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), USA

1.1 ACIP meeting: 20–21 June 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 June 2018 meeting are pending. Therefore, this summary has been developed from the presentation slides and video recordings.

Influenza vaccines

- Preliminary estimates of 2017–18 influenza vaccine effectiveness from the US Flu VE Network
  - Test-negative design; 8,635 patients aged ≥6 months enrolled from Nov 2017 to April 2018; 36% positive, 64% negative; majority of cases were A/H3N2 (A/H3N2: 58%; A/H1N1: 10%; A not typed: 1%; B/Yam: 30%; B/Vic: 0.2%)
  - VE estimates against medically attended influenza adjusted for site, age, sex, race/ethnicity, self-rated general health status, interval from onset to enrolment, and calendar time
  - Overall adjusted VE: 40% (95% CI 34–46); by age group – 6mo–8yrs: 53% (95% CI 42–62), 9–17y: 29% (95% CI 8–46), 18–49y: 35% (95% CI 23–46), 50–64y: 33% (95% CI 17–47), ≥65y: 20% (95% CI –9 to 41)
  - Adjusted VE by strain: A/H3N2 – 24% (95%CI 15–33); A/H1N1 – 65% (95%CI 55–73); B/Yam – 49% (95% CI 40–56%). All strain-specific VEs were non-significant for ≥65 years. VE for A/H3N2 only significant for 6m–8y (37% [95% CI 17–52]) and borderline for 50–64y (25% [95% CI 0–44]).
- Preliminary estimates of 2017–18 influenza vaccine effectiveness from US Hospitalised Influenza Vaccine Effectiveness Network (HAIVEN)
  - Test-negative design; 3,597 patients aged ≥18 years enrolled from Oct 2017 to April 2018; 25% positive, 76% negative
  - VE estimates against influenza hospitalisation adjusted for age, site, days from illness onset to specimen collection, timing of illness onset, home oxygen use and number of self-reported hospitalizations in the prior year
  - Overall adjusted VE: 22% (95% CI 8–35); by age group – 18–49y: 18% (95% CI –20 to 44); 50–64y: 32% (95% CI 9–49); ≥65y: 24% (95% CI 0–41)
  - Adjusted VE by strain: A/H3N2 – 16% (95% CI –5 to 32); A/H1N1 – 58% (95% CI 36–73); B/Yam – 35% (95% CI 11–52).
- Relative effectiveness of cell-cultured versus egg-based influenza vaccines, 2017–18
  - Analysis was undertaken based on the hypothesis that egg-adaptation led to lower VE against A/H3N2 among ≥65 year olds in the 2017–18 season
  - Study population: Medicare fee-for service beneficiaries who received the cell-cultured (n=653,099 or any of 4 egg-based influenza vaccines QIV, TIV-HD, aTIV or TIV-SD (n >12.5m); enrolled Aug 2017–Apr 2018
  - The cell-cultured (10.7% [95% CI 7.5–13.7]) and high-dose vaccines (8.4% [95% CI 6.6–10.1]) were marginally more effective than the egg-based QIV for hospital outcomes.
- End-of-season update: 2017–18 influenza vaccine safety monitoring
  - VAERS data show no new safety concerns detected during 2017–18
  - Vaccine Safety Datalink (VSD) analysis did not detect any statistical signals or elevated risks for pre-specified outcomes (including acute disseminated encephalomyelitis, anaphylaxis, Bell's palsy, encephalitis, GBS, seizures or transverse myelitis) for any influenza vaccine type
  - FDA surveillance for Guillain–Barre Syndrome (GBS) among Medicare beneficiaries did not show a risk of GBS higher than the pre-specified threshold (≥2.5-fold increased risk of GBS compared with the five prior historical seasons used as controls)

- Ongoing clinical trial (NCT03183908) of safety and immunogenicity of Fluad versus Fluzone High-Dose in older adults – 279 participants enrolled and randomised; no substantial safety concerns observed to date
- Ongoing RCT (NCT03165981) of 221 children aged 12–16 months randomised 1:1 to receive PCV13+DTaP+QIV or PCV13+DTaP; primary outcome is fever following vaccination; analysis in progress.

