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)

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Contents

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

1.1 ACIP meeting: 24–25 October 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 October 2018 meeting are pending. Therefore, this summary has been developed from the presentation slides and video recordings.

Hepatitis A vaccines

- Hepatitis A epidemiology:
  - increasing proportion of adults are susceptible to hepatitis A because of reduced exposure to HAV in early life, decreases in seroprevalence of anti-HAV and low HAV vaccination coverage in adults, including in those at high risk
  - community outbreaks are often prolonged and difficult to control
  - outbreak in San Diego County 2016–2018: Test-negative case–control study found increased risk of HAV infection (aOR = 3.3 [95% CI 1.5–7.9]) and severe outcomes (hospitalised aOR: 2.5 [95% CI 1.6–3.9]; died aOR: 3.9 [95% CI 1.1–17]) was associated with homelessness
- Policy consideration: should routine inactivated 2-dose HAV vaccination be recommended for protection against HAV among persons experiencing homelessness?
  - ACIP Evidence to Recommendations framework used to assess evidence; key considerations below
    - homelessness is an independent risk factor for HAV infection
    - homeless people are more vulnerable due to poor hygienic conditions, overcrowding and poor sanitation
    - homeless people have an increased risk of severe disease, hospitalisation and death
    - indication for vaccination would make homeless service providers more likely to consider HAV vaccination
    - homeless population is not stable so a national approach is needed
    - vaccinating homeless in an outbreak setting is very challenging and post-exposure prophylaxis is not as effective; pre-exposure prophylaxis is a more feasible and effective approach
    - conclusion: homelessness should be an indication for HAV vaccination and there should be a specific recommendation for routine HAV vaccination among homeless persons (aged ≥1 year).

Pneumococcal vaccines

- PCV13 impact on IPD and serotype distribution for the remaining disease burden with a focus on adults ≥65 years old
  - Active Bacterial Core surveillance (ABCs) – active laboratory and population-based surveillance at 10 sites
  - overall IPD incidence significantly lower in 2016–17 compared with 2007–2010 following PCV13 introduction for children – reductions driven by 19A, 7F and 6C (cross-protection); no changes in type 3; rates have plateaued since 2014
  - PCV13 direct effects on IPD among older adults were likely very limited during this observation period
  - no evidence of serotype replacement
  - new PCVs covering top 7 non–vaccine-type paediatric strains would have limited impact on children, but potentially reducing a large burden among older adults through indirect effects.
- Impact of PCV13 on non-invasive pneumococcal pneumonia among adults ≥65 years old

- ABCs – prospective data collection since 2015 with retrospective data collection to 2013; cases were defined as adults hospitalised with clinically or radiographically confirmed pneumonia and a positive pneumococcal UAT (IPD cases excluded)
- changes in incidence of pneumococcal pneumonia similar to those observed in IPD during 2013–16
- adjusted total incidence per 100,000 by age group pre-PCV13 (2013–14) versus post-PCV13 (2015–16) recommendation for ≥65-year olds:
  - 18–49y: 11 (95% CI: 8–16) versus 7 (95% CI: 5–11), –35% change (95% CI: –49 to –14)
  - 50–64y: 39 (95% CI 27–53) versus 36 (95% CI: 26–49), –12% change (95% CI: –29 to 7)
  - ≥65y: 128 (95% CI: 92–174) versus 83 (95% CI: 60–113), –35% change (95% CI: –45 to –28)
- decreases most dramatic before 2014 (indirect PCV13 effects), with no additional reductions apparent after 2014.

- Impact of introduction of infant vaccination with PCV13 on pneumonia and IPD in the United States, 2005–2014
  - Key question: did the switch from PCV7 to PCV13 in 2010 result in further declines in pneumonia and IPD hospitalisations in the US population?
  - statewide hospitalisation data 2005–14 obtained from Healthcare Cost and Utilization Project and from state organisations or directly from 6 ABCs sites
  - significant declines in all-cause pneumonia only observed in children <5 years old after PCV13 introduction (cumulative number of hospitalisations averted – 0–1y: 38,418 [95% CI: 18,383–66824]; 2–4y: 17,026 [95%CI: 6,736–73,763])
  - pneumococcal pneumonia hospitalisations significantly declined in all age groups except for adults aged ≥75 years
  - significant declines in IPD hospitalisations observed for all age groups except those aged 40–64 years and ≥75 years.
- Economic analysis of continuing a recommendation to immunise with PCV13 for adults ≥65 years in the context of continuing herd immunity from the childhood immunisation program
  - purpose was to evaluate the cost effectiveness of continuing to recommend PCV13 at age 65 years for all adults, compared with PPV23 only
  - health outcomes included IPD, inpatient and outpatient pneumococcal pneumonia, deaths due to IPD or pneumonia, QALYs and life years
  - base case analysis found ICER to be $648,845 per QALY in 2019, compared with an analysis in 2014 which found ICER to be $64,880 per QALY projected to be $286,855 in 2019 (all values in 2017$)
  - differences between the 2014 and 2018 analyses include that in the latter analysis indirect effects are half the size, PCV13 assumed to be ineffective against serotype 3, the proportion of PCV13-type pneumonia disease is half the size, and pneumonia burden was decomposed by risk status.
- Preliminary Evidence to Recommendations for the ongoing review of the PCV13 recommendation for adults ≥65 years old
  - Policy question: should PCV13 be administered routinely to all immunocompetent adults aged ≥65 years given sustained indirect effects (i.e. PCV13 given in a series with PPV23 versus PPV23 given alone)?
  - Brief summary of statement of problem (IPD and pneumococcal pneumonia) and benefits and harms discussed; completed EtR framework with GRADE to be discussed at next ACIP meeting (February 2019).

Adult immunisation schedule

- Updates in ACIP recommendations for 2019 adult immunisation schedule:
  - Influenza: use of LAIV recommended
  - HAV: homelessness as an indication

- Hepatitis B: use of CpG-adjuvanted HepB (Heplisav-B) recommended as one of the hepatitis B vaccine options
- Updates made to adult schedule to improve usability and standardise language and text structure

Childhood immunisation schedule

- Updates in ACIP recommendations for 2019 childhood immunisation schedule:
  - Influenza: use of LAIV recommended
  - HAV: Homelessness as an indication
  - Hepatitis B: use of CpG-adjuvanted HepB (Heplisav-B) as recommended as one of the hepatitis B vaccine options
  - dTpa: vaccination of a person who received dTpa at 7–10 years of age (i.e. these children should still receive routine dTpa dose at 11–12 years)

Japanese encephalitis (JE)

