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: 23/01/2018 to 21/05/2018

Contents

1 Advisory Committee on Immunization Practices (ACIP), U.S.A.

1.1 ACIP meeting: 21–22 February 2018

- 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 2018 meeting are pending. Therefore, this summary has been developed from the presentation slides and video recordings.

Hepatitis Vaccines

- GRADE summary of HEPLISAV-B (TLR9-conjugated recombinant hepatitis B vaccine) compared with the licensed hepatitis B vaccine, Engerix-B
  - Non-inferior seroprotection rate
  - No differences detected between vaccinated and comparison populations for mild adverse events
  - HEPLISAV had 4.6% more local injection site reactions
  - No differences detected between vaccinated and comparison populations for serious adverse events
  - More cardiovascular adverse events in HEPLISAV group, but not statistically significant
- Proposed recommendations regarding HEPLISAV-B:
  - Recommended in a 2-dose schedule with 4 weeks interval
  - Likely to improve vaccine series completion and have earlier protection – important for persons with low adherence (e.g. injection drug users)
  - Improved immunogenicity with typically poor vaccine response (e.g. elderly, diabetics, dialysis)
  - Interchangeability: 2-dose series applies when all doses consist of HEPLISAV-B; if a vaccine series is initiated with another dose of vaccine and completed with HEPLISAV-B, 2 doses of HEPLISAV-B (4 weeks apart) should be given
- GRADE summary of hepatitis A vaccine for post-exposure prophylaxis in adults >40 years of age
  - Policy question: Should hepatitis A vaccine be recommended instead of immune globulin (IG) as post-exposure prophylaxis for prevention of hepatitis A disease in adults >40 years of age?
  - No randomised controlled trials were identified comparing hepatitis A vaccine and immune globulin in healthy adults >40 years of age
  - Only one study (sub-analysis) contained immunogenicity data on discrete age ranges over age 40 years
  - No articles provided explicit estimates of the efficacy of hepatitis A vaccine in adults >40 years of age against disease endpoints
- Considerations for use of hepatitis A vaccines for post-exposure prophylaxis and international travel
  - Current recommendation: People exposed to hepatitis A virus (HAV) and who previously have not received hepatitis A vaccine should be administered a single dose of single-antigen hepatitis A vaccine or IG (0.02 mL/kg) as soon as possible
  - Challenge with current recommendation: timely receipt of IG in outbreaks has been difficult since most providers and health departments do not routinely stock it; need for multiple injections of IG per dose, particularly for adults due to increased dosing (0.1mL/kg); vaccination provides long-term protection
  - Proposed recommendations:
    - IG in infants <12 months;
    - vaccination in healthy persons ≥12 months;
    - vaccination with addition of IG (based on provider guidance risk assessment and availability of IG) in healthy persons >50 years and pregnant women;
    - vaccine and IG in immunocompromised, chronic liver disease and those with contraindication to vaccine

- Rationale: limited data and evidence of lower efficacy of vaccination in older adults >50 years at 15 days and >60 years at 30 days; HAV more severe in these age groups
- Considerations for the use of hepatitis A vaccines for international travel
  - Current recommendation: All susceptible persons traveling to or working in countries that have high or intermediate hepatitis A endemicity should be vaccinated with an age-appropriate dose or receive IG before departure. Vaccination is preferred to IG.
  - Hepatitis A vaccine use in infants 6–11 months who are travelling: IG cannot be administered with MMR vaccine. Due to the severity of measles in infancy compared with HAV infection, MMR vaccine should be administered preferentially to IG. IG may be given if travel is to a region where measles is not endemic.
- Consideration for the use of hepatitis A vaccine in pregnant women due to the risk of adverse fetal outcomes if the woman is infected with HAV during pregnancy
  - Administration of HAV in pregnancy is safe
  - Vaccination is recommended for pregnant women travelling and vaccination + IG as post-exposure prophylaxis

Influenza Vaccines

- Fluarix Quadrivalent (QIV) (GSK): efficacy in children 6–35 months of age
  - Phase III, observer-blind, randomised (1:1), non-influenza vaccine comparator-controlled study
  - 12,018 healthy children 6–35 months of age in 5 independent cohorts vaccinated over 5 influenza seasons (2011–2014) (QIV n = 5707; control n = 5697)
  - Control vaccine: Prevenar 13 in <12-month olds; Havrix, Varivax/ProVarivax/Varilrix in 12–35 months olds
  - Vaccine efficacy (VE) results (RT-PCR confirmed, any influenza strain): moderate–severe influenza: 63.2%, any influenza: 46.8% (95% CIs not provided, shown graphically). Attack rates: moderate–severe influenza: QIV – 1.6%, control – 4.3%; any influenza: QIV – 6.0%, control – 11.6%
  - VE results by subtype (95% CI): A/H1N1 – 72.1% (49.9–85.5); A/H3N2: 52.7% (34.8–66.1); B/Vic: 80.1% (39.7–95.4); B/Yam: 70.1% (52.7–81.9). Proportion of antigenic matching strains for each subtype, respectively: A/H1N1: 84.8%; A/H3N2: 2.6%; B/Vic: 14.3%; B/Yam: 66.6%
  - Reduction in healthcare utilisation among vaccinated subjects, relative risk reduction: GP visits – 47%; ER visits: 79%; antibiotic use: 50%
  - Seroprotection rate: A/H1N1: 85%; A/H3N2: 81%; B/Vic: 72%; B/Yam: 85%
  - Frequency of all adverse events (all and Grade 3 for injection site, systemic and serious adverse events) similar in QIV versus control group
- Surveillance update: 2017–2018 season
  - Influenza A (H3N2) viruses have predominated during the 2017–18 season; influenza B activity is increasing; activity may not have peaked yet (at time of presentation, February)
    - Of 33,130 specimens reported to US public health labs: A/H1N1 – 9.1%; A/H3N2 – 71.8%; A/subtype unknown – 1.3%; B/Vic – 1.3%; B/Yam – 11.5%; B/lineage unknown – 5.2%
  - ILI activity highest since 2009
  - Severity for adults, hospitalisation rates and mortality could be similar to or exceed that seen during the 2014–15 season
  - Majority of circulating strains similar to those contained in the 2017–18 vaccine; B/Vic lineage viruses are the only viruses clearly showing antigenic drift, but they represent <1% of circulating viruses
- Interim VE estimates, 2017–18 season, from US Flu VE Network
  - Test-negative design, 5 sites, 4,562 enrolled (38% RT-PCR positive [n=1712]; 62% RT-PCR negative [n=2850])

