# Summary of recent issues considered by four national immunisation technical advisory groups (NITAGs) and WHO immunisation-related advisory committees

**Prepared by the National Centre for Immunisation Research & Surveillance (NCIRS)**

**Period of review: 16/01/2019 to 16/05/2019**

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## Contents

# 1 Advisory Committee on Immunization Practices (ACIP), USA

## 1.1 ACIP meeting: 27–28 February 2019

- Agenda, minutes, presentation slides and video recordings of this meeting: http://www.cdc.gov/vaccines/acip/meetings/meetings-info.html
- Full minutes of the February 2019 meeting are pending. Therefore, this summary has been developed from the presentation slides and video recordings.

**Japanese encephalitis (JE) vaccines**

- Risk of JE for most travellers is very low; 12 JE cases reported among US travellers or expatriates between 1993 and 2017 with estimated risk of <1 case per million trips to Asia
- JE-VC (Ixiaro®) registered for adults since 2009 and children ≥2 months since 2013; current recommendation only for adults
- Changes to JE vaccine recommendations:
  - Additional information on factors that increase JE risk to assist providers with decision making
  - Longer-term travel no longer specifically defined as a cut-off of ≥1 month
  - Removed consideration of vaccination for travellers to an area with an ongoing JE outbreak
  - Small wording changes
- JE-VC recommendations:
  - Recommended for persons going to a JE-endemic country to take up residence or longer-term (e.g. ≥1 month) travellers, and frequent travellers to JE-endemic areas
  - Should be considered for shorter-term (e.g. <1 month) travellers with an increased risk of JE on the basis of planned travel duration, season, location, activities and accommodation, as well as those uncertain of duration of travel, destinations or activities
  - Not recommended for travellers with low risk, such as shorter-term travel to urban areas or travel that occurs outside of the well-defined JE virus transmission season
- Additional recommendations updated:
  - Accelerated vaccination series for adults approved (previously only 0 and 28 days): In adults aged 18–65 years, the primary vaccination schedule is two doses administered on days 0 and 7–28 days. This is not applicable to children.
  - Booster dose recommendation strengthened and updated to include paediatric ages (previously only adults): For adults and children, a booster dose (i.e. third dose) should be given at ≥1 year after completion of the primary JE-VC series if ongoing exposure or re-exposure to JE virus is suspected
- Recommendations to be published in MMWR

**Anthrax vaccines**

- AVA (Anthrax Vaccine Adsorbed; BioThrax®; sponsor: Emergent BioSolutions) is the only licensed anthrax vaccine in the US for use as post-exposure prophylaxis (PEP) in adults aged 18–65 years
- AV7909 (NuThrax®) is the next generation anthrax vaccine – available for emergency use authorisation
  - Anthrax Vaccine Adsorbed with CPG 7909 adjuvant; sponsor is Emergent BioSolutions Inc.
  - Administered via intramuscular (IM) route, 0.5mL per dose, 2 doses given 2 weeks apart
  - Anticipated to be added to the Strategic National Stockpile starting July 2019 for PEP
  - Currently only phase 1 and 2 studies available; phase 3 study planned for 2019–2021
  - FDA biologics license application (BLA) submission expected Q4 2021
- AVA is preferred for PEP; however AV7909 is an option if AVA supplies are exhausted or unavailable
  - Based on limited immunogenicity data from phase 2 clinical trials, AV7909 generates a similar magnitude but faster immune response than AVA given by the IM route
  - Safety data are limited; however given the high mortality associated with inhaled anthrax, the benefits of AV7909 outweigh the risk of potential unknown adverse events

- Consideration of booster dose interval for AVA used for pre-exposure prophylaxis (PrEP) in individuals with potential future exposure to *B. anthracis* spores (i.e. not at current high risk):
  - Current recommendation is a 3 dose schedule of AVA at 0, 1, 6 months followed by boosters at 12 and 18 months then annually; evidence was considered regarding whether the 3 dose schedule can be followed by boosters every 3 years
  - New recommendation: a booster dose of AVA may be given every 3 years to persons not currently at high-risk of exposure to *B. anthracis* who have been previously primed with AVA and wish to maintain protection
  - Based on immunogenicity data from non-human and human trials supporting sustained immunological memory to at least month 42
  - While in the high-risk area, the licensed booster schedule for high risk exposure risk applies
  - Persons who have initiated but not completed the pre-exposure priming series can transition to the post-exposure schedule prior to entering an area of high risk

**Influenza vaccines**

- Surveillance update – 2018/19 season
  - As of February 2019, influenza activity remained elevated
  - A/H1N1 has predominated overall, but A/H3N2 viruses were detected more commonly in the Southeast and have increased in other regions in recent weeks
  - An increasing proportion of the H3N2 viruses belong to the 3C.3a genetic group which is antigenically different from the 3C.2a genetic group
- Interim estimates of vaccine effectiveness (VE) of the 2018–19 seasonal influenza vaccine against medically attended influenza
  - Data from the US Flu VE Network: test-negative design; 5 sites enrolling outpatients (Nov 2018–Feb 2019) aged ≥6 months with acute respiratory illness with cough ≤7 days duration
  - 3254 patients enrolled, 14% (n=465) influenza RT-PCR positive
  - Cases by subtype: 63% A/H1N1, 22% A/H3N2, 13% A unsubtyped, 1% each B/Yam and B/Vic
  - Adjusted VE against medically attended influenza by age group – overall: 47% (95%CI: 34–57); 6m–17y: 61% (95%CI: 44–73); 18–49y: 37% (95%CI: 9–56); ≥50y: 24% (95%CI: -15 to 51)
  - Adjusted VE against A/H1N1 influenza by age group: 46% (95%CI: 30–58); 6m–17y: 62% (95%CI: 40–75); 18–49y: 45% (95%CI: 14–64); ≥50y: 8% (95%CI: -59 to 46)
  - Adjusted VE against A/H1N1 influenza (overall): 44% (95%CI: 13–64)
  - No estimate of LAIV effectiveness anticipated this season from US Flu VE Network
- Recent vaccine licensure changes:
  - 0.5 mL dose of Fluzone QIV (Sanofi Pasteur) approved by FDA in January 2019 for all ages (0.25 mL or 0.5mL can now be used in children aged 6–35 months)
  - Age indication for Afluria and Afluria quadrivalent (Seqirus) expanded from ≥5 years to ≥6 months in October 2018 (children 6–35 months receive 0.25 mL vs 0.5 mL for ≥3 years)
- Afluria quadrivalent (Seqirus) for children aged 6–59 months (presentation by vaccine sponsor)
  - Phase 3 RCT in children 6–35 months (n=935; Afluria QIV=700, comparator QIV=235) and 36–59 months (n=1312; Afluria QIV=984, comparator QIV=328) conducted during the Northern Hemisphere 2016–2017 season; comparator QIV was Fluzone QIV
  - Concomitant vaccinations were an exclusion criteria for the purpose of evaluating safety without confounders that may impact reactogenicity
  - 8 co-primary endpoints reported as overall for all ages included – 2 endpoints (geometric mean titre ratios [GMTRs] and seroconversion rate [SCR]) for 4 strains
  - Safety data reported by age group
    - 6–35 months: similar frequency of local adverse reactions (~3–25%) and systemic adverse events (~5–33%) between two vaccine groups with most events being mild or moderate in

intensity; mild fever more common in comparator QIV (overall ≥99.5°F[1]: 7.2% vs 11.9%; vaccine-related ≥99.5°F: 4% vs 7.9%), severe fever (≥101.3°F[1]) made up slightly less than half of all fever cases among Afluria QIV recipients
        - 36–59 months: similar frequency of local adverse reactions (~5–36%) and systemic adverse events (~3–15%) between two vaccine groups with most events being mild or moderate in intensity; fever rates approximately the same in both groups though slightly higher with comparator QIV (overall ≥99.5°F: 4.8% vs 6.0%; vaccine-related ≥99.5°F: 3.1% vs 4.7%), lower proportion with severe fever (<2%)
        - No vaccine-related SAEs or AESIs in any age or vaccine group reported
    - Conclusions: Afluria QIV demonstrated non-inferior immunogenicity to a licensed QIV comparator and has comparable safety and tolerability
- Inactivated influenza vaccine and spontaneous abortion in the Vaccine Safety Datalink (VSD)
    - Background: matched case control study in 2010–11 and 2011–12 seasons found increased risk of spontaneous abortion in the 28 days following receipt of inactivated influenza vaccine (IIV) in pregnant women; increased risk limited to 2010–11 season in women who had received IIV in the prior influenza season
    - Matched case-control study (1:1 matching ratio) in 2012–13, 2013–14 and 2014–15 seasons of pregnant subjects 18–44 years enrolled at a VSD site with outcome of live birth or spontaneous abortion; 50% in each season vaccinated in previous influenza season
    - 1236 matched pairs (627 vaccinated in previous season, 609 not vaccinated in previous season); imbalance in some baseline characteristics including age, race, diabetes, asthma and BMI
    - No significant association between IIV receipt and spontaneous abortion found, regardless of prior season vaccination status, season or risk window – findings support safety of influenza vaccine in early pregnancy