- JE vaccine Evidence to Recommendations
  - Policy question: Should JE-VC (inactivated Vero cell culture-derived JE vaccine; Ixiaro) be recommended for use in people aged ≥2 months at risk of travel-related exposure to JE virus?
  - On the basis of economic evaluation, the Work Group concluded that use of the vaccine is probably not an efficient use of societal resources; however, travel vaccines are typically purchased by individuals who consider what the risk to themselves is.
  - Minor changes only were proposed to the current recommendations for JE vaccination
    - additional information on factors that increase JE risk to assist providers with decision-making
    - longer-term travel no longer specified 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 accelerated schedule recommendation for adults
  - standard series: 0 and 28 days; accelerated series: 0 and 7 days
  - FDA-approved accelerated primary series in October 2018
  - data from 1 RCT among adults aged 18–65 years conducted at 7 sites in Europe
  - 4 study arms: 1) JE-VC with rabies vaccine in accelerated schedule; 2) JE-VC with rabies vaccine in standard schedule; 3) JE-VC in standard schedule; 4) Rabies vaccine in standard schedule. There was no study arm examining JE-VE alone in a standard schedule. Data presented compared arms 1 (n=206) and 2 (n=157) only (i.e. both groups received rabies vaccine).
  - seroprotection rates at 28 days post 2nd dose of JE-VC by schedule group – accelerated: 99%, standard: 100%; GMTs: accelerated 690 (95% CI: 595–801), standard: 299 (95% CI: 254–352)
  - seroprotection rates at 1 year post 2nd dose of JE-VC by schedule group – accelerated: 94%, standard: 86%; GMTs: accelerated 117 (95% CI: 100–137), standard: 39 (95% CI: 33–47)
  - no significant differences in local or systemic adverse event frequencies between schedule groups
  - Proposed new recommendation: In adults aged 18–65 years, JE-VC can be administered in an alternate primary schedule of two JE-VC doses administered 7 days apart.
- JE-VC paediatric booster dose recommendations
  - FDA approved booster dose for adults aged ≥17 years in 2010, and for children <17 years in April 2018
  - Current recommendations for booster doses are for people aged ≥17 years: if the primary series of JE-VC was administered >1 year previously, a booster dose may be given before potential JE virus exposure.
  - Data supporting use of booster dose in children comes from 1 open-label RCT in 300 children aged 2 months to 17 years, conducted in the Philippines (JE-endemic); booster dose was administered 11 months after 2nd dose of the 2-dose primary series (Kadlecek et al, PIDJ, 2018).

- Among 81 children aged 14 months to 2 years, seroprotection ($PRNT_{50}$ titre ≥10) rates pre versus post booster: 98% versus 100%; GMTs: 67 (95% CI: 54–84) versus 2,911 (95% CI: 2,235–3,791).
- Among children aged 3 years to 17 years, seroprotection rates pre versus post booster: 90% versus 100%; GMTs: 40 (95% CI: 31–53) versus 1,366 (95% CI: 988–1,889).
- In a comparison group of children who did not receive a booster dose, 90% were seroprotected and GMTs were 59 (95% CI: 48–73) .
- Solicited adverse reactions were less frequent following the booster dose compared with the primary series; fever was the most frequent adverse event (8%).
- Work Group proposed to modify the current recommendation for JE-VC booster to include children aged ≥14 months (0.25mL in children aged 14 months to 2 years, 0.5mL in children aged ≥3 years).

- Data to support strengthening the current permissive JE-VC booster dose recommendation
  - 3 clinical trials in Europe providing data on the persistence of protective response after 12–15 months following a primary series; studies showed rates of seroprotected varied between studies (58%, 69% and 83%), as did GMTs.
  - Some of the variability in results could be potentially explained by the availability of tick-borne encephalitis (TBE) vaccine in some countries, which is a flavivirus related to JE virus and could boost effect; post-hoc analysis showed seroprotection rates among recipients of TBE vaccine were higher than among those who did not receive TBE vaccine at 1, 3 and 5 years post JE-VC primary series vaccination (presented to ACIP in February 2016).
  - Work Group recommended strengthening the permissive booster dose recommendation: For adults and children aged ≥14 months, if the primary series of JE-VC was administered >1 year previously, a booster dose should be given before potential JE virus exposure.
- Conclusions and next steps: ACIP to vote on JE vaccine recommendations at February 2019 meeting

Anthrax

- New anthrax vaccine (AV7909) for post-exposure prophylaxis (PEP)
  - AV7909 consists of Anthrax Vaccine Adsorbed (AVA) drug substance with CPG 7909 Adjuvant
  - AV7909 is being developed for PEP of disease resulting from suspected or confirmed Bacillus anthracis exposure, when combined with the recommended course of antimicrobial therapy
  - 3 clinical trials of AV7909 (phase 1a, 1b and 2) in 244 adults demonstrate safety and immunogenicity; phase 2 study examined 2-dose schedule (1 and 15 days)
  - 2-dose schedule is comparable to 3-dose schedule (3rd dose given at day 63)
  - Safety profile of AV9709 is similar to that of BioThrax vaccine
  - Two further clinical trials planned – phase 3 lot-to-lot consistency and phase 2 drug-drug interaction study (with ciprofloxacin or doxycycline)
- Anthrax antitoxin for PEP
  - Anthrax antitoxins all have an indication for the treatment of adult and paediatric patients with inhalation anthrax due to B. anthracis in combination with appropriate antimicrobials.
  - Three anthrax antitoxins are currently FDA approved: raxibacumab, anthrasil and anthim (obiltoxaximab).
  - The monoclonal antitoxins, raxibacumab and obiltoxaximab, are also indicated for PEP of inhalation anthrax when alternative therapies are not available or are not appropriate.
  - The data show that anthrax antitoxin administered 12-18 hours post exposure to Bacillus anthracis spores can prevent 90–100% of disease in rabbit and non-human primate models. However, survival frequencies have been shown to be dependent on antitoxin concentration and time of administration post exposure.
  - Protection frequencies are significantly lower with increasing time to intervention after exposure.

- Data suggest that anthrax Mab antitoxin does not interfere with the development of protective immunity.
- Data on immune response support the co-administration of raxibacumab and AVA on the currently approved dose schedule; no data are available on a dose-sparing schedule.
- No data on immune response are available for co-administered obiltoxaximab and AVA on either a normal or dose-sparing schedule.
- Data suggest that the co-administration of AIGIV and AVA significantly diminishes the immune response to AVA, and AIGIV does not have an indication for PEP use.

Vaccine supply

- Hepatitis B vaccine:
  - Merck will not be distributing its adult HepB vaccine through the end of 2019; GSK and Dynavax have sufficient supply of adult HepB vaccine to address the anticipated gap.
  - Merck's supply of paediatric HepB vaccines has been constrained since mid-2017 and Merck will continue to direct its limited supply to the public sector; a limited supply of monovalent HepB vaccine will be available through mid-Q2 2019; GSK will continue to cover the supply gap.
- Shringrix: because of high levels of demand, GSK has implemented order limits and providers have experienced shipping delays; the number of doses available for the US market in 2018 and 2019 are planned to be increased.

HPV vaccine

- Primary Ovarian Insufficiency (POI) and adolescent vaccination
  - Objective of study: to identify and describe characteristics of POI in females aged 11–34 years, describe prevalence and age-specific incidence of POI, and estimate the risk of idiopathic POI in females following 4vHPV vaccination and other adolescent vaccinations (dTpa, MenACWY and inactivated influenza)
  - Study population: females aged 11–34 years enrolled for at least 30 days at the Kaiser Permanente Northwest Vaccine Safety Datalink site; study period August 2006 – December 2014
  - 199,078 subjects enrolled, with 58,871 having received at least 1 dose of 4vHPV, 119,078 received dTpa, 46,231 received MenACWY, and 84,783 received inactivated influenza vaccine
  - Of 53 presumptive idiopathic POI cases found, there were 33 probable POI, 13 possible and 7 not POI cases
  - Prevalence of idiopathic POI in the study period: 2.31 per 10,000 females (incidence increased with age from 0.87 [95% CI: 0.12–6.16] per million person-months among those aged 11–14 years to 12.85 [95% CI: 7.87–20.97] per million person-months among those aged 31–34 years)
  - 28 confirmed cases of idiopathic POI occurred on or after 1 August 2006; exposure status of the 28 confirmed cases – 4vHPV: 1 case, dTpa: 6 cases, MenACWY: 3 cases, influenza vaccine: 11 cases
  - Age-adjusted hazard ratios for POI incidence in vaccinated and unvaccinated – 4vHPV: 0.30 (95% CI 0.07–1.36); dTpa: 0.88 (95% CI: 0.37–2.10); MenACWY: 0.94 (95% CI: 0.27–3.23); influenza vaccine: 1.42 (95% CI: 0.59–3.41)
  - Conclusions: in this study of nearly 200,000 young women, no evidence of increased risk of POI following HPV vaccination or other routine adolescent exposures was observed.
- Expanded age range for 9vHPV – summary of background for policy considerations
  - Data submitted to FDA in support of expanded age range through age 45 years
    - Include an RCT: efficacy high in women naïve to vaccine type; lower efficacy in intent-to-treat population
  - US data to inform the policy considerations indicate:
    - HPV vaccine coverage is increasing in adolescents
    - Impact of the vaccination program has been observed among females in teens and twenties