- Cases by subtype: /H1N1 – 12%; A/H3N2 – 67%; A/subtype unknown – 3%; B/Vic – 0.2%; B/Yam – 15%; B/lineage unknown – 3%
- Overall VE (95% CI): unadjusted – 33% (24–41); adjusted – 36% (27–44) (adjusted for site, age, sex, race/ethnicity, self-rated general health status, interval from onset to enrolment and calendar time)
- Adjusted VE by age (95% CI): 6m–8y – 59% (44–69); 9–17y – 5% (–38 to 34); 18–49y – 33% (16–47); 50–64y – 17% (–15 to 40); ≥65y – 18% (–25 to 47)
- Adjusted VE against medical attended influenza by strain (95% CI): A/H3N2 – 25% (13–26); A/H1N1 – 67% (54–76); B – 42% (25–66)
- VE against A/H3N2 significant only for 6m–8y (51%, 95%: 29–66), overlapping CIs for all other age groups
- VE against A/H1N1 and B significant for all age groups except ≥65y

- Results of randomised trial of a new H1N1 LAIV strain in US children (AstraZeneca)
  - A clinical trial was conducted in US children (n=200) to determine if new A/Slovenia strain was more immunogenic compared to the A/Bolivia strain used in 2015–2016
  - The new A/Slovenia H1N1 strain induced antibody responses that were significantly higher than those seen with the A/Bolivia strain
  - Subjects seroconverting were higher with A/Slovenia strain than the two A/Bolivia strains (p=0.006 for HAI antibodies, p=0.081 for neutralising antibodies, p=0.076 for IgA antibodies); seroconversion measured by any antibody response was the same across the three strains after 1 dose, but was significantly higher with A/Slovenia strain after 2 doses (68.2% versus 41.9% and 39.1%)
  - Key changes made in the way LAIV strains are selected annually:
    - Human nasal epithelial cell culture now used to assess the replicative fitness of new LAIV strains
    - $TCID_{50}$ assay added to quantify new LAIV strains
    - All future strains now only selected if they have high levels of replication in human nasal epithelial cells and when the FFA and $TCID_{50}$ assays give similar results
- ACIP review of effectiveness of LAIV
  - Individual patient-level data meta-analysis of LAIV and IIV effectiveness among US children aged 2–17 years, 2013–14 through 2015–16 influenza seasons: results of most studies favoured IIV for endpoints against any influenza (all 3 seasons) and A/H1N1 (2013–14 and 2015–16); studies about neutral for A/H3N2 (2014–15 season); studies favour LAIV for any influenza B (all 3 seasons)
  - Systematic review and meta-analysis of studies reporting LAIV effectiveness, 2010–11 through 2016–17:
    - Studies in children aged 2–17 years
    - 15 TND case-control studies (9 US, 3 UK, 2 Canada, 1 Germany), 1 prospective cohort (US), 2 cluster RCTs (Canada)
    - Pooled VE estimates of LAIV versus unvaccinated (95%CI) : Influenza A or B – 45% (32–56); A/H1N1 – 25% (6–40) (US: 17% (–6 to 35), non-US: 48% (15–68))
    - Odds of influenza among children receiving LAIV versus IIV (95%CI): A/H1N1 – 2.52 (1.58–4.02); A/H3N2 – 1.01 (0.73–1.38); B – 0.55 (0.27–1.12) [Note: odds <1 favour LAIV; odds >1 favours IIV]
    - VE varies with many factors, for example, host factors (age, health status), influenza type/subtype, different seasons
    - Conclusion: IIV better for A/H1N1 and all influenza in some age groups, no clear difference in performance for A/H3N2; however, decision to recommend or not recommend individual vaccines not generally based on effectiveness comparisons to other products
  - Policy question: should LAIV be recommended for the 2018–19 season?

        - Benefit of LAIV for H3N2 comparable to that of IIV.
        - Data suggest good effectiveness for influenza B compared with no vaccine.
        - Limited immunogenicity and shedding data suggest new H1N1pdm09 virus in LAIV4 may promote improved effectiveness (however, this is not yet known).
        - No new vaccine safety concerns raised regarding LAIV vaccine at the time that the recommendation for its use was removed.
        - Potential for harm if vaccine ineffective.
        - Several papers and unpublished and published letters indicate support for availability of a non-injectable formulation of influenza vaccine
        - While national coverage appears not to have been impacted by lack of LAIV recommendation, LAIV is an important option for school-based clinics and may contribute to efforts to increase vaccination coverage
    - ACIP voted to recommend LAIV for use in 2018–19 season
    - ACIP discussed and voted against preferentially recommending IIV over LAIV, rationale including:
        - Evidence for preferential recommendation not robust
        - Variability in influenza seasons
        - Can cause confusion among providers and users (especially if changes to recommendations occur in future seasons), potential loss of confidence in influenza vaccines