- Systematic observational method for narcolepsy and influenza immunisation assessment (SOMNIA study)
  - Objectives: To evaluate trends in incidence of narcolepsy over time, and to evaluate a possible association between vaccination (particularly AS03- and MF59- adjuvanted monovalent A/H1N1 influenza vaccines), infections and narcolepsy
  - Incidence rate study data did not show a rise in the rate of narcolepsy following vaccination except in the one signalling country included (Sweden, which used Pandemrix)
  - Case-control analyses for AS03-adjuvanted pH1N1 vaccines (Arepanrix and Pandemrix) did not show evidence of an increased risk of narcolepsy, though data were limited for Pandemrix
  - Case-coverage analysis for Pandemrix in children in the Netherlands did not show evidence of an increased risk of narcolepsy, but the number of exposed cases was small (N=7)
  - Cases-control analysis for MF59-adjuvanted vaccine (Focetria) did not show evidence of an increased risk of narcolepsy
- MF59 adjuvanted quadrivalent influenza vaccine (aQIV) in young children <6 years
  - RCT with 10,644 children aged 6–72 months randomised 1:1 to receive aQIV (n=5,278) or TIV/QIV (n=5,193); primary outcome was PCR confirmed influenza, secondary outcome was immunogenicity examined in a subset of subjects (aQIV n=1,481; TIV/QIV n=1,405)
  - Relative vaccine efficacy (rVE) for any age and strain: –0.67% (95%CI –19.81 to 15.41); varied by strain – A/H1N1: 59.39% (95%CI 2.06–83.16); A/H3N2: –1.33% (95%CI –23.41 to 16.79); B/Yam: 2.09% (95%CI –55.44 to 38.33); B/Vic: –54.47% (95%CI –256.90 to 33.14)
  - rVE in 6–24 months – overall: 31.37% (95%CI 3.14–51.38); A/H3N2: 34.50% (95%CI 4.05–55.28); rVE not calculated for A/H1N1, B/Yam and B/Vic as case numbers were <20
  - rVE in 24–72 month olds not shown
  - Immunogenicity results show GMTs, GMT ratios and seroconversion rates in favour of aQIV for all ages and strains
  - Overall aQIV elicited a superior immune response in all ages; superior efficacy of aQIV only demonstrated in 6- to 24-month olds
  - Increased incidence of local and systemic reactogenicity is seen after vaccination with aQIV, consistent with past paediatric aTIV trials; in particular some local reactions, irritability, sleepiness appeared to be more frequent among the aQIV group aged 24–72m relative to those who received TIV or QIV in the same age group, but differences were minor and frequencies were low (all ≤2%)
  - Fever rates appeared higher in both age groups in aQIV group versus TIV/QIV group: 6–24m – any fever: 20% vs 14%, ≥39°C: 5% vs 3%, ≥40°C: 0.6% vs 0.3%; 24–72m – any fever: 19% vs 9%, ≥39°C: 4% vs 2%, ≥40°C: 0.4% vs 0.3%; 2 vs 1 febrile convulsions occurred in aQIV vs TIV/QIV groups
- Significant updates to the 2018–19 recommendations include:
  - No preference for influenza vaccine type – any age-appropriate vaccine (IIV, RIV4 or LAIV4) may be administered (LAIV4 previously not recommended due to lack of observed effectiveness)
  - LAIV can be used in people with a history of egg allergy
  - Fluarix Tetra licensed from ≥6 months of age
- Other updates: a Maternal Influenza Sub-working group has been formed and will provide advice on a study of spontaneous abortion following inactivated influenza vaccine

Anthrax vaccines

- Options for policy questions were presented particularly related to use of anthrax vaccine (AVA) during a large mass vaccination event and the use of antimicrobials. The following were proposed:
  - While subcutaneous route of administration is preferred, intramuscular administration is supported when operationally challenging and may be used during a large-scale emergency response.
  - Dose sparing schedules of AVA (2 full doses or 3 half doses instead of 3 doses) provided high levels of protection; either schedule may be used in the event of supply shortage with the choice determined by the anticipated vaccine shortage.
  - In immunocompetent individuals, antimicrobial use can stop once peak immune response is reached (i.e. 42 days after first dose or 2 weeks after last dose, whichever is last).