        - Most adults have already been exposed to a 9vHPV type, but not all 9vHPV types
        - HPV incidence is lower at older ages, but new infections can occur in adults
        - New sex partner is a risk factor for incident HPV infection
    - Post-licensure vaccine effectiveness evaluations indicate VE is lower with increasing age at vaccination
    - Update on global HPV vaccination
        - Less than 50% of countries have introduced HPV vaccination
        - Global vaccine shortage is limiting introductions in some countries
        - No current HPV vaccine shortage in the United States
- GRADE for HPV vaccination of mid-adults
    - PICO question: Should catch-up vaccination with HPV vaccine be recommended for primary prevention of HPV infection and HPV-related disease in US adults aged 27–45 years (i.e. 'mid-adults') who were not vaccinated previously at the routinely recommended age?
    - Evidence of benefits came from efficacy (persistent HPV infection, warts, CIN and CIN2+), immunogenicity and immunobridging (supplementary) studies; all included studies examined impact of 4vHPV and 2vHPV on these outcomes, with only 1 immunobridging study of 9vHPV being included
    - Studies of harms (any serious adverse events, vaccine-related serious adverse events, any deaths and vaccine-related deaths) included studies of 2vHPV and 4vHPV; 1 study of 9vHPV provided supplementary data on harms related to specific adverse events
    - Additional unpublished and other relevant data were included, including previous ACIP presentations, Cochrane reviews, FDA label for 9vHPV and clarification of data from vaccine manufacturer
    - Summary of GRADE:
        - 9vHPV is more efficacious against HPV-related outcomes than no vaccination in women and men
        - 9vHPV is immunogenic
        - There are similar harms among people receiving placebo versus 9vHPV
        - There are few vaccine-related serious adverse events, and no vaccine-related deaths
- Impact and economic analysis
    - Primary question: what is the cost-effectiveness of extending the upper recommended catch-up age of HPV vaccination up to 45 years for males and females?
    - Three 9vHPV models available (all are dynamic and include a wide range of health outcomes): 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)
    - Results of HPV-ADVISE model, ICERs shown as costs per QALY gained:
        - Vaccination through age 30 years (versus current recommendation): $204,400
        - Vaccination through age 35 years (versus 30): $310,000
        - Vaccination through age 40 years (versus 35): $1,671,000
        - Vaccination through age 45 years (versus 40): dominated (i.e. no significant population gains in QALYs could be measured compared to the comparator)
    - Conclusions from HPV-ADVISE model:
        - Current US HPV vaccination program (i.e. vaccination for females aged ≤26 years and males ≤21 years) offers good value for cost; vaccination of adolescents only is cost-saving
        - Extending HPV vaccination above 26 years of age results in a substantially higher cost per QALY gained
    - Differences in ICERs across models because of varying inputs, no single factor accounts for differences in ICER estimates
- Expanded age range for 9vHPV

- Policy considerations: Should the upper age for HPV vaccine catch-up vaccination be expanded beyond current recommended ages?
- Work Group discussed the following:
  - No changes to routine age for vaccination (i.e. age 11–12 years)
  - Upper age for catch-up recommendation for females and males should be harmonised
  - Individual decision making should be used for catch-up for persons older than the routine catch-up age through to 45 years
- Next steps: EtR framework will be completed and preparation for a potential vote at February 2019 ACIP meeting

General recommendations

- Updates made to ACIP general best practice guidelines for immunisation, full guidelines available at https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/index.html
- List of updates available at https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/general-recs-errata.html
- Draft of "addition to general best practices", covering advice for healthcare personnel who themselves have precautions or contraindications and may nonetheless administer those vaccines to patients

Influenza vaccines

- Afluria and Afluria Quadrivalent FDA licensure indication expanded from ≥5 years to ≥6 months in October 2018
- Influenza vaccine effectiveness in preventing influenza-associated hospitalisations during pregnancy
  - A multi-country retrospective test-negative design study 2010–16; study sites in Australia (WA), Canada (Alberta and Ontario), Israel and USA (California, Oregon and Washington); conducted over different seasons at different sites (each site contributed data for 3–6 seasons for a total of 25 study seasons)
  - Pregnant women aged 18–50 years with records of live or still birth with gestations ≥20 weeks with acute respiratory or febrile illness (ARFI) hospitalisations (defined by ICD codes for influenza, pneumonia and other respiratory codes or febrile, sepsis-like and other acute conditions associated with influenza) were eligible; cases were rRT-PCR confirmed influenza positives and controls were influenza negatives
  - 1,717,354 pregnancies identified overlapping flu season (84% of all pregnancies), of which 19,450 had hospitalisations with ARFI (3%); 1,030 admissions had rRT-PCR test results (corrected for 95 re-admissions)
  - Of 1,030 admissions, 598 were flu-positive (83% A flu positives, with A/H1 prominent in half of the seasons and A/H3 prominent in >70% of seasons)
  - Of 1,030 admissions, 169 (16%) were vaccinated, with highest coverage in USA (50%) compared with other sites (8–14%)
  - Overall VE for all sites and all seasons (adjusted for site, season, season timing and high-risk medical conditions): 40% (95% CI: 12–59%)
  - VE varied across sites and seasons, but similar when stratified by season timing, high-risk medical conditions and pneumonia/influenza diagnosis
  - If SH 2014 and NH 2014/15 season were excluded (poor vaccine match), VE=49% (95% CI: 22–67%)
- Fluzone Quadrivalent 0.5mL dose for children aged 6–35 months
  - Study GRC88 – aimed to evaluate the safety (namely fever) and immunogenicity (GMT ratios and seroconversion rate differences) of a 0.5mL dose of Fluzone Quadrivalent vaccine compared to a 0.25mL dose in healthy children aged 6–35 months
  - Phase IV, randomised, observer-blinded, 2-arm, multicentre study in the US

