimates from this study and considered the narrow time window's 25% reduction in influenza attributable hospitalisations with aTIV to be an overestimate. The Subcommittee considered that it would be more appropriate to look at the broad time window in order to assess effectiveness across the whole influenza season. The Subcommittee also noted that the intermediate time window improvement of 17% reduction in hospitalisations was not statistically significant. The Subcommittee considered that the considerable variation between time windows, makes it difficult to ascertain which data is most valid to use to inform future modelling.

3.14. The Subcommittee noted that the Mannino study was limited by not using PCR or culture to confirm influenza, but rather measured rates of hospitalisations corresponding to the influenza seasons as a surrogate indicator for influenza. The Subcommittee also noted that the administration of aTIV versus TIV was not randomised and that aTIV was given to a frailer population with more comorbidities, as per local guidelines, hence introducing a potentially large selection bias. The Subcommittee noted that Mannino study used a propensity score to adjust for multiple confounders, and that several variables used in the derivation of the propensity score had also been used as explanatory variables in their multivariate model. The Committee noted that adjusting for the same confounders twice may lead to type 1 error, underestimating the true extent of uncertainty.

3.15. The Subcommittee noted a number of additional studies comparing the efficacy of aTIV to TIV:

3.15.1. Iob et al. Epidemiol Infect. 2005;133(4):687-93: a prospective non-experimental study (n=3173) of residents of long-term care facilities, aged mostly 65 and over in which the primary endpoint was incidence of influenza-like-illness (ILI). The Committee noted that the OR for any vaccination was 0.56 (95% CI, 0.45 to 0.68) with a point estimate relative any vaccine effectiveness of 44%. The Subcommittee noted that when PTAC considered the study's analysis of results at its August 2020 meeting , it considered the analysis to be incorrect as it had failed to adjust for individuals clustered within residential care facilities and so the study, when properly analysed from the reported summary data, had no evidence of a difference between residents who had or had not received any vaccination (PTAC's recalculated OR 0.83 (95% CI 0.58 to 1.12), P=0.31).

3.15.2. van Buynder et al. Vaccine. 2013;31(51):6122-8: a small prospective case control study (n=282) of patients aged 65 years and older, with a primary endpoint of incidence of laboratory confirmed influenza over a single influenza season. The Subcommittee noted that the odds ratio for aTIV relative to TIV was 0.37 (95% CI, 0.14 to 0.96), with a point estimate for relative vaccine effectiveness of 63%.

3.15.3. Lapi et al. Expert Rev Vaccines. 2019;18(6):663-70: a retrospective case control study (n=43,000) of patients aged 65 years or older, with a primary endpoint of hospitalisation from influenza associated complications. The Subcommittee noted that the odds ratio for aTIV relative to TIV was 0.61 (95% CI, 0.39 to 0.96).

3.15.4. Gravenstein et al. Unpublished -IDWeek Abstract 996. 2018: a prospective open-label cluster randomised controlled trial (n=50,012 total participants) for those aged 65 years or older living in a nursing home for at least 100 days. In all, 411 US nursing homes were reported to be randomised to provide aTIV as standard of care for their residents, with 409 nursing homes randomised to provide TIV as standard of care. There were three primary outcomes for the study, of which the first listed was time to any hospitalisation. The Subcommittee noted that the unadjusted hazard ratio (HR) for all-cause hospitalisations was 0.94 (95% CI 0.88 to 1), P=0.05 for aTIV relative to TIV. The incidence of all-cause hospitalisation was 18.8% in the aTIV group and 20.0% in the TIV group, consistent with a point estimate for relative vaccine effectiveness of 6% greater than TIV. The Subcommittee considered the likely more elderly and morbid population seen in American nursing homes was unlikely to be reflective of the whole New Zealand aged 65+ years population, limiting the ability to generalise these results to the New Zealand setting.

3.16. The Subcommittee considered that although all of the above comparisons of aTIV to TIV as evidence for aQIV are indirect comparisons, the studies signalled adjuvanted vaccines are likely to have superior effectiveness in the elderly population compared to non-adjuvanted vaccines. The Subcommittee also noted that vaccine effectiveness comparisons vary substantially between the studies, and that influenza seasons can differ greatly from year to year, so that observing only one influenza season may not be as effective as longer-term, multi-season analysis.

3.17. The Subcommittee noted that the variability between influenza seasons means that there will be consistent variability in vaccine effectiveness seen across studies and considered that the data from these studies should be used only to generally inform mathematical modelling and not taken as fact. The Subcommittee considered that future studies are likely to show the same level of variability.

3.18. The Subcommittee noted that the PBAC in Australia reviewed the same evidence during their appraisal of aQIV in 2019 and was satisfied that aQIV is likely to provide a significant improvement in effectiveness over QIV in adults aged 65 and over.

3.19. The Subcommittee considered that the aQIV would be well tolerated in the proposed population, with minimal side effects as the MF59C.1 squalene adjuvant is safe and generally well tolerated. The Subcommittee noted that aQIV has a shorter shelf life than QIV (12 vs 15 months). The Subcommittee noted that healthcare practitioners routinely stock many different types of vaccines in the same refrigeration unit and did not consider that the addition of aQIV would lead to an increase in human error in administration of the correct vaccines to patients.

3.20. The Subcommittee considered that even a small decrease in influenza attributable hospitalisation rates from using aQIV over QIV would reduce hospital costs, but considered that the full benefit cannot be modelled accurately due to the considerable variation in vaccine effectiveness seen in the evidence. The Subcommittee also considered that PHARMAC should include changes in rates of GP visits in its consideration of the potential outcomes if aQIV were to be funded.

3.21. The Subcommittee noted that the highest burden of disease from influenza in the elderly occurs in influenza seasons where the predominant strain of influenza is AH3, which is compounded by immunosenescence seen in the elderly. The Subcommittee considered that although there is no head-to-head evidence comparing aQIV to QIV, there are signals of improved effectiveness with adjuvanted vaccines and that the aQIV might be expected to be more effective than QIV in the

elderly population in reducing the burden of disease from influenza, especially in seasons where the predominant influenza virus is an A(H3N2) subtype.