**HPV vaccine**

- Primary issue discussed is whether HPV vaccination should be recommended for persons aged 27–45 years who were not previously vaccinated (expansion of age indication for 9vHPV approved in October 2018)
- HPV natural history
    - Rapid acquisition of HPV in late teens and early twenties
    - Progression from incident infection to cervical precancer can be within a few years; from precancer to cervical cancer can be >20 years
    - >90% of infections and 30–40% of cervical precancers clear
    - Less is known about the natural history of HPV at non-cervical sites and in males
    - Model-based estimates of the burden of disease due to incident HPV infection in mid-adults depends on assumptions regarding probability of infection, immunity after clearance of natural infection, sexual behaviour and partner mixing, and progression and regression of precancer lesions
- Economic modelling to estimate the impact and cost-effectiveness of mid-adult (27–45 years in females and 22–45 years in males) HPV vaccination in the US (HPV-ADVISE model)
    - Individual-based transmission-dynamic model, with outcomes including anogenital warts, cervical cancer and cancers of the anus, oropharynx, penis, vagina and vulva
    - Current HPV vaccination program (females up to 26 years and males up to 22 years) is likely cost-saving (vs no vaccination)
    - Extending vaccination to 45year-old females and males is predicted to produce small additional reductions in HPV disease burden (e.g. 0.2–0.4% reduction in genital warts and cervical cancers)

[1] 99.5°F=37.5°C; 101.3°F=38.5°C

- Cost-effectiveness ratios for mid-adult vaccination (vs current recommendation) are ≥$360,000 per QALY gained in 95% of model simulations (median = $1.5 million)
- Cost-effectiveness of mid-adult vaccination is highly sensitive to level of natural immunity after infection, rate of progression to cervical lesions and historical vaccination coverage

- Overview of health economic results of 9vHPV use in mid-adults from 4 modelling groups
  - Models have been reviewed by ACIP: US HPV-ADVISE model (Brisson et al), simplified model (Chesson et al), Merck model (Daniels et al, CoI all authors are employees of Merck & Co), and two CISNET models (Harvard & Policy1-Cervix [Cancer Council NSW]) [first 3 were reviewed at ACIP's October 2018 meeting, highlighted findings included in previous NITAG summary)
  - All models are dynamic and include a range of health outcomes (as for HPV-ADVISE, above)
  - All models found that mid-adult vaccination is much less cost-effective than current program: estimates of ICERs ranged from $105,700 to $830,00 for vaccination through age 30 years, and $149,100 to $1,471,000 for vaccination through age 45 years; ICERs were lowest for Merck model and highest for HPV-ADVISE model
  - In HPV-ADVISE, Simplified and Merck models, vaccination up to age 45 years had a higher cost per QALY than vaccinating up to 30 year olds; this was reversed in the two CISNET models, likely due to herd effects (i.e. current program likely extends greater herd benefits to <30 year olds than to ≥30 year olds) and interactions with screening
  - Differences across models attributed to:
    - Health economic parameters – vaccination costs, treatment costs and QoL assumptions
    - Historical and future vaccination coverage assumptions
    - Model structure and assumptions regarding sexual behaviour, HPV transmission dynamic, natural history of HPV infection and cervical cancer screening, diagnosis and treatment
- Mid-adult HPV vaccination: patient values and acceptability
  - Pubmed search for "HPV vaccine acceptability" – US studies of mid-adult women or men (>50% of sample was age ≥26 years); 10 studies selected for inclusion (6 women, 2 men, 2 MSM)
  - Overall value and acceptability of HPV vaccination was moderate (≥50% in all studies except 1)
  - Willingness to receive vaccine was high in both MSM studies
  - HPV vaccination not valued by all respondents primarily because of low perceived HPV risk (e.g. marriage, monogamous relationship, few sex partners)
- Program and vaccine provider surveys on acceptability of HPV vaccination
  - 4 surveys (2 of programs and 2 of primary care physicians) conducted between 2016–2019 to determine acceptability of: 1) harmonising current HPV vaccine recommendations (26 years for both females and males), 2) individual clinical decision making regarding vaccination in mid-adults
  - Harmonisation would likely be acceptable, 98% of programs and 93% of physicians were in favour
  - Individual decision making for vaccination of mid-adults might be acceptable, though majority anticipated challenges in communicating such a recommendation and determining who would benefit from vaccination – will be considered in the Evidence to Recommendations framework
- Work group considerations
  - Majority were in favour of harmonising catch-up vaccination recommendations for HPV vaccine
  - Majority were in favour of a recommendation for individual decision making through age 45 years; none were in favour of a catch-up recommendation through 45 years
  - A minority favoured no recommendation for mid-adults given: few benefits, diversion of focus from adolescent program, potential harms to the HPV vaccination program due to temporally associated adverse events in this age group, and global HPV vaccine shortage
- Next steps: continue review of health economic modelling data, complete Evidence to Recommendations Framework, and prepare for vote in June 2019

**Combination vaccines**

- Immunogenicity and safety of a paediatric hexavalent vaccine (presentation of vaccine data by Merck)
  - DTaP-IPV-HepB-Hib (Vaxelis™) – a joint venture with Merck and Sanofi Pasteur; BLA approved and licensed by the FDA on 21 December 2018 for use in children 6 weeks to 4 years old (this vaccine is already licensed in the EU and commercially available in 5 EU countries)
  - Given in a 3 dose series (2, 4, 6 months); no reconstitution required
  - Licensed vaccines containing the same antigens are: Pedvax Hib, Recombivax HB (HepB), Daptacel (DTPa), Pentacel (DTPa-IPV-Hib), and Ipol (IPV); aluminium (0.319mg) used as adjuvant
  - Data from 6 phase 3 trials (doses given to over 5000 infants aged 6–12 weeks) show robust immunogenicity and an acceptable safety profile consistent with its components
    - GMCs for FHA (pertussis antigen) post-dose 3 did not meet non-inferiority criterion in 1 study (but criteria met post-toddler dose); all other endpoints met; comparator was Pentacel
    - GMS for one pneumococcal serotype (6B) lower post-dose 3 in 1 study and did not meet non-inferiority criterion; all other endpoints met; comparator was Pentacel
    - Across the 6 trials, safety profile was similar to that of comparator vaccines, though pyrexia was slightly higher (approximately 60% vs 50%)
    - Fever rates were similar in studies where control was a hexavalent vaccine
    - Fever rates from 2 studies where Pentacel was the comparator showed statistically significant differences in overall (49.1% vs 35.6%), mild (26.2% vs 21.9%) and moderate (20.6% vs 12.5%) temperature elevations; severe fever also elevated (2.3% vs 1.2%) but not statistically significant; there were no febrile convulsions related to vaccination
- Hib vaccines in American Indian/Alaskan Native (AI/AN) population
  - AI/AN children aged <5 years historically (prior to vaccine) have higher rate of Hib disease
  - Hib disease has declined since introduction of vaccine but continues to occur in Navajo children aged <5 years (compared to virtually no disease in general US population)
  - Preferential recommendation for use of PRP-OMP (Pedvax-Hib) Hib conjugate vaccine by the Indian Health Service on the basis of seroconversion rates of 60% after 1 dose compared with 20% for other Hib conjugate vaccines
  - Immunogenicity studies of hexavalent vaccine in AI/AN populations report robust responses after 2nd and 3rd doses, but not post dose 1 which could be important to inform policy
- Two policy topics under consideration
  - Use of new hexavalent vaccine in Vaccines For Children Program for the infant series at 2, 4, 6 months of age – vote potentially in June 2019 (supply unavailable until at least 2020)
  - Preferential recommended use of this vaccine in AI/AN population – Work Group considers post dose 1 data are needed before ACIP can consider this

**Pneumococcal vaccines**

- Policy question: should PCV13 be routinely administered to all immunocompetent adults aged ≥65 years in the context of indirect effects from paediatric use of PCV? (comparison is PPV23 alone)
- PCV13 direct and indirect effects on serotype (ST) 3 disease
  - ST3 has unique genetic, phenotypic and physiologic characteristics associated with invasiveness and disease severity; vaccine effectiveness is lower against ST3
  - WHO statement, based on systematic review: “Despite immunogenicity data, evidence for direct or indirect reduction in IPD due to ST3 after administration of PCV13 was inconclusive, though most studies showed no effect.”
  - Introduction of PCV13 (2010) resulted in non-significant decrease in ST3 IPD in children <5 years in the US between 2007/08 and 2016/17 (% change: –31% [95% CI: –67 to 44])
  - No decline in ST3 IPD in adults ≥65 years since introduction of PCV13 for children or adults