- 1,941 children enrolled, 949 received 0.25mL dose and 992 received 0.5mL dose; median age 20.1 months (both groups), no differences in demographics between groups
- Rates of fever (95% CI) – 0.25mL group: 11.31% (9.31–13.57%); 0.5mL group: 12.15% (10.12–14.42%); difference: 0.84% (–2.13 to 3.80%) (non-inferiority criteria met)
- Rates of other AEs, solicited and unsolicited, were similar between groups, though absolute values were slightly higher in 0.5mL group particularly for injection-site reactions (by 0–4%, CIs not provided)
- GMTs 28 days after final vaccination were higher in the 0.5mL group; GMTs 0.25mL versus 0.50mL dose by strain – A/H1: 214 versus 310 (ratio: 1.45 [95% CI: 1.19–1.77]); A/H3: 221 versus 332 (ratio: 1.50 [95% CI: 1.23–1.83]); B/Vic: 261 versus 348 (ratio: 1.33 [95% CI: 1.10–1.62]); B/Yam: 243 versus 349 (ratio: 1.44 [95% CI: 1.20–1.73]); all GMT ratios met non-inferiority criteria
- Seroconversion rates 28 days after vaccination were generally higher in the 0.5mL group, though differences were significant only for A/H1; seroconversion rates for 0.25mL versus 0.50 mL dose by strain – A/H1: 78.9% versus 84.1% (difference: 5.1% [95% CI: 0.489–10.0%]); A/H3: 81.9% versus 86.2% (difference: 4.3% [95% CI: –0.283 to 8.99%]); B/Vic: 87.2% versus 88.6% (difference: 1.4% [95% CI: –2.78 to 5.56%]); B/Yam: 87.8% versus 91.2% (difference: 3.4% [95% CI: –0.465 to 7.36%]); non-inferiority criteria met for all strains
- An application for licensure has been submitted to the FDA to permit use of a 0.5mL dose in children from 6 months of age; action date expected in January 2019

Rabies

- Newly formed Work Group with first meeting in October 2018
- Work Group will review: epidemiology and burden of rabies exposures and PEP administration; recommendations regarding the use of rabies vaccine(s) and immunoglobulin products; and efficacy, immunogenicity, safety, cost-effectiveness and vaccination schedules (including route and location of vaccine administration) of rabies vaccine(s) for PrEP and PEP, including review of new WHO recommendations
- Update of guideline recommendations expected to be presented in 2020 or 2021

Meningococcal

- Current activities include review of data for MenB vaccines regarding antibody persistence and response to booster doses, and safety and immunogenicity of MenB vaccines in children aged <10 years
- Data on MenB booster dose in people aged ≥10 years, particularly in those at high risk for meningococcal disease, planned to be presented at February and June 2019 ACIP meetings

Pertussis

- Questions to be addressed by ACIP:
  - Should the current recommendation that non-pregnant adults receive a single lifetime dose of dTpa and dT boosters every 10 years be changed to allow any dT-containing vaccine (dTpa or dT) to be used for the decennial dT booster in adults?
  - Should any dT-containing vaccine (dTpa or dT) be allowed for use for tetanus prophylaxis in the setting of wound management?
- Current ACIP recommendations regarding dT and dTpa vaccination
  - Single dose of dTpa for persons aged ≥10 years (preferably at age 11–12 years)
  - Booster of dT every 10 years – single dTpa can replace decennial dT booster dose; interval should be 5 years if needed for tetanus prophylaxis for wound management
  - dTpa during every pregnancy

- Two dTpa vaccines available (Adacel [Sanofi] and Boostrix [GSK], both licensed as single use vaccines) and two dT vaccines (Tenivac [Sanofi] & unbranded dT [MassBiologics])

- Previous policy considerations for dTpa vaccination (in 2013 and 2014)
  - Evidence of waning protection from acellular pertussis vaccines with high VE (~75%) in first year but substantial waning in 2–4 years – emergence of disease in adolescents who had received dTpa
  - Second dTpa booster after 5 or 10 years showed robust antibody response with persistence comparable to dT; economic impact of a second dose would be substantial with limited reduction of disease burden (unlikely to be cost-effective)
  - Conclusions of previous discussions: despite expected increase in pertussis, data did not support recommendation for second dTpa
  - Current situation: application for FDA label change to remove "single use" language currently under review expected to be complete by January 2019, and could simplify clinical practice (many providers do not stock both dT and dTpa, and simplification of schedule)
- Safety and immunogenicity of Adacel revaccination 8–12 years after a previous dose
  - Study Td537: observer-blinded, randomised, multicentre study in subjects in US and Canada previously vaccinated in study Td506 (currently aged 21–64 years) and in school (aged 11–14 years at initial vaccination, currently aged 18–24 years), respectively
  - Subjects randomised 3:1 to receive Adacel (n=1002) or Tenivac (dT) (n=328)
  - Safety profile was similar between the two vaccines
  - Seroprotection (defined as post-dose concentration ≥0.1 IU/mL) rates for tetanus and diphtheria toxoids were similar between the groups; rates for Adacel versus dT – tetanus: 100% versus 100% (difference: 0% [95% CI: –0.4 to 1.2%]); diphtheria: 99.8% versus 99.4% (difference: 0.42% [95% CI: –0.3 to 2.1%]); non-inferiority criteria met
  - Booster response rates similar for diphtheria but not tetanus; booster response rates for Adacel versus dT – tetanus: 74.5% versus 81.6% (difference: –7.12% [95% CI: –12.0 to –1.7%]); diphtheria: 83.2% versus 84.1% (difference: –0.95% [95% CI: –5.4 to 4.0%]); non-inferiority criteria met for diphtheria toxoid but not tetanus toxoid
  - Anti-pertussis responses were compared to a historical group that received Daptacel vaccine. Anti-pertussis GMCs were similar in the Adacel and historical group; GMCs for Adacel versus historical group – PT: 102 versus 98.1 (ratio: 1.04 [95% CI: 0.92–1.18]); FHA: 209 versus 39.9 (ratio: 5.22 [95% CI: 4.51–6.05]); PRN: 318 versus 108 (ratio: 2.94 [95% CI: 2.46–3.51]; FIM: 745 versus 341 (ratio: 2.18 [95% CI: 1.84–2.60]); non-inferiority criteria met for all antigens
  - Booster response rates were compared to expected booster rates derived from previous study Td506. Booster response rates were similar for some antigens and lower for others; response rates for Adacel versus expected rate – PT: 77.5% versus 61.4% (difference: 16.12% [95% CI: 13.27–18.73%]); FHA: 68.9% versus 73.1% (difference: –4.21% [95% CI: –7.23 to –1.34]); PRN: 65.3% versus 83.9% (difference: –18.61% [95% CI: –21.7 to –15.6%]); FIM: 56.8% versus 75.9% (difference: –19.07% [95% CI: –22.3 to –16.0%]); non-inferiority criteria (LL of 95% CI: >–10%) met for PT and FHA but not PRN and FIM
  - Despite lower booster response rates for some antigens, clinical protection is not expected to be affected as seroprotection rates for diphtheria and tetanus toxoids and GMCs for pertussis responses were non-inferior to their comparators
- Two studies of safety and immunogenicity of Boostrix revaccination (studies 009 & 012)
  - Boostrix studies 009 and 012 were revaccination studies with Boostrix at 9 and 10 years, respectively
  - Study 009 was a phase III, open-label, multicentre study in the US where subjects received Boostrix (n=442) or control (n=327); subjects were aged 28–73 years and had received either Boostrix (306/442) or Adacel (136/442) approximately 9 years earlier

- Study 012 was a phase III, open-label, non-randomised, multicentre study in the US where all subjects (n=160) received Boostrix approximately 10 years after receiving either Boostrix (n=124) or dT vaccine (n=26)
- Both studies met non-inferiority criteria for primary endpoints: seroprotection rate (% subjects ≥0.1 IU/mL) for diphtheria and tetanus; GMC ratio for PT, PRN and FHA (see ACIP slides for detailed study results)
- Both studies groups' that received revaccination with Boostrix missed booster response endpoints (secondary endpoint); however, seroprotection for diphtheria and tetanus of ≥0.1 IU/mL and ≥1.0 IU/mL, respectively, were achieved by >99% and >91%, of subjects in both studies, and pertussis antigen GMC fold rise pre to post re-vaccination were at least 6-fold in both studies
- Solicited symptoms (local and general) were generally higher after dose 2 than dose 1, Grade 3 symptoms similar were after dose 1 and dose 2.