Evidence-based Recommendations

- ACIP Evidence to Recommendation (EtR) Framework proposed to the current ACIP evidence-based recommendation process consistent with the expansion of GRADE methodology guidance
- Frameworks assist users of recommendations by enabling them to understand the judgements made by the panel and the evidence supporting those judgements
- Three content areas presented in the framework:
    - Background (formulating the question): Details of the question and a brief summary of information to understand the question and why recommendation is needed
    - Criteria (assessment/communication of evidence): criteria for making the decision, judgements that must be made in relation to each criterion, evidence to inform each of those judgements, additional considerations that inform or justify each judgement
    - Conclusions: based on the judgements made for all criteria
- Proposed framework:
    - Statement of problem: public health importance, burden of disease
    - Benefits and harms: balance of desirable and undesirable effects, certainty in evidence
    - Values and preferences of target population
    - Acceptability to stakeholders
    - Resource use: health economic analysis
    - Feasibility: implementation considerations
- Type of recommendation (to replace former “category A” and “category B” labelling of recommendations)
    - “We do not recommend the Intervention”
    - “We recommend the intervention for individuals based on clinical decision-making”
    - “We recommend the intervention”

Anthrax

- Update on route of administration for Anthrax Vaccine Adsorbed (AVA)
    - The SC route of administration is preferred over the IM route of administration for PEP due to the higher antibody titres achieved at 4 weeks in healthy adults.

    - In the absence of data, the working group considers it reasonable to anticipate similar risk–benefit of post-exposure vaccination in pediatric or special populations as in general adult population. Therefore, SC is preferred over the IM route of administration for AVA PEP in all populations.
    - During a large-scale emergency response, AVA for PEP may be administered using an IM route if the SC route of administration poses significant materiel, personnel or clinical challenges that may delay or preclude vaccination
- Dose-sparing strategies when demand for AVA exceeds supply
    - All dose-sparing schedules studied provided high levels of protection by two weeks after the last dose
    - If number of potentially exposed individuals exceeds vaccine supply, it may be beneficial to protect larger numbers of individuals with slightly lower protective levels
    - Either of the following dose-sparing strategies provide high levels of protection by two weeks after the last dose:
        - Two full doses (0.5 mL) at 0 and 2–4 weeks
        - Three half doses (0.25 mL) at 0, 2, and 4 weeks
    - The two-full-dose strategy will expand the vaccine supply by 50% and the three-half-dose strategy will expand it by 100%.
- Duration of antimicrobial component of PEP when used in combination with anthrax vaccine
    - High levels of protection are achieved two weeks after the last dose in all schedules
    - Allowing antimicrobial use to stop once peak immune response is reached would shorten antimicrobial requirement and potentially reduce adverse events related to continued antimicrobial use.
    - (Detailed recommendations on antimicrobial duration available in the ACIP slides online)

Human Papillomavirus (HPV) Vaccines

- Adverse events following 9-valent HPV (9vHPV) vaccine reported to the Vaccine Adverse Event Reporting System (VAERS)
    - ~29 million doses of 9vHPV vaccine distributed in US between December 2014 and December 2017
    - VAERS – spontaneous adverse event reporting system; identifies potential vaccine safety concerns that can be studied in more robust data systems, but cannot assess causality
    - 7244 reports in total, 186 serious (3%), 7 deaths (0.1%)
    - Of serious reports, most common were: headache (34%), dizziness (27%), nausea (26%), fatigue (23%), pyrexia (19%).
    - Syncope occurred in 488 non-serious reports (7%) and 29 serious reports (16%)
    - Of 9 anaphylaxis reports, 3 were confirmed, of which 2 received 9vHPV vaccine only
    - Of 8 GBS reports, 4 were confirmed. Of these, 3 had viral respiratory illness 2–4 weeks prior to presentation of GBS symptoms
    - Of 7 deaths, 5 were based on indirect information. Of the 2 confirmed, causes of death were cardiac arrest and cerebellar aneurysm
    - 1 report of complex regional pain syndrome (CRPS), insufficient information
    - 17 reports of possible postural orthostatic tachycardia syndrome (POTS); 6 partially met diagnostic criteria; no pattern of concern noted
    - 3 reports of possible primary ovarian insufficiency which did not meet diagnostic criteria and had insufficient information
    - Conclusions: no new safety signal or unexpected patterns were observed. Safety profile is consistent with data from pre-licensure trials and post-licensure data of 4vHPV vaccine
- Rapid Cycle Analysis of the 9vHPV vaccine in the Vaccine Safety Datalink (VSD)

- VSD is a collaboration between CDC and 8 integrated healthcare plans to monitor vaccine safety using active surveillance and observational studies
- Prospective cohort study from 10/4/2015 to 10/3/2017, subjects were males and females aged 9–26 years; 2 methods of analysis (MaxSPRT and ESA)
- MaxSPRT results: No signal detected for anaphylaxis, GBS, appendicitis, seizures, stroke, venous thromboembolism, chronic inflammatory demyelinating polyneuropathy
- Signal detected for pancreatitis in males 18–26 years (RR=3.1, 8 cases)
  - 6 cases had 1 dose, 2 had 2 doses
  - Medical record review found other underlying causes
- ESA results: No signal detected for anaphylaxis, GBS, pancreatitis, seizures, stroke, venous thromboembolism, chronic inflammatory demyelinating polyneuropathy
- Signal detected for syncope, injection site reactions, allergic reactions, appendicitis
  - Signals for syncope and injection site reactions expected based on RCT results and experience from 4vHPV vaccine
  - 26 cases of allergic reaction among ED/admitted patients (18 after 1st dose, 8 after 2nd or 3rd dose) – 8 with no alternative cause, 9 at injection site or localised reaction, 9 with other underlying causes
  - 15 cases of allergic reaction among outpatients – 6 with no alternative cause, 9 with other causes
  - Signal for appendicitis in males 9–17 years after the 3rd dose: follow-up self-controlled risk-interval analysis found no evidence of elevated risk