- Case–control study among US Medicare beneficiaries found significant effectiveness of PCV13 against PCV13-type+6C, but no effectiveness against ST3; VE estimates – PCV13: 36% (95% CI: –18 to 65); PCV13+6C: 47% (95% CI: 4–71); PCV13+6C, no ST3: 67% (95%CI: 11–88); ST3: 26% (95%CI: -58 to 65)
- Moderate (non-significant) effectiveness against ST3 community acquired pneumonia (CAP) among adults in 2 Pfizer-supported trials (CAPiTA and Louisville TND); effectiveness demonstrated in post-hoc and mITT analysis of CAPiTA (61.5% [95% CI: 18–83] and 60.0% [95% CI: 5–18], respectively)
- Limited data on population-level impact on ST3 pneumonia; no evidence of impact in one cohort study by 2016 (~36% coverage)
- Conclusions: PCV13 may provide some level of direct protection against ST3 IPD and CAP, but findings are inconsistent across studies and there is no evidence of population-level impact on ST3 disease; there is a high level of uncertainty regarding the benefits of PCV13 against ST3 disease

- PCV13 direct effects on pneumonia hospitalisations in adults ≥65 years
  - Cohort study of Medicare beneficiaries enrolled in part A/B on 1 September 2017, observed until 31 December 2017
  - Four models run stratified by influenza season and influenza vaccination status (i.e. flu season vaccinated or unvaccinated, and non-flu season vaccinated vs unvaccinated) due to interaction between flu vaccine and outcome of interest, relationship between pneumococcal and flu vaccines, and differences in characteristics between flu vaccinated and unvaccinated people
  - CAP incidence is highest among individuals ≥85 years and those with risk conditions
  - VE against all-cause CAP ranged from 6.0% to 11.4% (all non-overlapping with 0); highest VE observed in flu season/flu unvaccinated group, lowest in flu season/flu vaccinated group
  - VE against non-healthcare associated (HA) CAP ranged from 5.0%–11.0%, similar trend as above
  - Point estimates of VE against lobar pneumonia ranged from 1.3% to 11.0% among the 4 stratified models, with the 95% CI of the VE overlapping 0 for flu season/flu vaccinated
  - Total hospitalisations averted due to PCV13 between Sep 2014 and Dec 2017 = 28,6000 (95%CI: 21,000–36,600), with majority averted in 2017 alone (18,700 [95%CI: 13,000–25,000])
- Comparison of three economic analyses of PCV13 use among adults ≥65 years
  - Models conducted by CDC, Pfizer and University of Pittsburgh
  - Primary question: should PCV13 be administered routinely to all immunocompetent adults aged ≥65 years in the context of indirect effects from paediatric PCV use experienced to date?
  - ICER examines PCV13+PPV23 versus PPV23 alone
  - Base case ICER results, S/QALY (sensitivity analyses range):
    - CDC: $562,000 ($112,000–$2.3 million); $222,000 with alternate scenario of higher VE against ST3
    - Pfizer: $199,000 ($46,000–$650,000); $186,000 with inclusion of immunocompromised
    - Pittsburgh: $765,000 ($461,000–$2.2 million); higher ICER in black versus non-black population
  - Compared with CDC model:
    - Pfizer assumed higher VE (especially against ST3 CAP), lower indirect effects from paediatric program, higher utility losses for outcomes and higher CFR
    - Pittsburgh assumed higher VE, no indirect effects, higher utility losses for outcomes and more detailed modelling of black and non-black populations
    - Differences in VE of PCV especially against ST3 pneumonia appear to be most important reason for variation between models
- GRADE and Evidence to Recommendations (EtR) for PCV13 use among adults ≥65 years old in the context of indirect effects experience to date

- PCV13 program for adults considered warranted in 2014 because of remaining PCV13-type disease burden, but long-term utility was considered uncertain because of paediatric program indirect effects
- Summary of benefits and harms:
  - PCV13 is effective/efficacious in preventing PCV13-type IPD and PCV13-type non-invasive pneumococcal pneumonia though data for pneumonia are inconsistent across studies
  - At the population level, no impact has been observed on IPD and data on impact on pneumonia are inconsistent
  - No impact on mortality has been demonstrated
  - No safety signals detected
  - Overall benefits are expected to be small and harms are expected to be minimal; certainty of benefits is low and harms is high
  - The balance of benefits and harms favours the intervention
- Additional GRADE considerations:
  - Intervention is probably not cost-effective
  - Discontinuing PCV13 will probably have minimal impact on PCV13-type disease in the context of indirect effects from paediatric PCV program
  - PCV13-type disease has been reduced through indirect effects but not eliminated
  - Frequent changes to recommendations may have negative impacts on perception of future recommendations and implementation challenges
  - Universal age-based recommendations easier to implement than risk-based recommendations

- Vote on this issue expected in June 2019
- Near future PCVs – two new products are currently in adult phase 3 trials: PCV15 and PCV20; both conjugated to CRM197 and working towards licensure in adults first
  - PCV15 (Merck) – serotypes PCV13 + 22F and 33F; trials projected to be complete in Q3 2020
  - PCV20 (Pfizer) – serotypes PCV13 + 8, 10A, 11A, 12F, 15B, 22F and 33F; trials projected to be complete end 2019/early 2020

**Meningococcal**

- Both MenB vaccines licensed in the US for ages 10–25 years; recommended by ACIP for those aged ≥10 years at increased risk for serogroup B meningococcal disease
- Immunogenicity and safety of MenB-FHbp (Trumenba) booster dose (presentation by Pfizer)
  - Subjects (n=393) from 3 phase 2 trials enrolled in a phase 3 extension study to examine antibody persistence 48 months following vaccination, and some subjects continued on to receive a booster dose at 48 months (n=156) and were then followed for another 26 months; subjects were aged 11–18 years or 10–12 years, respectively, at time of vaccination and most received a 3-dose schedule (n=277) but some received a 2 dose schedule (n=116); 70 controls were enrolled (persistence for 2 and 3 dose schedule examined separately)
  - Safety of booster dose similar to primary vaccination series: 84.4–93.5% reported local reaction (pain most common); fatigue (51.9–65.6%) and headache (37.5–56.3%) most common systemic reactions; no SAEs reported up to 26 months post booster
  - 2-dose schedule persistence: data indicate that following initial vaccination, 1 month–post-vaccination titres increase and then decline by 12 months and plateau out to 48 months (but remain higher than baseline); following the booster dose, a greater % of subjects achieve a threshold response (hSBA ≥1:4) than following the primary series, and although there is decline in immunogenicity to 12 months and further to 26 months following booster dose it is still higher than following primary vaccination at those same timepoints
  - 3-dose schedule persistence has similar profile to that of 2-dose schedule

- Data from study 1015 compare 3-dose schedule to no vaccination (controls): persistence data show decline in % of vaccinated subjects with hSBA titre ≥1:4, with greatest decline in first 12 months following by slight declines or plateauing of antibodies; however, they were greater than control subjects at all timepoints up to 48 months when there is some overlay of the 95% CIs
- Data on GMTs show no difference in persistence of antibodies by 2- or 3-dose schedule
- However there is a range of values by strain type, indicating there may be varying duration of protection depending on the circulating strain following initial primary vaccination, but there appears to be better persistence and less variation in protection against the various strains post booster dose

- Immunogenicity and safety of MenB-MC (Bexsero; MenB-4C) booster dose (presentation by GSK)
  - Data on persistence available from 4 trials at the following timepoints: 11 months (18–24 year olds, UK), 2 years (10–25 year olds, US & Poland); 4 years (11–17 year olds, Canada & Australia); 7.5 years (11–17 year olds, Chile); all studies used a 2-dose 0, 1 month schedule
  - Antibodies elicited by each component of the vaccine waned at different rates in the studies; however, across studies fewer subjects retain protective titres for PorA indicating antibodies to this component wane relatively quickly (consistent with studies of other OMV vaccines)
  - 2 studies of booster dose with MenB-MC in subjects 4 and 7.5 years post primary vaccination show that booster dose elicited robust responses against each of the components 1 month following booster; responses were also higher than the responses 1 month following primary vaccination series (data not shown on slide)
  - GMT data show subjects who are boosted achieve protective antibodies within 7 days of booster
  - No evidence of increased reactogenicity after booster dose (frequency of adverse events not shown) – fatigue and headache most frequent AEs, and pain at site of injection most common following each dose
  - Persistence data up to 12 months post MenABCWY (investigational vaccine containing components of MenB-MC plus MenACWY) booster available from small study of subjects booster 2 years following priming with MenB-MC (2-dose 0, 2 month schedule): robust 1 month post booster results similar to boosting with MenB-MC; robust responses maintained for fHbp, NadA and NHBA (with non-significant declines for fHbp and NHBA), but substantial (yet non-significant) decline in PorA; transferability of these findings to MenB-MC is unknown
  - Integration of immunogenicity and strain coverage MATS data from the US suggests protective benefits of 2-dose primary series may be sustained for several years (modelled up to 5 years)
- Immunogenicity of MenB-MC among persons at increased risk (slide by GSK)
  - Responses similar in healthy children and those with asplenia/asplenic dysfunction
  - Reduced responses in children with terminal chain complement deficiencies and those being treated with eculizumab
  - Published study: Martinon-Torres et al Pediatrics 2018; 141(3):e20174250
  - Immunogenicity not expected to differ in individuals at increased risk of exposure (e.g. occupational exposure, outbreaks)
- GRADE and EtR for MenB booster doses
  - Policy question: should persons vaccinated with a MenB primary series who remain at increased risk for serogroup B meningococcal disease receive a MenB booster dose?
  - EtR completed separately by population at increased risk: 1) people with underlying medical condition (complement deficiency, complement inhibitor use, asplenia) and microbiologists, 2) people exposed during an outbreak of serogroup B disease
- EtR for MenB booster doses in people with underlying medical conditions and microbiologists
  - No data on vaccine effectiveness or duration of protection in persons with underlying medical conditions
  - Immunogenicity and antibody persistence may differ in persons with these conditions