1.2 Newly published or updated recommendations

1.2.1 Update: Recommendations of the ACIP for use of hepatitis A vaccine (HAV) for post-exposure prophylaxis and for pre-exposure prophylaxis for international travel

- Published MMWR 2 November 2018 – https://www.cdc.gov/mmwr/volumes/67/wr/mm6743a5.htm
- This report provides recommendations for PEP use of HAV vaccine and IG, and use of HAV vaccine and IG for PrEP for people who will be travelling internationally, including infants aged 6–11 months
- Current recommendations include:
  - HepA vaccine should be administered to all people aged ≥12 months for PEP
  - In addition to HepA vaccine, IG may be administered to people aged >40 years depending on the provider's risk assessment
  - HepA vaccine be administered to infants aged 6–11 months traveling outside the United States when protection against HAV is recommended
  - The travel-related dose for infants aged 6–11 months should not be counted towards the routine 2-dose series
  - The dosage of IG has been updated where applicable (0.1 mL/kg)
  - HepA vaccine for PEP provides advantages over IG, including induction of active immunity, longer duration of protection, ease of administration, and greater acceptability and availability

1.2.2 Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 update on diagnosis, treatment, chemoprophylaxis, and institutional outbreak management of seasonal influenza

- Published Clinical Infectious Diseases 19 December 2018 – https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciy866/5251935
- Updates clinical recommendations for diagnostic testing, treatment and chemoprophylaxis with antiviral medications, and issues related to institutional outbreak management

2 Immunisation Advisory Centre (IMAC), New Zealand

2.1 PTAC Considerations

- A meeting was held on 9–10 August 2018 – https://www.pharmac.govt.nz/assets/ptac-minutes-2018-08.pdf
  - There were no vaccine-specific considerations at this meeting.
- Meeting held on 1–2 November 2018 – meeting agenda and minutes not yet published

2.2 Other updates

- IMAC has provided guidance for health professionals on meningococcal disease and the use of meningococcal vaccines in the context of rising incidence of MenW disease, a declaration of an outbreak in Northland (prompting implementation of a vaccination program) and increasing demand for MenACWY vaccine, available here: http://www.immune.org.nz/meningococcal-disease-information-health-professionals
- 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.

Meningococcal epidemiology

- Overall in the last epidemiological year (2017–18), MenB accounted for 57% of IMD cases, MenW 25%, MenY 9% and MenC 5%
- The incidence of MenC IMD rose slightly in 2017–18, and was seen predominantly in infants and mid to older age adults; there were no underlying population-based causative factors for the increased incidence of MenC IMD, and no region-specific genetic strains were responsible
- MenB vaccination program:
  - National coverage of 2 doses of Bexsero in infants by 12 months was 92.5%
  - In the second and third years of the program, there had been an estimated 72% and 60% reduction, respectively, in the number of MenB IMD cases in infants
  - Data to date indicate protection from the 2-dose schedule up until the 12-month booster dose, and at least until the end of the second year of life
  - Effectiveness estimates for those younger than 12 months were 64% against all MenB strains, and 82.9% against vaccine-preventable strains (based on MATS, not taking into account any cross protection)
  - Vaccine effectiveness for the 2+1 schedule was estimated at 70% against all MenB strains, and 88% against vaccine-preventable strains (based on MATS, not taking into account any cross protection)
  - There have been no safety concerns to date after administration of ~3 million doses

- MenW vaccination program: there has been a small overall reduction in MenW cases in England since the program was introduced; targeted cohorts have seen a marked reduction with smaller reductions in those aged 1–4 years; no reduction has been seen in cases among infants
  - Coverage: 80–85% in 14–16-year olds; 70–80% in 16–18-year olds; up to 40% in 18–21-year olds
- Overall approximately 250 cases of MenB and 50 MenW cases have been prevented by MenB and MenACWY programs, respectively; this is in contrast to the increase in MenC cases. JCVI's position is that optimal control of MenC disease can only be achieved if vaccine coverage of MenACWY vaccine in older adolescents and young adults is improved, and advised that GPs be strongly encouraged and supported to improve coverage in those aged 18–25 years.

Influenza

- Summary of 2017–18 season:
  - 2017–18 had been an intense influenza season, with mainly influenza A/H3N2 and B Yamagata in circulation
  - Influenza morbidity and mortality and all-cause mortality was highest in the elderly
  - influenza B had also impacted quite highly on morbidity in the elderly as the main B strain in circulation was not included in the trivalent inactivated vaccine predominantly used in this age group
  - vaccine effectiveness against A/H3N2 across all age groups was very low and not statistically significant; contributing causes were thought to include genetic drift with different subclades circulating, waning immunity, immunosenescence in the elderly and egg adaptation of the A/H3N2 vaccine strain
- JCVI considered evidence on the use of cell-cultured inactivated vaccine (QIVc) from the 2019–20 season, including 3 studies from the US:
  - A retrospective cohort analysis of electronic medical records from a nationally representative data set (age range 4 to >75 years) by the manufacturer found an adjusted relative effectiveness against ILI of 36% (95% CI: 26.1–44.9) for QIVc versus compared with egg-based quadrivalent inactivated vaccine (QIVe); age-stratified analysis showed non-significant results for those aged 4–17 and ≥65 years
  - A retrospective observational study of >13 million Medicare beneficiaries aged ≥65 years by the FDA found a rVE of 10.7% of QIVc over QIVe for influenza-related hospital visits; QIVc was non-inferior to TIV-HD[1]
  - An abstract provided by the Kaiser Permanente Northern California Vaccine Study Centre reported rVE against PCR-confirmed influenza consultations of 8% (95%CI -10 to 23) compared to egg-based inactivated vaccine (IIVe) (predominantly TIV); absolute VEs were 31% (95% CI: 18.7–42.6%) for QIVc and 20.1% (95% CI: 4.5–25.4%) for IIVe
  - PHE presented on an impact and cost-effectiveness analysis of QIVc relative to TIVe and aTIV in the elderly and at-risk groups aged <65 years (assumed rVE of 36% and 25% for QIVc and aTIV, respectively, over TIVe); key findings included:
    - There was a greater benefit in terms of QALYs gained in vaccinating the at-risk groups aged <65 years with QIVc compared with TIVe
    - There was a greater benefit in terms of QALYs gained in vaccinating people aged ≥65 years with QIVc compared with TIVe
    - When compared incrementally with aTIV, QIVc provides more benefit in terms of QALYs gained; however, the difference in willingness to pay was small and there was greater uncertainty over this difference

[1] Note this study is unpublished but results are available in a presentation to ACIP in June 2018, available at https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2018-06/flu-03-Lu-508.pdf (accessed 7/1/2019)

    - Sensitivity analysis based on rVE estimates from FDA study found similar results
- JCVI agreed that the data support use of QIVc alongside QIVe in at-risk groups <65 years and in all adults ≥65 years (noting greater uncertainty for data in the elderly) alongside aTIV, but there was not enough data to express a preference for QIVc over QIVe or aTIV/TIV-HD, respectively.