- Harmonisation of HPV vaccination age recommendations for females and males
  - Current recommendation for HPV vaccination: routine at age 11 or 12 years; catch-up for females through age 26 years and males through age 21 years (though males aged 22–26 years may be vaccinated); males at high risk (immunocompromised, transgender or MSM) recommended through age 26 years
  - Considerations: would simplify immunisation schedule; might facilitate reaching males, including those at high risk
  - Proposed to harmonise age recommendations for females and males (no vote at present meeting)
- Trends in HPV-associated cancers in the US
  - 34,864 cases of HPV-associated cancer diagnosed between 1999–2014 (38% males, 62% females); incidence rates: overall – 11.4 per 100,000; male – 9.1 per 100,000; female – 13.7 per 100,000
  - Cancers with increased rates: oropharyngeal cancer among men and women; anal cancer among men and women; and vulvar cancer
  - Cancers with decreasing rates: cervical cancer
  - Cancers with stable rates: penile and vulvar cancer
  - Oropharyngeal cancer now most common HPV-associated cancer and increasing, particularly among males
- Epidemiology of HPV infection in males
  - Rising incidence rates of oropharyngeal cancers: 28% rise in incidence; rising proportion of cancers are HPV positive (72% in 2000–04, ~90% caused by HPV16); projected to be most common HPV-associated cancer and most common head and neck cancer by 2030. Majority of cases are men.
  - Epidemiology of oral HPV infection:
    - Higher oral HPV prevalence in men (10.5%) than women (3.1%) in US (2009–2012); prevalence of oral HPV16 infection: men – 1.6%, women – 0.3%
    - Sexual behavioural differences do not entirely explain higher oral HPV prevalence in men than women; steeper increase in prevalence with increasing number of sexual partners among men compared with women; lower seroprevalence in males versus females

        - Few natural history studies – step between oral HPV acquisition and development of HPV-positive oropharynx cancer are unknown
    - Vaccination is the most promising strategy for prevention of HPV-positive oropharynx cancers
        - Secondary prevention through screening not feasible at this time as an HPV-induced precancerous lesion has not yet been identified
        - Significantly lower oral vaccine-type HPV prevalence observed in vaccinated men and women (18–33 years) in US (ref: Chaturvedi, JCO 2017)

Pneumococcal Vaccines

- PCV13 effectiveness against invasive pneumococcal disease (IPD) among adults 65 years or older
    - Two case–control evaluations conducted in parallel
    - Study 1: IPD among ≥65 years identified through Active Bacterial Core surveillance from 10 January 2015 onwards, controls through the commercial database ReferenceUSAGov (4 controls per case matched on age group and zip code); cases n=267, controls n=1065; mean age cases – 74.8 years, controls – 74.6 years
        - Characteristics of cases versus controls: chronic conditions – 83% versus 60%; immunocompromising conditions – 60% versus 32%
        - Effectiveness among those who received PCV13 only: 37% (2-60); VE among those who received any PCV13: 24% (-9 to 47)
            - VE higher against PCV13-types; non-significant for PPSV23-unique types
    - Study 2: IPD among ≥65 years identified through Active Bacterial Core surveillance (ABCs) from 1/1/2015-12/31/2016, controls through CMS Medicare part B beneficiaries (matched on age group, census tract and length of enrolment in Medicare part B); cases n=699, controls n=10,152; mean age: cases – 74.8 years, controls – 77.9 years
        - Characteristics of cases versus controls: chronic conditions – 88% versus 58%; immunocompromising conditions – 54% versus 32%
        - Effectiveness among those who received PCV13 only: 24% (2-41); against PCV13-types: 36% (-18 to 65); against PCV13-type+06C: 47% (4-71); non-significant for PPSV23-unique types
    - Conclusions: PCV13 was moderately effective in preventing IPD caused by PCV13-types; not effective against PPSV23-unique; estimates slightly lower than VE from clinical efficacy trial of 75%
- Estimating PCV13 direct and indirect effects on IPD among adults ≥65 years:
    - 2 mathematical models evaluated to estimate direct and indirect effects of vaccination
    - Both models predicted that there were:
        - no or limited additional indirect effects (arising from childhood PCV13 use) for IPD caused by PCV13 serotypes post 2014 in the absence of a PCV13 adult recommendation
        - limited direct effects (confidence limits include null value) observed in a setting of ~40% PCV13 uptake, based on small numbers of PCV13 type cases remaining following observed PCV13 indirect effects
- PCV13 effectiveness against pneumococcal pneumonia among US adults – presentation and slides not publicly available
- Estimating pneumococcal pneumonia burden among US adults and progress on the research agenda for potential policy change
    - Surveillance for non-invasive pneumococcal pneumonia (SNiPP) built into ABCs
    - Cases were adults ≥18 years hospitalised with clinically or radiographically confirmed pneumonia and a positive pneumococcal urinary antigen test; n=1213; median age 64 years (range: 18-102)
    - Prospective since 2015 with retrospective data collection to 2013

- Crude incidence: 6 cases/100,000; adjusted annual incidence: 99 cases/100,000 (crude estimate based on reported urinary antigen test (UAT) positive pneumococcal pneumonia cases only; adjusted estimate was adjusted for percent of pneumonia tested by UAT at each hospital)