- Risk of bias assessed as serious for all 3 critical outcomes (short-term immunogenicity, persistence of immune response and serious adverse events) for MenB-fHbp; risk of bias assessed as serious for observational studies of MenB-MC (immunogenicity and adverse events) and not serious for RCT findings related to the three outcomes, though components of the assessment (indirectness and imprecision) were assessed as having serious or very serious concerns
- Work group recommended the intervention as the desirable effects were considered to outweigh the undesirable effects, despite very low certainty of the evidence for critical outcomes and uncertainty about its value to key stakeholders, cost-effectiveness or feasibility

- EtR for MenB booster doses in people at increased risk during a serogroup B outbreak
  - No data on vaccine effectiveness or duration of protection in US adolescents and adults; some data following 4 years following mass MenB-MC vaccination of people aged <20 years in Canada report vaccine effectiveness of 79% (95%CI: -231 to 99)
  - Risk of bias assessed as serious for all 3 critical outcomes (short-term immunogenicity, persistence of immune response and serious adverse events) for MenB-fHbp due to concern about selection bias; risk of bias assessed as serious for observational studies of MenB-MC (immunogenicity and adverse events) due to concerns about selection bias and not serious for RCT findings related to the three outcomes, though components of the assessment (indirectness and imprecision) were assessed as having serious concerns due to small numbers of subjects and use of MenABCWY as a proxy for MenB-MC in one study
  - Work group recommended the intervention as the benefits (anticipated to be large) outweigh the harms (likely to be minimal) and the expected acceptability, feasibility and efficiency of the intervention, despite very low certainty of the evidence for critical outcomes
- Work Group interpretation of data, considerations and next steps
  - Persistence of immune response following primary vaccination with a MenB vaccine:
    - MenB-fHbp: antibodies wane by 12 months and then remain stable for up to 4 years in healthy adolescents
    - MenB-MC: difficulty in generalising findings of persistence; in general antibodies wane by 2 years following the primary series in healthy adolescents and adults, but cannot rule out earlier waning given data limitations
    - Conclusion by Work Group: by 1–2 years following primary MenB vaccination, booster vaccination is indicated in persons who remain at increased risk
  - Immunogenicity and persistence of a MenB booster dose:
    - MenB-fHbp: immune response to a MenB-fHbp booster dose persists for at least 2 years in healthy adolescents
    - MenB-MC: immune response to a MenB-MC booster dose likely persists for several years in healthy adolescents and adults; a precise estimate is not possible because of lack of observed data (data are modelled)
    - Conclusion by Work Group: MenB booster elicits robust immune response and persists for at least 2–3 years; persistence appears to exceed that of a MenB primary series
  - Additional data on vaccine effectiveness and duration of protection in adolescents/adults is not expected from manufacturers and may take years to generate
- The Work Group did not reach consensus on need for and timing of MenB booster doses, as a minority of members felt there was insufficient evidence on safety and efficacy of MenB booster doses
- However the majority felt that MenB booster vaccination is necessary to sustain protection against MenB in persons who are at increased risk
  - Immunogenicity and persistence of MenB vaccination may be limited in persons with underlying conditions
  - Studies indicate antibody waning 1–2 years following the primary series and then persistence of the booster for up to 2 years

- Therefore MenB booster dose was felt to be indicated 1 year following completion of the primary series; with greater persistence expected after the booster dose, a longer interval for repeat boosters may be considered. However in outbreak scenarios booster doses may be considered for individuals who completed the primary series within the previous 6 months
- While harmonisation with MenACWY booster doses is desired, the data do not support a 5-year interval for MenB booster doses; however, booster recommendations for MenB-fHbp and MenB-MC should be harmonised to minimise complexity
- Regarding safety, despite limited data and no data in people with underlying medical conditions, the Work Group felt the benefits outweighed the risks
- Implementation challenges may be present in outbreak scenarios (e.g. determining eligibility, completion of primary series, vaccine type, date of completion)

- Further data to be presented on MenB epidemiology and potentially a vote on MenB booster doses to be held at the June 2019 meeting

**Zoster vaccines**

- Zoster vaccine uptake
  - ~8.59 million doses of recombinant zoster vaccine (RZV; Shingrix®) distributed through 2018
  - 2-dose RZV series completion >75% among Medicare beneficiaries
  - Uptake of live zoster vaccine (ZVL; Zostavax®) has declined to close to 0 since ACIP's preferential recommendation for RZV
- Zoster vaccine supply
  - RZV demand continues to outpace supply
  - GSK plans to manage RZV supply by continuing order limits in 2019
  - Number of doses available for US market was increased in the second half of 2018
  - Planned for more frequent, higher volume shipments to increase supply and deliver doses more consistently for all customer types during 2019
- RZV safety update
  - VAERS review: post-licensure safety monitoring findings are generally consistent with the safety profile observed in pre-licensure clinical trials, with self-limited systemic symptoms and injection site reactions the most commonly reported events; serious adverse events were rare
  - Vaccine Safety Datalink Rapid Cycle Analysis: Among 106,121 doses of RZV, no evidence of increased risk of any of the pre-specified outcomes except Guillain-Barre syndrome (GBS)
    - Preliminary statistical signal for GBS observed based on 4 claims in administrative data
    - 2 of 4 cases were ruled out (history of GBS), 1 was verified to be incident post-vaccination, 1 was unclear (diagnosed post-vaccination but may have had symptoms pre-vaccination)
    - Work Group agrees there is insufficient evidence at this time to support a change in policy or practice; further investigations are underway

**Hepatitis vaccines**

- Hepatitis A vaccines (HAV) and persons with HIV infection
  - Increasing proportion of adults are susceptible to HepA due to reduced exposure in early life; however 2-dose vaccination coverage is low in adults including those at high risk
  - In a Tennessee outbreak, 14 of 249 cases had HIV; of these 5/14 (36%) had been vaccinated with at least 1 dose of HAV at least 1 month prior to hepatitis exposure
  - Approximately 40% of people with HIV don't have any other risk factors for which HAV is a current indication
  - Data suggest that up to 87% of people with HIV are susceptible to hepA infection and of those newly diagnosed with HIV 75% are at risk of infection
- GRADE: use of HAV among persons with HIV infection

- Policy question: should routine 2-dose vaccination (vs no routine vaccination) to prevent hepatitis A be given to adult HIV-positive persons regardless of another indication for vaccination?
- 24 studies included on HAV and people living with HIV
- No serious risk of bias identified for outcomes (hepA infection, mild and serious adverse events)

- EtR framework: use of HAV among persons with HIV infection
  - The potential benefits of vaccination were assessed as large while the potential harms were assessed as minimal; thus the potential benefits outweigh the potential harms
  - Costs of routine immunisation may be lower per capita than cost of large, rapid vaccination campaigns for outbreak response
  - HepA infection may increase HIV replication
  - People with HIV may experience milder infection but resolution of infection may be delayed potentially prolonging infectious period
  - However seroconversion may be lower or may take longer especially in those with low CD4 counts; immunity may wane
  - EtR assessment: desirable consequences probably outweigh the undesirable consequences in most settings
  - The Work Group recommended the intervention regardless of other indications

**Vaccine supply update**

- Merck is not currently distributing its adult hepatitis B vaccine or dialysis formulation and will not be distributing vaccine through 2019; GSK and Dynavax have sufficient supply of adult hepatitis B vaccine to address the anticipated gap (unchanged from October 2018 meeting)
- Merck's supply of paediatric hepatitis B vaccine continues to be constrained and they will continue to direct limited supply to CDC; Merck expects to have a limited supply of monovalent hepatitis B vaccine through 2019 (full calendar year); GSK is able to cover the supply gap with a combination of monovalent and combination vaccine (including birth dose)