Tetanus post-exposure prophylaxis

- In the context of a severe shortage of tetanus specific immunoglobulin (TIG) and human normal immunoglobulin (HNIG), PHE has issued updated recommendations on the use of TIG, supported by JCVI, namely: assessment of susceptibility to inform the need for TIG and/or vaccination; and recommending booster doses of vaccines for those individuals likely to mount a rapid and sufficient memory response thereby restricting use of TIG.

BCG vaccination and severe combined immunodeficiency (SCID) screening

- The National Screening Committee (NSC) had recommended that administration of the birth dose of BCG vaccine (which can cause complications in infants with SCID) be delayed until SCID screening could be undertaken.
- JCVI and NSC agreed that infants in hospital for more than 4 weeks should receive BCG vaccination as soon as their SCID result is known rather than waiting for vaccination in the community setting.
- JCVI noted its concern regarding a change of delivery setting from secondary care to the community and the risk of lower uptake levels; additional work would be required to plan for delivery of BCG vaccine after discharge from hospital.

CMV: Initiative for cooperation between EMA and European NITAGs

- The EMA has requested JCVI and other NITAGs around Europe to provide scientific advice regarding vaccines going through the licencing process in a parallel procedure. These parallel consultations would enable vaccine development plans to generate data addressing the needs of all the stakeholders involved in vaccine authorisation, reimbursement and deployment.
- The overall aim is that in the future, when industry goes through licencing processes, it does it in a way that EMA and NITAGs can ensure what they are licencing is going to be useful for public health programmes. The way they propose to do this is to make a part of the early advice given to industry about the development of their products, indications of the type of trials that NITAGs may wish to see when making a public health decision. This may also result in better licencing decisions. Further meetings with EMA are planned.
- A trial candidate vaccine selected by EMA was discussed; information on the vaccine is unavailable. JCIV made comments regarding the target group for vaccination, how the trial best addressed data for this population and size of the study.

Upcoming planned or proposed evaluations by the National Immunisation Schedule Evaluation Consortium (NISEC)

- The impact of concomitant administration of alternative hexavalent vaccines with Bexsero
- A follow-up study (IMAP3) of an observational cohort study (IMAP2) comparing vaccine responses in children born to mothers who received pertussis vaccine in pregnancy
- Optimal timing of the maternal pertussis vaccination (OptiMUM)
- Two doses of non-live zoster vaccine 12 months apart
- Immunogenicity of 2+1 Bexsero schedule against MenW and MenC disease
- A sero-epidemiology study

Travel sub-committee update

- Changes were proposed to the Green Book chapter on travel vaccinations, with more substantial changes including the following:
  - Updates regarding when to restart a course of oral cholera vaccination, aligning with the WHO position paper
  - Clarification of the use of yellow fever vaccination for those who have had a thymectomy – contraindicated in those with a dysfunctional thymus, but safe to give in those with an incidental thymectomy when the thymus was not disease/dysfunctional

3.2 Newly published or updated statement/recommendations

3.2.1 JCVI statement on meningococcal vaccination

- Published 24 October 2018 – https://www.gov.uk/government/publications/meningococcal-vaccination-statement-from-jcvi/jcvi-statement-on-meningococcal-vaccination
- Although the number of MenC cases remains low, there has been a very gradual risk over the last few years, mainly seen in infants and older adults.
- JCVI believes that optimum control of MenC disease can only be achieved if vaccine coverage in older adolescents and young adults is improved.
- GPs should be strongly encouraged and supported to improve coverage of MenACWY vaccine in those aged 18 to less than 25 years who are eligible for vaccination.

3.2.2 Updated guidance for tetanus – Green Book chapter 30

- Updated 26 November 2018 – https://www.gov.uk/government/publications/tetanus-the-green-book-chapter-30
- Updated guidance on the use of immunoglobulins for the treatment of clinical tetanus and the management of tetanus prone wounds, following updated guidance for healthcare professionals (available at: https://www.gov.uk/government/publications/tetanus-advice-for-health-professionals)

3.2.3 Updated guidance for yellow fever – Green Book chapter 35

- Updated 3 January 2019 – https://www.gov.uk/government/publications/yellow-fever-the-green-book-chapter-35
- Updated contraindication section for thymectomy and incidental thymectomy (as per JCVI discussion)

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4 National Advisory Committee on Immunization (NACI), Canada

There have been no new meetings since the previous NITAG summary report (October 2018). The more recent meeting was conducted on 26–27 September 2018 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 23–25 October 2018: https://www.who.int/immunization/sage/meetings/2018/october/en/ and https://www.who.int/immunization/sage/meetings/2018/october/presentations_background_docs/en/
- Full report: published on 7 December http://apps.who.int/iris/bitstream/handle/10665/276544/WER9349.pdf
- Summary report: https://www.who.int/immunization/policy/sage/summary_sageoct18_report.pdf?ua=1

Global Vaccine Action Plan – 2018 review of progress and recommendations

- SAGE noted that while progress has been made towards the goals set out in the GVAP, many targets are unlikely to be attained by the end of the decade
- SAGE has issued three broad recommendations to keep the momentum to address GVAP goals:
  - Countries, regions and global immunisation partners should commit to developing an integrated post-2020 global immunisation strategy, including undertaking a comprehensive review, reviewing the monitoring and evaluation framework for the GVAP, and strategising for post-2020 based on the lessons learned.
  - GVAP priorities, adapted to reflect changing contexts and lessons learned, should drive immunisation activities until the end of the Decade of Vaccines, with a focus on tailored country support to build national immunisation systems, develop a best practice framework to ensure equitable access particularly for migrant, displaced and disadvantaged populations, and nurturing individual and community demand for immunisation.
  - The contributions of research to immunisation should be enhanced and expanded, including vaccine research and development, research on immunisation systems, and building immunisation research capacity in LMICs.

Report of activities from international immunisation partners

- PREVENT is an initiative committed to developing concrete, actionable, consensus-driven ethics guidance on how to equitably include the interests of pregnant women and their offspring (<5 years old) in vaccine R&D for priority pathogens and emerging epidemic threats. SAGE welcomed this initiative and highlighted that aspects related to healthcare provider attitudes, vaccine hesitance and complexities related to pregnancy comorbidities needed consideration, and the need for careful risk–benefit assessment when studying live vaccines. SAGE suggested expansion to other marginalised groups in vaccine and drug trials.

Polio

- Ongoing efforts of the Global Polio Eradication Initiative in Afghanistan, Nigeria and Pakistan were noted, as well as outbreaks of circulating vaccine-derived polioviruses (cVDPVs) in Nigeria, the Democratic Republic of Congo, Somalia and Papua New Guinea.
- The importance of the polio program to work closely with the Expanded Program for Immunization (EPI) was stressed, as it is known that weak routine immunisation is the underlying cause of outbreaks of cVDPV; responses to outbreaks do not address how to maintain, sustain and strengthen routine immunisation .
- IPV supply is now sufficient to support routine IPV immunisation globally, but is insufficient to meet news for supplementary immunisation activities (SIAs) and to cover catch up for approximately 42 million children who have not received IPV due to supply constraints.

- The appraisal paper from the Global Certification Commission was noted as suitable for reviewing the criteria for certification of eradication of polioviruses; SAGE highlighted the necessity of including eradication of cVDPVs in the criteria for certification of eradication.