Vaccines and Other Biologics for Prevention and Treatment of Healthcare-associated Infections

- Candidate vaccines still under development (list below excludes vaccines that have discontinued development):
  - Clostridium difficile vaccine (Pfizer): bivalent vaccine: toxins A and B. Genetically engineered and detoxified; aluminium adjuvant – phase 3 trial in 16,000 patients
  - Staphylococcus aureus vaccine SA4Ag (Pfizer): capsular polysaccharides CP5 and CP8 conjugated to the carrier protein CRM197, mutated recombinant clumping factor A, manganese transporter protein C – Phase 2b/3 trial

Meningococcal Vaccines

- Epidemiology of meningococcal disease among college students –United States, 2014–2016
- Review of cases aged 18-24 years reported to NNDSS during 2014–2016
- 1178 cases reported in 2014–16, of which 166 (14.1%) occurred in people aged 18–24 years; of those, 83 were college students and 79 were non-college students (unknown for 4 cases)
- Incidence of meningococcal disease, per 100,000: all – 0.17; serogroup B – 0.09; serogroup C/W/Y – 0.04; Incidence highest among 18-19 years and declines with increasing age
- Relative risk of serogroup B disease higher among college students for those aged 18-21 years
- Incidence of serogroups C/W/Y similar between college and non-college students, likely due to adolescent MenACWY program
- Cost-effectiveness of serogroup B vaccination updated with 2014-16 data: similar conclusions despite higher more accurate incidence estimates (highly cost-ineffective, vaccination of college students only cost per QALY is $9,600,000)

1.2 Newly published or updated recommendations

1.2.1 Recommendations of the Advisory Committee on Immunization Practices for Use of Herpes Zoster Vaccines

- Published MMWR 26 February 2018 – https://www.cdc.gov/mmwr/volumes/67/wr/mm6703a5.htm
- The following recommendations are new or updated:
  - Zoster Vaccine Recombinant (RZR), Adjuvanted (Shingrix) recommended for use for prevention of herpes zoster in persons aged ≥50 years
  - Recombinant zoster vaccine (RZV) is preferentially recommended over Zoster Vaccine Live (ZVL) (Zostavax)
  - People who have received ZVL in the past can receive RZV
  - A decision to recommend RZV for people on medium to high immunosuppressive therapy has not been made and will be discussed at a future ACIP meeting

1.2.2 Prevention of Pertussis, Tetanus, and Diphtheria with Vaccines in the United States: Recommendations of the Advisory Committee on Immunization Practices

- Published MMWR 27 April 2018 – https://www.cdc.gov/mmwr/volumes/67/rr/rr6702a1.htm
- No changes to previous recommendations; this report is a comprehensive summary of all previously published recommendations, and replaces all previous reports and recommendations.

2 Immunisation Advisory Centre (IMAC), New Zealand

2.1 PTAC Considerations

- Meeting held on 10–11 August 2017 – https://www.pharmac.govt.nz/assets/ptac-minutes-2017-08.pdf
    - No vaccine-specific considerations at this meeting, but noted under the discussion on the Nephrology Sub-committee minutes that PTAC recommended the use of HPV vaccine in patients with CKD 5 or on dialysis be referred to the Immunisation Subcommittee for consideration. Additionally, PTAC recommended that the Immunisation and Transplant Immunosuppressant Subcommittees consider the use of HPV vaccine in patients pre/post transplantation who are >26 years of age and not currently funded, as the risk of cancer in this patient group is a relevant issue for consideration.
- Meeting held on 9–10 November 2017 – https://www.pharmac.govt.nz/assets/ptac-minutes-2017-11.pdf
    - There were no vaccine-specific considerations at this meeting.
- Meeting held on 8–9 February 2018 – https://www.pharmac.govt.nz/assets/ptac-minutes-2018-02.pdf
    - No vaccine-specific considerations at this meeting
    - The Immunisation Subcommittee is urgently reviewing the need to provide advice and a recommendation regarding widening access to maternal vaccination to include women in their second trimester of pregnancy
- A meeting was held on 3–4 May 2018 – no minutes available yet but agenda does not indicate any vaccine-specific considerations

2.2 Other updates

- Antigen literature review for the NZ National Immunisation Schedule, 2017: Influenza
    - Published by IMAC February 2018, part of a series of antigen literature reviews commissioned by the Ministry of Health – http://www.immune.org.nz/sites/default/files/publications/AgRev2017_influenza_final.pdf
    - Main objective is to provide information around the use of vaccines and to help inform decisions relevant to immunisation programs in NZ. This review summarises selected literature published from January 2013 to November 2017 around the use of influenza vaccines to inform decisions around the New Zealand seasonal influenza immunisation program, to identify target groups for seasonal influenza vaccination, to provide information about which vaccines are available and most appropriate to use and how community immunity would be better achieved to protect those in whom the vaccines may be less effective or contraindicated.

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

3.1 JCVI meeting: 7 February 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.

HPV vaccination

- Stakeholder concerns regarding the equality of JCVI recommendations regarding HPV vaccination in boys was highlighted. The Department of Health and Social Care (DHSC) indicated that the JCVI could take a different methodological approach in making its advice, if it felt justified in doing so.
- JCVI will see the results of the independent peer review of the modelling work by PHE and additional analyses undertaken before concluding its advice. Legal advice will also be obtained.