## 1.2 Newly published or updated recommendations

### 1.2.1 Recommendations of the ACIP for use of hepatitis A vaccine for persons experiencing homelessness

- Published MMWR 15 February 2019 – https://www.cdc.gov/mmwr/volumes/68/wr/mm6806a6.htm
- This report provides recommendations for HAV use among persons experiencing homelessness for pre-exposure protection against HAV infection
- Current recommendation is that all persons aged ≥1 year experiencing homelessness should be routinely immunised against hepatitis A (2- or 3-dose schedule when combined hepatitis A and B vaccine is administered)
- The recommendation is based on the epidemiology of HepA infection in the US (majority of cases in outbreaks were among persons reporting homelessness or drug use), and the difficulty in implementing other recommended non-vaccine strategies to prevent HepA infection (e.g. handwashing, access to clean toilet facilities, avoidance of crowded living conditions)

## 1.3 New or updated recommendations – not yet published

### 1.3.1 Japanese encephalitis (JE) vaccine

- Updated recommendations for people moving to or visiting JE-endemic areas (see details above in 1.1)
- Primary vaccination schedule for adults is 2 doses administered on days 0 and 7–28
- For adults and children, a booster dose should be given at ≥1 year after completion of the primary series if ongoing exposure or re-exposure to JE virus is expected

### 1.3.2 Anthrax vaccine

- A booster dose of AVA may be given every 3 years to persons not currently at high risk of exposure to *B. anthracis* who have been previously primed with AVA and wish to maintain protection

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# 2 Immunisation Advisory Centre (IMAC), New Zealand

## 2.1 PTAC Considerations

Meeting on 1–2 November 2018 – https://www.pharmac.govt.nz/assets/ptac-minutes-2018-11.pdf

- There were no vaccine-specific considerations at this meeting
- Minutes of the Immunisation Subcommittee meeting on 16 May 2018 were reviewed (see below)

Meeting was held on 21 & 22 February – https://www.pharmac.govt.nz/assets/ptac-minutes-2019-02.pdf

- There were two immunisation-relevant considerations: MenB vaccine (Bexsero) and MenACWY
- MenB vaccine – application from GSK for universal childhood vaccination
  - PTAC recommended that MenB-MC be listed:
    - For universal childhood vaccination as part of the infant immunisation schedule with a 2+1 dosing schedule, with a medium priority
    - For adolescents in close-living situations with a medium priority
  - PTAC considered that Men B is a relatively uncommon condition with a high health need and there is indirect evidence of MenB-MC effectiveness; additionally the high cost of MenB-MC and low cost-effectiveness for MenB-MC for infants and for close-living populations was noted
- MenACWY vaccine – application for consideration from PHARMAC
  - PTAC recommended that MenACWY be listed:
    - With a high priority for adolescents (13–19 years) in close-living situations
    - With a low priority for universal adolescent (aged 13–19 years) vaccination
    - With a low priority for children aged 1–4 years
  - PTAC agreed that adolescents in close-living situations (household crowding found to be an independent risk factor for meningococcal disease in New Zealand) would likely benefit the most from MenACWY vaccination; additionally universal adolescent vaccination would aim to achieve herd immunity (as observed in the UK) but there was no direct evidence of benefit
  - PTAC considered that there was no direct evidence of benefit for universal childhood vaccination

## 2.2 Meetings of the Immunisation Subcommittee

### 2.2.1 Meeting on 16 May 2018

https://www.pharmac.govt.nz/assets/ptac-immunisation-subcommittee-minutes-2018-6.pdf

**Influenza**

- An influenza vaccine overview paper prepared by PHARMAC was reviewed, seeking advice about possible future strategic options for seasonal influenza vaccine
- The Subcommittee made the following recommendations:
  - High-dose and adjuvanted influenza vaccines for people aged ≥65 years should be included in the next commercial process
    - Based on studies demonstrating the additional health benefits from use of these vaccines over standard dose TIV, and minimal additional risks compared with TIV or QIV

- LAIV for children 5–12 years should be included in the next commercial process, and that PHARMAC conduct cost-effectiveness analysis on universal vaccination compared to childhood school vaccination
  - Based on evidence indicating LAIV generates a broader immune response than inactivated influenza vaccines, and potential herd benefit that could be derived from a universal childhood influenza vaccination program
  - No LAIV product is currently registered in New Zealand
- The application for ring protection (i.e. vaccinating close contacts) of high risk groups should be declined (due to limited evidence to support this approach)
- Widened access to Maori people and Pacific people aged <65 years be declined
  - Despite higher disease burden in these populations, it was felt that current coverage of targeted groups is not high and expanding eligibility does not address this problem; additionally target strategies often lead to other inequities, and it would be better to work towards universal vaccination

**Meningococcal C vaccine**

- An analysis conducted by PHARMAC regarding funding of MenC vaccination for two possible scenarios: people living in close living situations and universal childhood vaccination of infants, toddlers and teenagers
- The Subcommittee deferred making a recommendation regarding funding the proposed programs until more recent epidemiological data are available
- The following points were noted:
  - MenC disease is rare in New Zealand; however, it is associated with higher morbidity and mortality than MenB; Maori, Pacific people and other groups are disproportionately affected
  - Adolescents would benefit most from a MenC vaccination program; given herd effects, universal vaccination would be optimal
  - Declines in MenC disease following introduction of vaccination programs in the UK and Australia
  - NeisVac-C (MenC vaccine) and Menactra (MenACWY vaccine) are funded for small sub-populations of patients who are considered to be high risk (medically at-risk and close contacts of meningococcal cases)
  - MenACWY vaccine offered additional health benefits over MenC vaccine given protection against additional strains
  - If a universal childhood vaccination program is introduced, an additional visit at 12 months of age would be required; if other schedule changes were made (such as funding MenB vaccine) then a 12-month visit to deliver varicella, MenACWY and MenB vaccines would be suitable
  - MenC vaccine should not be listed in the Pharmaceutical Schedule for use during declared epidemics; this use should be considered on a case-by-case basis

**Meningococcal B vaccine**

- The application by GSK for the MenB vaccine, Bexsero (MenB-MC) for universal childhood vaccination on the National Immunisation Schedule was reviewed
- The Subcommittee recommended the following:
  - MenB-MC be funded for universal infant vaccination as part of the Infant Immunisation Schedule, with a 2+1 dosing schedule, with a medium priority
  - MenB-MC be funded with a medium priority for high risk groups and close contacts, based on high clinical need
- The following points were noted:
  - Reactogenicity issues with the vaccine were noted
  - The health sector would incur significant costs for the vaccination and administration claims

- An additional schedule point at 12 months would be required as well as changes to the infant schedule to ensure optimal vaccine combinations at each visit
- The greatest benefit of vaccination would be to infants, particularly Maori and Pacific infants
- Data reviewed included epidemiological data, clinical trials results, data from the UK's MenB vaccination program, studies on impact of vaccination on carriage and MATS data; additional considerations were cross protection against other meningococcal serogroups and gonorrhoea

**Therapeutic Group Review**

- HPV vaccine: There have been shortages in supply, impacting distribution of the vaccine; supply to school based programs and high risk immunocompromised individuals is prioritised
- Hepatitis B recombinant vaccine: There have been ongoing supply issues for HBvaxPRO; Engerix-B is being used instead
- BCG vaccine: There has been a long-standing shortage since June 2015; stock is expected to be available later in 2018; initial focus should be on vaccinating those <6 months of age who meet the funding criteria, are at greatest risk and no testing is required
- Influenza vaccine: Influvac Tetra was funded for the 2018 influenza season, indicated for people aged ≥3 years only; Fluarix Tetra available for children aged 6 months to <3 years

### 2.2.2 Meeting on 18 September 2018

https://www.pharmac.govt.nz/assets/ptac-immunisation-subcommittee-minutes-2018-09.pdf

**MMR vaccine third dose**

- An application from the Ministry of Health about the use of a third dose of MMR to prevent an control outbreaks was reviewed
- The Subcommittee recommended that a third dose of MMR be funded with a high priority for local mumps outbreaks; a definition of an outbreak should be included in the funding criteria
- This was based on good evidence to support the use of a third dose of MMR in an outbreak, the epidemiology of mumps in New Zealand (50% of >1700 cases over 2 years were in Pacific peoples, and it is unknown what vaccine coverage for mumps is as many Pacific Island countries do not include mumps vaccination in their immunisation programs), and practicalities of implementing vaccination in the event of an outbreak