Human papillomavirus (HPV) vaccines

- Application to expand age indication for 9vHPV vaccine through to 45 years in males and females (currently licensed for 9- to 26-year olds)
  - Under FDA review as of June 2018, expected to be complete by early October 2018
  - No 9vHPV efficacy trial has been conducted in males or females among people >26 years; no 4vHPV efficacy trial among males in this age group; ongoing 9vHPV vaccine study in 6–26y and 27–45y women to demonstrate non-inferior GMTs in older women compared with younger women (analyses expected in Q2 2019)
  - Data available from 4vHPV efficacy trial in females aged 24–45 years showing high, statistically significant, efficacy against persistent infection (89.6% [95% CI 79.3–95.4]), CIN (94.1% [95% CI 62.5–99.9]) and external genital lesions (100% [95% CI 30.8–100]) due to vaccine types, with 10 years of follow-up data (no cases of 4vHPV type cervical disease or external genital lesions during follow-up years)
  - Bridging efficacy and immunogenicity data (post-hoc immunogenicity bridging analyses with cross-study comparison of 4vHPV vaccine trials), accepted for other HPV vaccine approvals, will inform consideration of the expanded age application
  - Work Group will be considering possible expanded age indication and recommendations for catch-up (routine age will remain unchanged at 11–12 years):
    - Based on HPV epidemiology, the population level benefit of vaccination of mid-adults would be low compared with vaccination at younger ages.
    - Sex with a new partner remains a risk for HPV infection in older age groups, though new sex partners decrease with increasing age.
    - Immunity after natural infection is an important determinant of potential impact of vaccination; might differ for males and females.

Update on NITAGs

- Summary provided of CDC's recent roles in NITAG strengthening, including providing technical assistance and training activities, partnerships, research and funding to WHO
- CDC, WHO and partners have developed a simplified tool to assess NITAGs on three main domains (functionality, quality of work processes and outputs, and integration into policy process); pilot testing in 2018
- Presence of a NITAG in all WHO member states by 2020 is a goal of the Global Vaccine Action Plan
- NITAG Resource Centre (NRC) is aimed to be a one-stop-shop for all NITAG-related information: http://www.nitag-resource.org/
- The Global NITAG Network (GNN) is a network of NITAGs to:
  - provide a platform to enable NITAGs to efficiently share and access knowledge
  - liaise with regional NITAG networks
  - develop standards for processes to ensure evidence-based decision-making

- facilitate evaluations and capacity building
- advocate for NITAGs.

Mumps vaccine

- In October 2017, ACIP recommended persons previously vaccinated with 2 doses of mumps vaccine who are identified by public health authorities as being part of a group or population at increased risk for acquiring mumps because of an outbreak should receive a third dose of mumps vaccine
- CDC guidance for use of a third dose of MMR vaccine during mumps outbreaks has been developed, and covers:
  - identifying group(s) of persons at risk for acquiring mumps during an outbreak – particularly definition of a 'close contact'
  - assessing transmission in the settings to determine if group(s) are at increased risk, based on evidence or risk of transmission in the setting; a decision matrix can assist with this assessment
  - implementing a third dose recommendation.

Herpes zoster vaccine

- GSK has the following postmarketing commitments for HZ/su (Shingrix):
  - assess its safety, reactogenicity and immunogenicity in adults ≥50 years of age with a prior episode of Herpes Zoster (Protocol submission: Q2, 2018 | Study complete: Q4, 2020)
  - conduct a targeted safety study to evaluate its safety in adults ≥50 years (Protocol submission: Q4, 2020 | Study complete: Q2, 2024)
  - assess its long-term efficacy, immunogenicity and safety in adults ≥50 years of age (Protocol submission: Q4, 2021 | Study complete: Q3, 2023).
- 680 reports to VAERS following HZ/su between Oct 2017 and Apr 2018 with majority (95%) non-serious; no unusual patterns or unexpected adverse events; 48 (7%) involved co-administration with additional vaccine(s); most common events reported were injection site reactions, pyrexia, chills and headache
- Publication on vaccine administration errors involving HZ/su in MMWR: https://www.cdc.gov/mmwr/volumes/67/wr/mm6720a4.htm?s_cid=mm6720a4_w
- Studies are being planned to evaluate effectiveness of 1 and 2 doses of HZ/su among adults ≥50 years, previous Zostavax recipients and immunocompromised via large health systems and administrative claims data
- Due to high levels of demand for HZ/su, GSK has implemented order limits and there have been shipping delays which will continue throughout 2018; however, supply is sufficient.