Herpes Zoster vaccination

- JCVI reviewed data on the efficacy of Shingrix in immunocompromised individuals, specifically autologous haematopoietic stem cell transplant recipients.
- Recipients were adults aged ≥18 years immunised 50 to 70 days post transplant. The primary endpoint presented for vaccine efficacy against Herpes Zoster in adults aged >18 years was 68.17%. Efficacy was also assessed stratified by age 18-49 and 50 years and over. In the absence of further breakdown of the ≥50 years age group, JCVI assumed that many of the participants were at the younger end of the age group.
- Immunocompromised individuals required 2 doses.
- Modelling was being carried out to inform the potential for the use of Shingrix in the wider UK program.
- JCVI concluded that the efficacy of Shingrix was good in the severely immunocompromised group studied. JCVI therefore advised used of Shingrix in those contraindicated to live herpes zoster vaccines due to immunocompromising conditions or treatment.

Pneumococcal vaccination

- JCVI discussed stakeholder comments regarding switching from 2+1 to 1+1 PCV13 infant schedule.
- Rational for decision: a 1+1 schedule would be very similar to the previous 2+1 schedule in terms of disease rates and was an important step to simplify the NHS immunisation schedule, and the needle burden for infants, without compromising population protection. The combination of herd protection and good immunological responses after the booster dose, with some protection offered by the first dose, would provide very similar protection to young children, with modelling predicting very little additional disease.
- JCVI will consider the timing of the first dose, and moving from week 12 to week 8.

Hepatitis B vaccination

- JCVI advised that health care workers who have completed a primary course and have responded will no longer require the booster at 5 years
- Rationale: protection from primary course probably persists for 20–30 years, management of vaccine shortages and WHO recommendation to drop the reinforcing dose

Rabies vaccination

- An expert group considered the revised WHO SAGE recommendations on pre-exposure and post-exposure vaccination against rabies (published October 2017), and provided advice specific to the UK context; JCVI agreed the needs were different as WHO was trying to provide a pragmatic regime for PrEP and PEP in endemic countries.
- With respect to the accelerated PrEP schedule, it was agreed that this was appropriate where vaccination was sought shortly before travel. Intramuscular (IM) rather than intradermal (ID) remained the preferred route of administration from the UK perspective. However, intradermal vaccination was acceptable where undertaken by appropriately trained staff on the prescriber's own responsibility. For post-

exposure treatment, the simplest regime (Essen; days 0, 3, 7 and 21–28) seemed to be the most appropriate.
- The Committee did not agree with the recommendation for the two-site ID regimen (days 0, 7) as a PrEP schedule, and felt the current guidance on a three-dose intradermal course should be maintained.

Meningococcal disease

- Update on MenACWY IMD epidemiology:
  - there were 749 cases of IMD in 2016–17 compared with 811 in the preceding year
  - rates of serogroup Y (MenY) IMD remained stable
  - there were fewer cases of serogroup W (MenW) IMD up to this point in the year than were seen up to this point in the preceding two years, with 7 cases in the 15–24 year age group targeted by the MenACWY vaccine
  - there had been increases in MenW IMD in the oldest age groups
  - overall numbers of MenC IMD remained very low, although there were more cases in the most recent epidemiological year than those in previous years, both in infants and in older adults
- It was noted that the number of cases of MenC IMD being seen in infants was the same as predicted following the removal of the MenC infant dose. Removal of the MenC dose was still justified, as it had been an important factor in the introduction of the MenB program which has likely prevented many cases of IMD.
- Regarding epidemiology of MenB:
  - Decreases of MenB IMD were observed in children aged <5 years; decreases not observed in teenagers, young adults and older adults
  - A number of the MenB IMD cases seen had been very mild, which may be attributable to vaccination
  - Overall decrease in MenB IMD since previous year, with 447 cases reported in 2015–16 and 396 in 2016–17
  - Vaccine effectiveness (95% CI) against MenB IMD for vaccination as follows:
    - At least one dose: 43% (–11 to 69)
    - At least 2 doses: 64% (4–84)
    - Booster dose: 82% (–81 to 97)

Polio containment

- JCVI noted the Global Action Plan to minimise poliovirus facility-associated risk (GAP III) and the progress in the UK towards establishing a GAP III containment certification scheme (CCS) which would apply the principles of GAP III in the UK to be consistent with current procedures and legal provisions.
- It was noted that it was more than 20 years since there has been a case of poliomyelitis in the UK and that clinical practice has changed; JCVI agreed to endorse a request from the PHE national polio reference laboratory to encourage clinicians to collect appropriate stool samples for enterovirus detection.

Influenza – update on 2017–18 season

- GP consultation rates for influenza like illness had reached a moderate level of activity
- Peak activity for admissions for high dependency units and intensive care units had been the highest in the last 6 seasons
- Majority of the hospitalisations had been in the elderly
- Significant excess all-cause mortality had been observed this season, mainly in the over 65 years olds, some of which would be attributable to flu but cold weather would also have been an important contributor

- Influenza A(H3N2) and B had been the major viruses in circulation but there had also been some A(H1N1)pdm09 circulating
- The circulating A/H3N2 viruses were similar to the previous season's viruses
- The circulating B viruses had mainly been of the Yamagata lineage which was included in the quadrivalent influenza vaccines but not the trivalent influenza vaccines (TIVs) for 2017–18
- Early mid-season estimates of vaccine effectiveness (VE) against all influenza for the live attenuated influenza vaccine (LAIV) was encouraging, though with wide confidence intervals, but VE estimates were lower for the inactivated vaccines in adults
- Overall, VE against influenza B was better with evidence of moderate protection than that against A(H3N2), where there was no significant evidence of effectiveness
- The UK mid-season VE estimates were in line with those observed in Canada and elsewhere in Europe
- The TIV is likely to have performed relatively well against the predominantly mismatched circulating B virus; reasons for this require further investigation

3.2 Newly published or updated statement/recommendations

There were no new or updated statements/recommendations since the previous report.