**Meningococcal ACWY vaccine**

- An application from PHARMAC to fund MenC or MenACWY vaccine for people in close living situations and universal childhood vaccination of infants, toddlers and teenagers was reviewed
- The Subcommittee recommended that MenACWY vaccine be listed for toddlers in the second year of life (1 or 2 doses to be determined) and an adolescent dose and a catch-up program to be determined, with high priority; review of the toddler dosing and possible options for a catch-up program would be reviewed following the commercial process due to be run in 2018
- The Subcommittee recommended that universal vaccination with MenC vaccine be declined
- The following points were noted:
  - While group B cases tend to be concentrated in children <1 year old, other serogroup cases tend to be spread more widely across the age groups
  - Cases due to serogroups other than B and C are rising
  - There was stronger evidence for including meningococcal vaccine in the Childhood Immunisation Schedule than for targeting adolescents in close living situations; ideally a program would include both infants and adolescents rather than target each group separately
  - The Subcommittee would like to review costings of possible vaccination programs, including catch up, following the commercial process for all vaccines

**Fluad (adjuvanted inactivated influenza vaccine; aTIV)**

- An application from Seqirus to list aTIV on the National Immunisation Schedule for people aged ≥65 years was reviewed
- The Subcommittee recommended that the application to list aTIV be declined
- The following points were noted:
  - A systematic review showed non-inferiority of the immunogenicity of aTIV compared with standard dose TIV; although higher antibody responses were generated by aTIV, superiority was not established
  - An unpublished meta-analysis conducted by the sponsor concluded that aTIV was superior to TIV for all three strains (A/H3, A/H1 and B); members noted that a meta-analysis of RCTs comparing aTIV to QIV found no statistical difference between treatment groups for immunogenicity measures of homologous strains
  - An indirect treatment comparison by the sponsor was noted to be problematic
  - Recommendations by other NITAGs (specifically ATAGI and NACI) were reviewed
  - Overall it was considered that there was evidence of effectiveness of aTIV versus TIV but limited evidence comparing aTIV with QIV (noting no head to head studies)
  - Funding a vaccine for a specific age group would add complexity to vaccine stock management and increase storage needs
  - Concern that the reactogenicity of aTIV would discourage the elderly from being vaccinated
  - Subcommittee considered that there was insufficient evidence at this time to support the use of aTIV and would like to review data comparing aTIV to TIV-HD as well as data on aTIV use in immunocompromised people; aQIV was noted to be in development

**Synflorix**

- The Subcommittee reviewed a clinical data update from GSK and recommended that it would be suitable for New Zealand to move from a 3+1 to a 2+1 dosing schedule for PCV10 or PCV13
- The following considerations were noted:
  - Evidence supporting the use of a 2+1 schedule of PCV10 is of good strength and quality
  - The evidence of similar efficacy of PCV10 and PCV13 is of good strength and quality
  - Surveillance reports to June 2018 showed an increase in total IPD since 2015; serotype 19A IPD in children <5 years has decreased since 2012
  - Evidence supporting PCV10 in a 2+1 schedule in high risk groups was considered to be of low strength and quality; PCV13 in a 2+1 schedule was considered suitable for high-risk groups
  - PCV10 is not licensed for people aged ≥5 years; PCV13 would be needed in these age groups

**Infanrix Hexa**

- The Subcommittee reviewed a clinical data update from GSK regarding Infanrix Hexa, currently given in a 3+0 schedule
- The following considerations were noted:
  - GSK provided data on a 2+1 schedule with the booster dose given at 12 months; this would remove the need for a separate Hib booster dose at 15 months
  - Data were also provided on a 3+1 schedule with 3 doses of Infanrix Hexa and a booster of DTaP-IPV-Hib in the second year of life; this would allow introduction of a toddler pertussis booster without increasing needle burden as the 15-month IPV booster dose would not be required
  - Changing to a 2+1 schedule (6 weeks, 3 and 12 months) would require high coverage to be effective and would impact the scheduling of other vaccines; prospectively planned pertussis surveillance should be implemented before such a change was made
  - The 3+1 schedule was considered to be a good option which would allow removing of IPV at 4 years and would defer the need for a further pertussis dose at age 4 years

- However it was considered that there is no compelling reason to change the schedule and it should only be implemented if there were benefits to the timing of the Immunisation Schedule
- If MenB-MC were introduced to the schedule, it would likely be given at the same time as a pertussis dose; studies on use of paracetamol in association with Infanrix Hexa were noted; the data are complex but do not support administration of paracetamol with Infanrix Hexa; this would be revisited if MenB-MC is added to the schedule

**TdaP-Booster™ (Seqirus dTpa vaccine)**

- The Subcommittee reviewed a clinical data update from Seqirus regarding its dTpa vaccine TdaP-Booster™
- The Subcommittee considered that there was still insufficient evidence to recommend the use of TdaP-Booster™ in pregnancy compared to other vaccine options (Boostrix® is funded) that are currently available, as no clinical studies had been performed with Tdap-Booster™ that included pregnant or breastfeeding women

**Other matters**

- Hepatitis B birth dose: The Ministry of Health's response to a WHO request to review New Zealand's hepatitis B strategy (which does not include a birth dose) was discussed and agreed, that is, it was supportive that a birth dose of hepatitis B vaccine is not required and would not be introduced; research on boosting of pertussis antibodies following hepatitis B vaccination will be reviewed

### 2.3 Other updates

- The Ministry of Health has modified the standard MMR vaccination catch-up advice in light of measles outbreak overseas and current vaccine supply concerns: http://www.immune.org.nz/hot-topic/measles-overseas-and-new-zealand
- Review of evidence to inform the Immunisation Schedule: tetanus http://www.immune.org.nz/review-evidence-inform-new-zealand-national-immunisation-schedule-2019tetanus
- Review of evidence to inform the Immunisation Schedule: pertussis http://www.immune.org.nz/review-evidence-inform-new-zealand-national-immunisation-schedule-2018-pertussis
- Additional updates relating to immunisation in New Zealand are available here: https://www.health.govt.nz/our-work/preventative-health-wellness/immunisation/updates-immunisation

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## 3 Joint Committee on Vaccination and Immunisation (JCVI), UK Department of Health

### 3.1 JCVI meeting: 3 October 2018

**Agenda/draft minutes:**
https://www.gov.uk/government/groups/joint-committee-on-vaccination-and-immunisation#minutes
This summary was based on the draft minutes only.

**Update from Department of Health and Social Care (DHSC)**

- A policy decision was awaited concerning JCVI's advice to move to a 1+1 PCV schedule
- Following JCVI's advice, the government had announced extension of the HPV program to boys; catch-up would not be available for older boys (boys who were eligible would remain so till age 18 years); boys are planned to be included in the HPV vaccination program for 2019/20

**Rotavirus epidemiology**

- An update on the impact of the rotavirus vaccine program in England was provided
- Within 6 months of the program being introduced in 2013, coverage was 89% by 3 months of age and 93% by 4 months of age; this has improved since then
- There was an 80–90% reduction in laboratory confirmed rotavirus infections in season following program introduction, with reduction in cases also seen in 1, 2–4 and 5+ year olds
- GP and emergency department attendances for rotavirus infection reduced substantially
- Within 1 year of the program, hospitalisations for gastroenteritis reduced across all ages
- Over the last 5 year there has been a dramatic impact on laboratory confirmed rotavirus infections and hospitalisations for all-cause gastroenteritis

**Meningococcal epidemiology**

- A small risk in serogroup C IMD cases in England in two regions was noted at the previous meeting
- The most recent data indicated a reduction in cases compared with the previous year across all age groups except those aged 20–24 years; cases were seen mainly in unvaccinated groups
- Coverage in those regions was as good as or better than the national average

**Herpes zoster vaccination program**

- Cost-effectiveness modelling of Shingrix undertaken by PHE concluded that the optimal age for immunisation of immunocompetent individuals was 65 years (though a greater number of cases would be prevented with vaccination at age 60) and that Shingrix would be cost-effective for any age from 50 to 90 years among immunocompromised people
- JCVI recommended that the zoster vaccination program be changed, with Shingrix offered routinely at the age of 60 years in a 2-dose schedule; those aged 60–70 years should also be offered Shingrix
- Given learnings from the implementation of the current zoster vaccination program of a large number of cohorts, JCVI advised that the program should be implemented in stages starting with vaccination at aged 65 and 70 years; then once all ages between 65 and 70 years had been vaccinated, vaccination should move to 60 years
- Those aged ≥86 years who were not offered Zostavax should be considered for vaccination with Shingrix, noting that capacity would be an issue
- JCVI will not presently discussed vaccination of 70- to 86-year-olds (i.e. those who would be eligible for the current program) as further modelling was required
- JCVI recommended that PHE consider a definition of immunocompromised for this purpose
- All recommendations are subject to procurement of a cost-effective price
- In 2009 when varicella control options were reviewed, a decision was made not to proceed with a vaccination program because of the possible impact on zoster as a result of the removal of exogenous boosting; the model will now be updated with current data and consider different assumptions on duration of exogenous boosting and take into account a program from 60 years with Shingrix

**NITAG update from WHO**

- WHO provided an overview of the work particularly by SAGE done to support NITAGs; additionally support was provided through the Global NITAG Network