Measles and rubella

- Substantial progress in the reduction of global measles incidence and mortality since 2000 and the all-time low measles incidence in the Western Pacific Region (WPRO) in 2017 was noted; however, concern was raised regarding the loss of the measles elimination status for the American Region and in some countries in the European Region, and the resurgence of measles in 4 of the 6 WHO regions compared to the status in 2016
- Co-administration of rubella- and measles-containing vaccines and yellow fever (YF) vaccines:
    - New evidence of interference with the magnitude of antibody response against rubella, mumps and YF when MR/MMR and YF vaccines are co-administered; however, although lower in magnitude, titres are robust (well above the cut-off points for seroconversion) in all groups
    - Co-administration of MR/MMR and YF vaccines does not interfere with measles seroconversion or the magnitude of antibody response against measles
    - There was no evidence of safety concerns in any of the studies
    - Conclusions: the programmatic implications of delaying one of these vaccines would likely have a far greater impact on population immunity than any potential reduction in the immune response because of co-administration
    - SAGE recommended to maintain current guidance that MR/MMR and YF vaccines be administered at the same visit or at least 4 weeks apart, and remove all qualifications about co-administration
    - Further data are required on the impact of co-administration on long-term immunity and potential for secondary vaccine failures
- A new guidance document has been developed to support countries to identify and address measles and rubella immunity gaps to raise population immunity; SAGE stressed that the vaccination campaigns are resource-intensive and are not sustainable as a strategy and that countries should prioritise routine strengthening activities.

HPV

- SAGE reviewed updated global epidemiology and evidence on the immunogenicity, efficacy and effectiveness of HPV vaccines, the schedules of their administration, including number of doses and intervals, as well as use in HIV-infected and in male populations, concluding that the 2017 position paper remains valid. SAGE noted there is insufficient evidence to recommend use of a 1-dose schedule at this time.
    - A comparative modelling collaboration showed that girls-only vaccination was highly cost-effective because of the high population-level effectiveness and strong herd effects, irrespective of the vaccine use; at all income levels, increasing coverage in girls provides greater impact on disease than expanding vaccination to boys. With optimistic assumptions, elimination could be achieved in all countries between 2085 and 2105.
    - The interim goal proposed was that by 2030 all countries should have introduced HPV vaccination to at least a single cohort of girls in their national immunisation program and achieved at least 80% final dose coverage.
    - In the context of a constrained HPV vaccine supply forecasted to last until at least 2024, SAGE urged globally equitable distribution of available doses.

Ebola

- Licensure of candidate Ebola vaccines remains a high and urgent priority. 13 candidate Ebola vaccines (including monovalent, bivalent and multivalent candidates) have undergone or are currently undergoing clinical trial evaluation.
- Over 20,000 individuals at risk in the Democratic Republic of Congo have received recombinant vesicular stomatitis virus–Zaire Ebola virus (rVSV-ZEBOV) vaccine.
- SAGE reiterated that should an Ebola outbreak due to the Zaire strain occur before a candidate vaccine is licensed, rVSVΔG-ZEBOV-GP vaccine should be promptly deployed under the Expanded Access framework. Ring vaccination is the recommended vaccination strategy. If the outbreak is caused by an Ebola virus strain other than Zaire, consideration should be given to the use of other candidate vaccines that target the respective viral strain.
- Safety of vaccinating pregnant women with the replicating live virus vaccine rVSV-ZEBOV-GP (GP=glycoprotein): data are limited, with a single RCT indicating the risk of pregnancy lost is 1.35 (95% CI: 0.73–2.52) and 1.33 (95% CI: 0.56–3.20) for those becoming pregnant within 60 and 14 days, respectively, of vaccination.

Lessons learned from diphtheria outbreaks: opportunities for early warning and preventive action

- Data on vaccination coverage, equity and disease surveillance at national and sub-national levels can identify at-risk populations and geographic areas and guide programmatic action.
- Opportunities to improve globally available data through the WHO Immunisation Information System (WIISE) were discussed.
- A multi-sectoral approach with collaborations with other stakeholders and UN agencies (e.g. the International Office of Migration) could make use of ongoing population mobility mapping exercises.
- At local levels, the issue is often not lack of data but lack of data analysis and use.
- Opportunities to improve immunisation and pre-empt outbreaks require data, investment in data and broad collaborations from countries, regions and the global level.

5.2 Updated WHO Position Papers

There have been no new or updated WHO position papers published since the previous update.

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

- A meeting was held in December 2018. The meeting agenda and report at not yet published. Previous meeting reports available at: https://www.who.int/vaccine_safety/committee/reports/en/

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
- 24–26 September 2018, Menthon Saint Bernard, France. The summary of recommendations report is available at: http://apps.who.int/iris/bitstream/handle/10665/279394/WER9401_02.pdf?ua=1
- Draft summary available at: https://www.who.int/immunization/sage/meetings/2018/october/IVIR_Recommendations_Sept_2018.pdf?ua=1

Research to minimise barriers and improve coverage of vaccines currently in use

- Global vaccine acceptance and demand

- The working group on Vaccine Acceptance and Demand presented its draft terms of reference and a draft generic IVIR-AC stakeholder framework for vaccine acceptance and demand.
- A project protocol from South Africa guided by this framework was presented, and testing is planned to inform the approach for HPV. Shortcomings of the protocol were identified, and it was recommended that general vaccine acceptance and health system issues also be addressed in this research.
- A draft country-level dashboard for HPV was presented as a tool to guide decision-makers, with information on demographics, national cervical cancer screening program, HPV burden and prevalence, vaccination and vaccination impact. IVIR-AC recommended exploring ways to ensure that country-level data are comparable (i.e. avoid problems of measurement) and can be used to make comparisons.

- Cervical cancer elimination model comparison
  - A model comparison to inform cervical cancer elimination thresholds and strategies towards global cervical cancer elimination was undertaken in response to the global call for action to eliminate cervical cancer by the Director-General of WHO in May 2018; the evidence generated from these models was discussed by WHO SAGE at its meeting in October 2018.
  - IVIR-AC found that the individual models (i.e. Policy-1, Harvard, HPV-ADVISE and Spectrum model) are well-established, well-suited for the purpose of work and that the model comparison exercise was well conducted. Despite their substantially different structure and set-up, the models produce broadly similar results in terms of estimating the evolving impact of various strategies over time.
  - IVIR-AC suggested that focusing on long-term arbitrary elimination targets underemphasises the most important public health impacts (reductions in cervical cancer cases and mortality), and suggests using terminology related to reductions in disease rather than elimination. This is particularly true for countries that would benefit most in terms of reduced numbers of cases as they are least likely to achieve elimination thresholds. Gains at different milestones were felt to be more important. Intermediate outcomes such as incidence of pre-cancerous lesions and detection of infection prevalence should be considered.
  - Next steps – the economic analysis should focus on marginal costs and marginal benefits over time, with and without discounting

Research to conduct impact evaluation of vaccines currently in use

- Total System Effectiveness (TSE)
  - The aim of the pilot project is to test ‘multi-criteria decision analysis’ as a framework to support decision making for countries in choosing vaccine products and/or prioritising pathogens to assess the full costs and benefits for different vaccine products. The TSE project was revised in response to IVIR-AC’s feedback in March 2018.
  - To ensure that TSE provides useful market signals to vaccine developers, it was suggested to get input from vaccine developers on characteristics of TSE that would be most helpful to them in making decisions about whether to try to develop and market potential vaccines.
- Measles-rubella investment case and intervals between SIAs
  - A working group was set up in March 2018 to assess measles-rubella modelling efforts related to the measles eradication investment case and optimal timing of and intervals between SIAs
  - The KidRisk model has been reviewed for the investment case work; however, it has not been used since 2013, and the working group determined further clarification is needed before it could be used to inform global policy.
  - IVIR-AC acknowledged the modelling work done to inform the timing of SIAs; considering that SIAs may be disruptive to routine immunisation systems and overall health systems, they recommended documenting protocols to assist program managers in assessing the positive and

negative impacts or opportunity costs of SIAs on the overall systems. When outbreaks occur after SIAs, it is important to investigate whether the cases are primarily due to an accumulation of susceptible persons born since the last SIA (i.e. earlier SIA is needed) or a problem with implementation and coverage of the previous SIA. It was also noted that the ultimate goal is a routine immunisation system that is capable of inducing adequate population immunity to interrupt transmission, making SIAs unnecessary.