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4 National Advisory Committee on Immunization (NACI), Canada

A meeting was conducted on 27–28 September 2017 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

4.1.1 Influenza Canadian Immunization Guide Chapter on Influenza and Statement on Seasonal Influenza Vaccine for 2018–2019

- Published 1 May 2018 – https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-statement-seasonal-influenza-vaccine-2018-2019.html
- Accompanied by a literature review on individuals with neurologic or neurodevelopment conditions and risk of serious influenza-related complications – https://www.canada.ca/en/public-health/services/publications/healthy-living/executive-summary-literature-review-individuals-neurologic-neurodevelopment-conditions-risk-serious-influenza-related-complications.html
- Accompanied by a literature review on the efficacy and effectiveness of high-dose (Fluzone® High-Dose) and MF59-adjuvanted (Fluad®) trivalent inactivated influenza vaccines in adults 65 years of age and older – https://www.canada.ca/en/public-health/services/publications/healthy-living/executive-summary-literature-review-update-efficacy-effectiveness-fluzone-high-dose-fluad-trivalent-inactivated-influenza-vaccines-adults-65-older.html
- Summary of new or updated recommendations:
  - Based on current evidence and expert opinion, NACI reaffirms its recommendation that children and adults with neurologic and neurodevelopmental conditions are groups for whom influenza immunisation is particularly recommended.
  - Regarding use of influenza vaccines in people ≥65 years, at a programmatic level NACI recommends that any of the four influenza vaccines available for use should be used: standard-dose TIV, high-dose TIV, MF59-adjuvanted TIV, and QIV. At an individual level, NACI recommends that high-dose TIV should be offered over standard-dose TIV to persons aged 65 years and older.

There is insufficient evidence to make comparative recommendations on the use of MF59-adjuvanted TIV and QIV over standard-dose TIV.

4.1.2 Update on immunisation in pregnancy with tetanus toxoid, reduced diphtheria toxoid and reduced acellular pertussis (Tdap) vaccine

- Published 28 February 2018 – https://www.canada.ca/en/public-health/services/publications/healthy-living/executive-summary-literature-review-update-immunization-pregnancy-tdap-vaccine.html
- Accompanied by a literature review on immunisation in pregnancy with tetanus toxoid, reduced diphtheria toxoid and reduced acellular pertussis (Tdap) vaccine: safety, immunogenicity and effectiveness
- The following recommendations are new or updated:
  - NACI recommends that immunisation with Tdap vaccine should be offered in every pregnancy, irrespective of previous Tdap immunisation history (Strong NACI Recommendation).
  - Immunisation with Tdap vaccine should ideally be provided between 27 and 32 weeks of gestation, but may be provided from 13 weeks up to the time of delivery.

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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 17–18 April 2018: http://www.who.int/immunization/sage/meetings/2018/april/en/
- The full meeting report will be made available in the WHO publication of the Weekly Epidemiological Record (WER) on 8 June 2018
- Summary report: http://www.who.int/immunization/sage/meetings/2018/april/sage_meeting_summary_apr2018.pdf?ua=1
- Polio eradication
  - SAGE noted that the IPV supply is sufficient to introduce IPV in routine immunisation globally in 2018, but not to conduct catch-up campaigns for cohorts that did not receive IPV because of supply constraints.
  - SAGE reviewed the available data on fractional IPV (fIPV) and emphasised that two doses of fIPV are superior to one full IPV dose.
  - SAGE agreed that IPV should not be used routinely in outbreak response except in specific situations such as where there is co-circulation of WPV1 and cVDPV2 and in these instances fIPV should be used. In addition, SAGE recommended that instead of using term “fractional” for fIPV, GPEI should think of other term such as “intradermal” to avoid impression that fIPV is sub-standard.
  - Studies to examine duration of immunity and protection following two doses of fIPV are in progress.
- Recommendations on the first licensed dengue vaccine
  - WHO’s initial recommendations on use of Dengvaxia (CYD-TDV) form 2016 have been revised following release of data by the vaccine sponsor.
  - See below (section 5.2.4) for a summary of the sponsor’s findings and SAGE recommendations.
- Measles and rubella
  - SAGE reviewed preliminary modelled scenarios of an investment case for measles and rubella eradication. Changes to key scenarios, as well as additional scenarios, have been requested. Revised versions will be presented to SAGE for recommendations.

5.2 Newly published WHO position papers

5.2.1 BCG vaccines: WHO position paper (February 2018)

http://apps.who.int/iris/bitstream/handle/10665/260306/WER9308.pdf?sequence=1

WHO position

- BCG vaccination is recommended in countries or settings with a high incidence of TB and/or high leprosy burden as well as where Buruli ulcer occurs.
- Countries with low incidence of TB or leprosy may choose to selectively vaccinate high-risk neonates.
- Countries with declining rates of TB are encouraged to evaluate the epidemiology of TB and leprosy and consider a switch to selective risk group vaccination.
- Revaccination is not recommended even if the tuberculin skin testing (TST) reaction or result of an IFN-release assay (IGRA) is negative.
- BCG is recommended for unvaccinated, TST-negative or IGRA-negative school children for those coming from or moving to high incidence/burden settings, as well as older groups at risk through occupational exposure.
- As a precaution, BCG vaccination is not recommended during pregnancy.
- BCG vaccination is contraindicated for immunocompromised persons (including HIV infected who are not receiving anti-retroviral therapy or are immunologically unstable) and for patients undergoing immunosuppressive treatment.
- Neonates born to women of unknown HIV status or born to an HIV-infected woman but have no clinical evidence of HIV should be vaccinated.