**Influenza**

- Mid-season influenza epidemiology and vaccine effectiveness
    - To date the 2018/19 season was dominated by the A/H1N1 pdm09 virus; primary care indicators showed it had been a quiet season with far fewer outbreaks than the previous season; however

impact on secondary care had been high and similar to last season with the burden mainly in young and middle-aged adults; no significant excess all-cause mortality was observed
    - Genetic typing indicated that there had been little change in the circulating A/H1N1 viruses since the previous season and they were antigenically similar to the current vaccine strain
    - Mid-season vaccine effectiveness was estimated to be 43.7% (95%CI: 3.9–67.1) for influenza A and B, and 56.9% (95%CI: 19.5–77) for A/H1N1; estimates for A/H3N2 were non-significant due to small numbers of cases
    - Vaccine effectiveness estimates were 56.9% for influenza A and B and 82.6% for A/H1N1 but statistically non-significant due to small numbers of cases and controls
    - Vaccine effectiveness for LAIV in children was 86.9% (95%CI: 3.6–100) against A/H1N1
- Timing of program delivery
    - A report by PHE on whether the timing of delivery of vaccination should be delayed to optimise immunity levels with the timing of peak influenza activity was discussed
    - PHE concluded that delaying influenza vaccination posed significant risks of infection before immunisation and that decreasing the period of vaccination would pose huge logistical challenges
    - PHE advised that the current timing of the program should not be changed and that the focus should be improving uptake in eligible groups, particularly children
    - JCVI considered that the current evidence was not sufficient to recommend changes to the timing of delivery of the program, and that recent advice had been provided on newly available vaccines to address some of the issues concerning poor effectiveness
- Sniffle 4
    - Presentation on the Safety of Nasal InFLuenza Immunisation in children with asthma – SNIFFLE-4
    - SNIFFLE-4 aimed to address the safety of LAIV in children with recurrent wheezing asthma and severe asthma and on high dose inhaled corticosteroids (ICS)
    - Current UK guidelines allow the use of LAIV in children with mild to moderate asthma but not those with severe or uncontrolled asthma or with active wheezing
    - SNIFFLE-4 showed LAIV to be safe in children receiving high-dose ICS
    - The Green Book chapter should be updated to reflect that LAIV can safely be given in those on high dose ICS; however, the advice concerning active wheezing in the previous 72 hours remained the same

## 3.2 Newly published or updated statement/recommendations

### 3.2.1 Advice on influenza vaccines for 2019/20

- Published October 2018 https://app.box.com/s/t5ockz9bb6xw6t2mrrzb144njplimfo0/file/334815965677
- For adults aged ≥65 years, the use of any of the following vaccines is advised: aTIV, TIV-HD, QIVc; the vaccines are considered equally suitable for use, and are preferable to standard egg-based inactivated trivalent and quadrivalent vaccines
- For those aged <65 years (including those who are in an at-risk group [including pregnant women]) and children (who are contraindicated to receive LAIV), the use of wither egg-based QIV or cell-culture QIV is advised; these vaccine are preferable to standard egg-based TIV

### 3.2.2 Updated guidance for influenza – Green Book chapter 19

- Updated 23 April 2019 – https://www.gov.uk/government/publications/influenza-the-green-book-chapter-19
- Updated the asthma and egg allergy sections and added information on newly licensed influenza vaccines

# 4 National Advisory Committee on Immunization (NACI), Canada

The more recent meeting was conducted 6–7 February 2019 in Ottawa, Ontario; however, the summary of discussions has not been released. The latest available summary was for its October 2016 meeting, which is available at https://www.canada.ca/en/public-health/services/immunization/national-advisory-committee-on-immunization-naci/immunization/national-advisory-committee-on-immunization-naci.html.

## 4.1 Newly published or updated statement/recommendations

There have been no new or updated statements or recommendations published since the previous update.

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# 5 Immunisation updates from the World Health Organization (WHO)

## 5.1 Strategic Advisory Group of Experts (SAGE) on Immunization, WHO

- Agenda, meeting background documents and presentations for meeting held on 2–4 April 2019: https://www.who.int/immunization/sage/meetings/2019/april/en/ and https://www.who.int/immunization/sage/meetings/2019/april/presentations_background_docs/en/
- The full report is expected to be published on 31 May 2019; summary report available at: https://www.who.int/immunization/sage/meetings/2019/april/SAGE_April_2019_meeting_summary.pdf?ua=1

**Report from the WHO Department of Immunization, Vaccines and Biologicals**

- A preview of the vision for the next decade of work was presented; despite great advances in the last decades, the world in 2019 is increasingly uncertain and volatile; the vaccine and immunisation agenda is being re-shaped with a central view toward equity, security and prosperity for all; vaccines and immunisation are central to achieving the Sustainable Development Goals
- Regional Offices highlighted major achievements and challenges, of note: concern over multiple outbreaks of measles and other vaccine-preventable diseases which highlight weakened immunisation systems; fragile and conflict-ridden countries face challenges in sustaining immunisation, as do many low- and middle-income countries from a financing aspect; several regions reported on efforts to increase life-course vaccination and on strengthening country decision-making

**Report from GAVI**

- New and expanded programs reflect a shift from infant vaccination to a life-course approach
- The Gavi 5.0 strategy focuses to the SDG vision of leaving no one behind; four key areas were highlighted including vaccine introductions, reaching the under-immunised, financial and programmatic sustainability, and healthy markets and innovations
- In 2019–2020, Gavi will update its core policies on country eligibility and transition, co-financing, health system investment framework and gender

**Data use and quality**

- Findings and knowledge gaps around data quality and use and possible interventions to strengthen governance, tools, assessment and improvement planning for immunisation program decision-making were discussed
- SAGE will further discuss this review of data use and quality in order to make decisions on recommendations at a future SAGE meeting

**Development of a post 2020 Global Immunization Strategy**

- An interim review and lessons learnt report on the Global Vaccine Action Plan (GVP) was presented (final report to be presented in October 2019) – findings highlighted achievements such as alignment of global actors, a strong monitoring and evaluation framework, emphasis on data quality and the increased numbers of NITAGs; shortcomings included the perception of a top-down plan, little guidance to offer solutions to address challenges, and weaknesses in communications
- The post 2020 global immunisation strategy will be developed via an accelerated approach (draft to be presented to SAGE in October 2019); a three-level approach was adopted:
    - An overarching vision for the decade through 2030
    - A framework strategy for immunisation stakeholders
    - A collection of global, regional and country goals, plans, partner strategies and disease strategies

**RTS,S/AS01 malaria vaccine and the Malaria Vaccine Implementation Programme (MVIP)**

- The framework for policy decision on RTS,S/AS01 Malaria Vaccine was presented to SAGE for consideration and endorsement; it describes how the data from the pilot implementation of the vaccine in Ghana, Kenya and Malawi will be used to inform future malaria vaccine recommendations
- Updated WHO recommendations on use of RTS,S/AS01 vaccine in Africa are possible if and when (a) safety signals observed in the Phase III trial are resolved, and (b) severe malaria or mortality data trends are assessed as consistent with a beneficial impact of the vaccine

**Polio**

- Progress has been made towards poliovirus eradication albeit with concerns about areas consistently inaccessible for vaccination in parts of Afghanistan and Nigeria
- There was concern about the large number of circulating vaccine-derived polioviruses, and the poor vaccination coverage with IPV in many countries
- IPV supply shortages are abating and will allow swift implementation of catch-up campaigns
- In anticipation of the certification in 2019 of Wild Polio Virus Type 3 (WPV3) eradiation, SAGE discussed the potential switch from bivalent OPV to monovalent OPV type 1
- SAGE endorsed guidelines for surveillance of poliovirus excretion among persons with primary immunodeficiencies

**Defeating meningitis by 2030: Global Roadmap**

- The global strategy to 'Defeat Meningitis by 2030' is a WHO-led multi-organisation initiative that includes partners addressing the specific organisms responsible for most causes of acute bacterial meningitis – roadmap to be shared for recommendation at the October 2019 meeting

**Ebola vaccines**

- WHO Health Emergency Responses provided an updated on the outbreak in the Democratic Republic of Congo; vaccination has contributed to reducing transmission
- SAGE reviewed the possible vaccination strategies and concluded that ring vaccination remains the most effective strategy in this outbreak; geographic targeting should remain as a fall-back strategy
- Although clinical data on the safety and efficacy of the rVSV-ZEBOV-GP Ebola vaccine for children <1 year old and lactating women are absent, SAGE considers that the high attack rates and high case fatality rates for these groups, together with the accumulating data on vaccine safety and efficacy for other groups, justify inclusion of children who are above the age of 6 months and of lactating women in the ongoing ring vaccination efforts in North Kivu