- WHO guide on typhoid vaccine cost-effectiveness: the need for cost-effectiveness evaluation for typhoid vaccine is driven by the availability of new Ti-Tetanus Toxoid conjugate vaccine (TCV) and availability of few economic evaluation studies that vary widely in methodologies. IVIR-AC commented on draft guidelines for economic evaluation of typhoid vaccination.
- Multi-model comparison guidelines: a draft of guidelines for multi-model comparison studies was presented. IVIR-AC recommended that the guidelines for model comparisons:
  - Include recommendations on how to describe models, including how structures differ
  - Recommend the inclusion of a mixture of different types of models/structures
  - Highlight what to do if model outputs differ
  - Recommend the use of intermediate outputs (e.g. infection) in addition to final outputs (e.g. disease)

Research to improve methods for monitoring of immunisation programs

- Data for risk groups:
  - A pragmatic MS Excel-based tool developed by the US CDC and WHO that aims to predict the level of diphtheria outbreak risk by country was presented. The purpose of the tool is to inform vaccination policy to prevent future epidemics and advise demand for diphtheria antitoxin, assisting manufacturers with an appropriate timeline and quantity for production.
  - Project Tycho: a project that aims to make existing data usable for country-level decision support. The project would compile various existing data at various levels of granularity and create a database based on FAIR data principles (findable, accessible, interoperable and re-useable).

5.5 Meeting of the Technical Advisory Group (TAG) on Immunization and Vaccine-preventable Diseases in the Western Pacific Region

- 19–22 June 2018, Manila, Philippines. http://iris.wpro.who.int/handle/10665.1/14309
- Several achievements have been made in immunisation systems strengthening in the region, including high regional coverage of three doses of DTP vaccine (97.3% in 2017), strengthening functions of NITAGs with six countries and areas meeting all global indicators of NITAG functionality, surveillance systems in place for AEFIs in 23 countries, and collaborative efforts to support the Philippines to strengthen immunisation systems. However, some issues and challenges have not yet been sufficiently addressed particularly in LMICs and Pacific island countries, including inadequate capacity for formulation of evidence-based immunisation policy, insufficient financing for subnational immunisation programs, vaccine stock outs, insufficient capacity for implementation of AEFI surveillance and response, inequities in vaccination coverage at the subnational level, and inadequate quality of immunisation data.
- There has been substantial progress in the introduction of new vaccines in LMICs in the region, with 89% of them introducing at least one new vaccine since 2010.
- 21 countries and areas have met the 2017 prevalence target of <1% hepatitis B surface antigen in 5-year-old children. Elimination of mother-to-child transmission of hepatitis B is a global goal, with the birth dose of HBV vaccine and high 3-dose coverage being the cornerstone of HBV control. Use of the birth dose of HBV vaccine outside of the cold chain or in a controlled temperature chain can help with some challenges. Package inserts for at least 2 monovalent HBV vaccines already indicate that the vaccine is stable for one month at 37°C and for one week at 45°C.

- Overall population immunity against poliovirus is quite high in the region and performance of AFP surveillance has exceeded established targets. WPRO has completed Phase I of the Global Action Plan for destruction or containment of wild poliovirus and vaccine-derived poliovirus type 2 in all polio laboratories. Mongolia and Vietnam plan to introduce IPV in the second half of 2018.
- The draft Implementation Guide for Sustaining Maternal & Neonatal Tetanus Elimination and 2017 WHO position paper on tetanus vaccines were noted. In particular the recommendation that all countries include six doses (3 primary plus 3 booster doses) of tetanus toxoid–containing vaccine in their schedules was noted. Papua New Guinea is the only WPRO country not to be validated for MNT elimination.
- WPRO has achieved the historically lowest reported incidence of measles and rubella in 2017. Several issues and challenges remain regarding progressing towards measles and rubella elimination, including rapid accumulation of susceptible children in states with inadequate or incomplete routine vaccine coverage, risk of outbreaks among adolescents and adults not targeted by routine or mass vaccination programs, risk of continuation of congenital rubella syndrome cases to occur in the absence of strategies to fill adult immunity gaps, inadequate national or subnational capacity for surveillance in some states, and insufficient capacity and preparedness to response to outbreaks in some states.
- TAG recommends that states progress control of JE in the region, noting that 8 of the 12 states with JE virus transmission risk areas have introduced vaccine in most or all risk areas with others at various stages of considering or implementing vaccination programs. Progression of JE control was discussed at the Second Consultation on Accelerated Control of JE in the WPRO in May 2018 in Manila.
- The draft Field Guide for Preparedness and Response to Diphtheria Outbreaks in the WPRO and the report on gap analysis for diphtheria diagnostic capacity for laboratories in the region were acknowledged. Challenges in availability of and access to diphtheria toxin were noted. The WHO recommendation for six doses of diphtheria vaccine (as per the WHO 2017 position paper) was noted.
- The importance of development of a post-2020 regional framework for action for immunisation and VPDs in the Western Pacific by the WHO Secretariat in collaboration with member states was noted in order to build on gains of the past decades and address issues and challenges that remain.

5.6 Third meeting of the Global NITAG Network

- 6–7 December, Ottawa, Canada. Agenda, minutes and other meeting documents are not yet available.

5.7 Global Immunization News and other items and resources

- Latest news available here: http://www.who.int/immunization/gin/en/
- SAGE 2018 assessment report of the Global Vaccine Action Plan https://www.who.int/immunization/global_vaccine_action_plan/sage_assessment_reports/en/
- WHO Immunological Basis for Immunization Series – Module 3: Tetanus, updated October 2018 http://apps.who.int/iris/bitstream/handle/10665/275340/9789241513616-eng.pdf?ua=1
- Work model for changing national vaccination programs in Sweden – a report outlining how the Public Health Agency of Sweden organises and investigates changes to national vaccination programs; published 18 December 2018 http://www.nitag-resource.org/uploads/media/default/0001/04/1fbccc4f650a27ee7462dfaca828a618c54b30fb.pdf

6 Other items

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

- There have been no new vaccines registered or major updates to the use of previously registered vaccines
- New Australian Public Assessment Reports (AusPARs) available for the following vaccines:
  - Fluarix Tetra – 4 November 2018

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7 Upcoming meetings and agendas

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

- 27–28 February 2019
- 26–27 June 2019

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

- 21–22 February 2019
- 23–24 May 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)

- 6–7 February 2019
- 5–6 June 2019

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

- 2–4 April 2019
- 8–10 October 2019