5.2.2 Rabies vaccines: WHO position paper (April 2018)

http://apps.who.int/iris/bitstream/handle/10665/272371/WER9316.pdf

WHO position

- The recommendations concern the two main immunisation strategies: post-exposure prophylaxis (PEP) and pre-exposure prophylaxis (PrEP).
- PEP includes extensive and thorough wound washing at the RABV-exposure site, together with rabies immunoglobulin (RIG) administration if indicated, and the administration of a course of several doses of rabies vaccine
- PrEP is the administration of several doses of rabies vaccine before an exposure to RABV.
- For both PEP and PrEP, vaccines can be administered by either the ID or the IM route.
    - One ID dose is 0.1 mL of vaccine
    - One IM dose is 0.5 mL or 1.0 mL depending on the product, that is, the entire content of the vial.
- If any doses are delayed, vaccination should be resumed, not restarted.
- WHO recommends PrEP for individuals at high risk of RABV exposure:
    - These include sub-populations in highly endemic settings with limited access to timely and adequate PEP
    - Individuals at occupational risk
    - Travellers who may be at risk of exposure
- WHO recommends the following PrEP schedule:
    - 2-site ID vaccine administered on days 0 and 7
    - 1-site IM vaccine administration on days 0 and 7

5.2.3 Typhoid vaccines: WHO position paper (March 2018)

http://apps.who.int/iris/bitstream/handle/10665/272272/WER9313.pdf

WHO position

- This paper re-emphasises the importance of vaccination to control typhoid fever and presents the WHO recommendations on the use of a new generation of typhoid conjugate vaccine (TCV).

- TCV is preferred to unconjugated Vi polysaccharide (ViPS) and oral live attenuated Ty21a vaccines at all ages in view of its improved immunological properties, use in younger children and longer duration of protection.
- A 0.5 mL single dose of TCV in children from 6 months and in adults up to 45 years in endemic regions is recommended.
- WHO recommends vaccination in response to confirmed outbreaks of typhoid fever and in humanitarian emergencies depending on the risk assessment in the particular setting.
- The need for revaccination with TCV is unclear. Revaccination is recommended every 3 years for ViPS, and every 3 to 7 years in most endemic settings for Ty21a or every 1 to 7 years for travelers from non-endemic to endemic areas, depending on national policies.
- Certain antimalarials (mefloquine) may suppress the Ty21a antibody response and should not be given from 3 days before until 3 days after giving the Ty21a vaccine.
- Vaccination is recommended for food handlers in endemic areas, travelers going to endemic areas and clinical microbiology laboratory staff with exposure risk.
- Immunocompromised and HIV-infected persons should receive TCV or VIPS. Ty21a can be administered to HIV-infected, immunologically stable individuals.

5.2.4 Dengue vaccines: revised WHO position (currently under revision)

http://www.who.int/immunization/diseases/dengue/revised_SAGE_recommendations_dengue_vaccines_apr2018/en/

- Data released by Sanofi Pasteur in November 2017 indicated that:
  - Overall population-level benefit of vaccination with Dengvaxia (CYD-TDV) remains favorable, but the vaccine performs differently in seropositive versus seronegative individuals.
  - Vaccine efficacy (VE) against virologically confirmed symptomatic dengue was high among inferred baseline seropositive participants ≥9 years of age: 76% (95%CI: 63.9, to 84.0), but much lower among baseline seronegative participants: 38.8% (95%CI: –0.9 to 62.9%) in the first 25 months after the first dose of vaccine.
  - There is an increased risk of hospitalised and severe dengue in seronegative individuals starting about 30 months after the first dose.
  - In areas of 70% dengue seroprevalence, over a 5-year follow-up, for every 4 severe cases prevented in seropositive, there would be one excess severe case in seronegative per 1,000 vaccinees; for every 13 hospitalisations prevented in seropositive vaccinees, there would be 1 excess hospitalisation in seronegative vaccinees per 1,000 vaccinees.
- Updated recommendations:
  - For countries considering vaccination as part of their dengue control program, a “pre-vaccination screening strategy” would be the preferred option, in which only dengue-seropositive persons are vaccinated.
  - Currently, the vaccine should be used within the indicated age range, which is typically 9 to 45 years of age. The age to target for vaccination depends on the dengue transmission intensity in a given country, and will be lower in countries with high transmission, and higher in countries with low transmission. The optimal age group to be targeted is the age at which severe dengue disease incidence is highest.
  - In the absence of data on vaccine efficacy and safety with fewer than three doses, CYD-TDV is recommended as a three dose series given 6 months apart. There is no current recommendation for a booster dose.

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

The next meeting of the GACVS Committee will be held on 6–7 June 2018.

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

Meetings occur annually. There has not been another meeting of the IVIR-AC since the previous report.

5.5 Global Immunization News

Available here: http://www.who.int/immunization/gin/en/

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6 Other items

6.1 Updates from TGA

- New/updated registrations for vaccines:
  - Menactra: updated 13 April 2018, eligibility extended to infants/children 9–23 months of age
  - Afluria Quad: updated 2 February 2018, eligibility extended to children 5–17 years of age
- Safety advisory released related to use of Fluad TIV in patients with latex allergy – advised that natural rubber latex is present in the sheath covering the needle of Fluad, and so the vaccine should not be given to anyone with a severe latex allergy.

7 Upcoming meetings and agendas

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

- 20–21 June 2018
- 24–25 October 2018

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

- 9–10 August 2018
- 1–2 November 2018

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)

- 6–7 June 2018
- September 26–27, 2018

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

- 23–25 October 2018