## 5.2 Updated WHO Vaccine Position Papers

### 5.2.1 Pneumococcal conjugate vaccines in infants and children <5 years: WHO position paper (February 2019)

https://apps.who.int/iris/bitstream/handle/10665/310968/WER9408.pdf?ua=1

*WHO position*

- WHO recommends the inclusion of PCVs (either PCV10 or PCV13) in childhood immunisation programs worldwide
- For infants, a 3-dose schedule administered as either 2+1 or 3+0 is recommended starting as early as 6 weeks of age, noting the 2+1 schedule has potential benefits over the 3+0 schedule when feasible
- In choosing between the 2 schedules for infants, countries should consider programmatic factors including timeliness of vaccination and expected coverage
- Product choice: While both vaccines have substantial impacts against pneumonia, vaccine-type IPD and nasopharyngeal carriage, there is insufficient evidence of a difference in the net impact of the two products on overall disease burden; PCV13 may have an additional benefit in settings where disease attributable to serotype 19A or 6C is significant
- Wherever possible, catch-up vaccination at the time of introduction of PCV should be used to accelerate its impact on disease in children aged 1–5 years particularly in settings of high disease burden and mortality; catch-up can be done with a single dose of vaccine for children aged ≥24 months; data are insufficient to make a firm recommendation for 1 versus 2 doses in children aged 12–23 months
- HIV-positive infants and pre-term neonates who have received 3 primary doses before 12 months of age may benefit from a booster dose in the second year of life
- Countries are encouraged to implement a comprehensive surveillance system for pneumococcal disease

## 5.3 Meeting of the Global Advisory Committee on Vaccine Safety (GACVS)

- 5–6 December 2018, Geneva, Switzerland. Full meeting report available at: https://apps.who.int/iris/bitstream/handle/10665/279829/WER9404.pdf
- Safety of typhoid conjugate vaccine (TCV): new safety data are available on the Vi-tetanus toxoid conjugate vaccine Typbar-TCV (the only TCV currently licensed internationally)
  - Data from 3 ongoing trials of field effectiveness representing adverse event data for ~24,000 children and serious adverse event data for ~99,000 children between 9 months and 15 years old; most events were mild or moderate; fever and pain reported in 3–8% and 1–7% in each of two trials; non-specific local and systemic reactions occurred in 0–3%
  - Passive and active surveillance data following 2 mass immunisation campaigns in 2018 found a similar safety profile to other routine vaccines; low rates of mild to moderate local and systemic events were reported
  - Post-licensure safety data reported to the manufacturer did not raise any safety signals
- Vaccine injury compensation programs (VICPs): the results of a global survey of the status of no-fault VICPs in WHO Member States were reviewed
  - 25 jurisdictions were identified as having a no-fault VICP, including 2 LMIC
  - Most are implemented and funded at central or federal government level
  - Eligibility criteria vary considerably – most cover injuries arising from vaccines that are registered in the country and are recommended by authorities for routine use; all require proof of a causal association between vaccination and injury
  - In most jurisdictions, claimants have the right to seek damages either through civil litigation or from the compensation scheme but not both
  - GACVS considers VICPs to be a measure to maintain confidence in immunisation programs, and will support WHO in developing guiding principles for countries ready to develop VICPs
- Immunisation stress-related responses: a draft manual to support program managers in preventing, identifying and responding to stress-related events related to immunisation was reviewed
- Vaccine safety strategy post 2020

- The findings of the 7th meeting on the Global Vaccine Safety Initiative (GVSI) were reviewed: the network has contributed new resources for pharmacovigilance, websites and an indicator of vaccine safety surveillance; the roles of GACVS (risk assessment) and GVSI (capacity-building) were seen as complementary with scope for increased interaction
- Progress in the Global Vaccine Safety Observatory was reviewed: its role is to enhance surveillance capacity by improving access to indicators of national and regional systems through WHO partners
- Plans for the post-2020 WHO immunisation strategy, including the next Global vaccine safety blueprint, were discussed

- Report of the sub-committee on vaccine safety communication
  - The subgroup was asked to prepare a series of case studies of vaccine safety communication to contribute to a common framework for vaccine safety crisis communication and capacity-building in member states
  - Case studies were discussed specifically around measles vaccine and 2 recent events in which children died because of program errors; GACVS discussed the need for: a concerted focus on training, supervision and support of national authorities and partners during planning of mass immunisation campaigns; acknowledgement of program errors and prompt proposal of corrective measures; preparedness for crisis management; and high-quality communication about the safety of immunisation, both routine and during mass campaigns

## 5.4 Meeting of the Immunization and Vaccine-related Implementation Research Advisory Committee (IVIR-AC)

- Previous meeting reports available at: https://www.who.int/immunization/research/committees/ivir_ac/en/index4.html
- No meeting appears to have been held since the previous update; the last meeting for which papers are available was held on 24–26 September 2018

## 5.5 WHO influenza meetings

- Meeting of the WHO Expert Working Group on the Global Influenza Surveillance and Response System for Surveillance of Antiviral Susceptibility https://apps.who.int/iris/bitstream/handle/10665/310846/WER9407.pdf
- WHO Working Group for the Molecular Detection and Subtyping of Influenza Viruses and the use of next-generation sequencing in the Global Influenza Surveillance and Response System
- Recommended composition of influenza virus vaccines for use in the 2019–2020 northern hemisphere influenza season https://apps.who.int/iris/bitstream/handle/10665/311440/WER9412.pdf

## 5.6 Global Immunization News and other items and resources

- Latest news available here: http://www.who.int/immunization/gin/en/
- Interim recommendations on vaccination against Ebola virus disease, published May 2019 https://www.who.int/immunization/policy/position_papers/interim_ebola_recommendations_may_2019.pdf
- An independent evaluation of SAGE is being carried out during 2018/19 https://www.who.int/immunization/policy/sage/sage_wg_evaluation_may2018/en/
- WHO/UNICEF Joint Policy Statement: promotion the exclusive use of injection safety devices for all immunisation activities https://www.who.int/immunization/documents/policies/RUP_JointStatement/en/

# 7 Other items

## 7.1 Published information on assessment and registration of vaccines in Australia by TGA

- New/updated registrations for vaccines:
  - Afluria Quad & Afluria Quad Junior: approved on 8 March 2019 for the prevention of influenza in persons aged ≥3 years (Afluria Quad) and children aged 6–35 months (Afluria Quad Junior) [previously Afluria Quad was registered for use in people aged ≥5 years; current PI still indicates it is indicated for use in people aged ≥5 years only]
- Update Product Information (major changes only):
  - Hexaxim – updated 11 April 2019 to include 2+1 dosing schedule, data on concomitant administration with other vaccines, and allowing temporary out-of-fridge temperature exposure
  - Menveo – updated 5 April 2019 and 20 May 2019; inclusion of 2+1 dose schedule for infants with supportive data, and advice on when to use the 4-dose schedule in infants
- Recently published AusPAR:
  - Afluria Quad – published 22 January 2019
  - Shingrix – published 12 February 2019
  - Dengvaxia – published 20 March 2019
- Media release on 9 May 2019 confirmed that latex is not present in the 2019 formulation of Fluad supplied in Australia: https://www.tga.gov.au/alert/fluad-trivalent-influenza-vaccine

## 7.2 Global measles outbreaks

- WHO is reporting that cases of measles continue to climb in 2019, with preliminary data showing that reported cases rose by 300% in the first 3 months of 2019 compared to the same period in 2018
- Current large outbreaks include the Democratic Republic of the Congo, Ethiopia, Georgia, Kazakhstan, Kyrgyzstan, Madagascar, Myanmar, Philippines, Sudan, Thailand and Ukraine
- Spikes have occurred in countries with high overall vaccination coverage, including the United States, Israel, Thailand and Tunisia, with the disease spreading quickly among clusters of unvaccinated people
- Global vaccine coverage of 1 dose of MMR stands at 85%; second dose coverage is 67%
- For more information, see:
  - https://www.who.int/immunization/newsroom/measles-data-2019/en/
  - https://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/active/measles_monthlydata/en/
  - https://www.cdc.gov/globalhealth/measles/globalmeaslesoutbreaks.htm

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# 8 Upcoming meetings and agendas

**ACIP, USA (http://www.cdc.gov/vaccines/acip/meetings/upcoming-dates.html)**

- 26–27 June 2019
- 23–24 October 2019

**PTAC, New Zealand (https://www.pharmac.govt.nz/about/committees/ptac/)**

- 23–24 May 2019
- 22–23 August 2019

**JCVI, UK (https://www.gov.uk/government/policy-advisory-groups/joint-committee-on-vaccination-and-immunisation)**

- Future meeting dates pending, but usually the 1st Wednesday of February, June and October

**NACI, Canada (http://www.phac-aspc.gc.ca/naci-ccni/meetings-reunions-eng.php)**

- 5–6 June 2019
- 25–26 September 2019

**SAGE WHO (http://www.who.int/immunization/sage/future_meetings/en/)**

- 8–10 October 2019
- 31 March–2 April 2020