Japanese encephalitis vaccine

- GRADE for inactivated Vero cell culture-derived JE vaccine (JE-VC; Ixiaro)
  - Policy question: Should JE-VC be recommended for use in persons aged ≥2 months at risk of travel-related exposure to JE virus?
  - Population: people ≥2 months travelling to JE risk areas; intervention: JE-VC in a 2 dose primary series; comparison: no JE vaccine recommended
  - Overall quality of evidence for JE-VC:
    - Seroprotection at 1 month: 4 RCTs, evidence type 1 (evidence from RCTs or overwhelming evidence from observational studies)
    - Seroprotection at 6 months: 2 RCTs, evidence type 1
    - Serious adverse events: 8 RCTs, evidence type 2 (evidence from RCTs with important limitations or exceptionally strong evidence from observational studies)
    - Events of special interest: 5 RCTs, evidence type 2
- Comparative analysis of JE vaccination strategies

- Purpose: To compare numbers needed to vaccinate and cost-effectiveness of strategies for JE vaccination for US travellers to Asia
- Risk groups: 1) Travel for ≥1 month; 2) travel <1 month but planning to spend >20% time in doing outdoor activities in rural areas; 3) remainder of US travellers to Asia (risk groups mirror current recommendations to 1) recommend 2) consider 3) not recommended for vaccination, respectively)
- Cost per JE case averted: $596M (Risk group 1) to $7,905M (Risk group 3) (Societal perspective)
- Number needed to vaccinate: ~736,000 (Risk group 1) to ~9.8 million (Risk group 3)
- Cost per case averted was at least $2million even when extensive sensitivity analyses conducted including increasing incidence and medical costs and decreasing vaccine cost

Pneumococcal vaccines

- Safety of PCV13 in adults aged ≥65 years
  - 5,822 reports to VAERS of adverse events in adults ≥65 years after receiving PCV13 between Aug 2014 and Dec 2017; majority were non-serious (94%) and most were injection site reactions; no unexpected data mining findings or new safety signals or unexpected patterns
  - Results of Vaccine Safety Datalink study of PCV13 in adults ≥65 years do not support an increased rate of adverse events for those studied (including cardiovascular events, Bell's Palsy, GBS, syncope, erythema multiforme, thrombocytopenia, cellulitis and infection, allergic reaction and anaphylaxis) following PCV13 compared with PPV23
- Pneumococcal pneumonia burden and PCV13 impact among adults old in Louisville, KY (Louisville pneumonia study)
  - Prospectively enrolled adults (≥18 years) living in Louisville, KY, who were hospitalised with community-acquired pneumonia (CAP) (based on clinical and radiographic criteria); all 9 adult acute-care hospitals included; estimated incidence between June 2014 and May 2016
  - Incidence increases with age; incidence in all ≥65 years: 2,300 per 100,000; overall ~700 per 100,000 (higher than incidence reported in other studies due to selection criteria, healthcare-associated CAP and immunocompromised included in this study)
  - Multisite SSUAD study: extension of Louisville study to examine PCV13 impact
  - Proportion of CAP due to PCV13 types in 18–64 years at-risk (PCV13 not recommended) did not change over study period; this proportion declined in all ≥65 years (PCV13 recommended): 5.1% (Oct 2013–Sep 2014) to 3.4% (Oct 2015–Sep 2016)
  - % relative reduction in PCV13-type CAP incidence (Louisville data only) only significant for all ≥65 years (31.5% [95%CI 8.3–48.9]); no significant impact on 18–64 year olds (all or at-risk only) indicating direct impact of PCV13
  - Large disparities in uptake in PCV13 with lower uptake in locations with higher poverty and non-white race; geospatial analysis indicated higher incidence of CAP associated with areas of high poverty and high proportion of African American residents
- Racial disparities in invasive pneumococcal disease and PCV13 impact
  - Study using data from Active Bacterial Core Surveillance (ABCs) – active laboratory and population-based surveillance
  - Compared overall and serotype-specific IPD incidence (cases/100,000 population) from 2008–2009 (pre-paediatric PCV13 introduction baseline) to 2015–2016
  - IPD incidence has dramatically decreased for all racial groups driven by reduction in PCV13-type IPD
  - PCVs have nearly eliminated the absolute difference in PCV13-type IPD incidence between people of black and white races
  - Disparities in IPD remain due to non–vaccine-type IPD
  - Further analysis is planned to look at the contribution of SES and underlying medical conditions by race

- Pneumococcal carriage, invasive disease and hospitalisations following CAP among Native American populations
  - PCV13-type pneumococcal carriage in adults was very low following PCV13 introduction and remains low (<5%)
  - Substantial indirect effects from the infant program had been achieved by 2014–2015, leaving little opportunity to assess impact of PCV13 in ≥65-year olds on carriage or IPD
  - Native American Adult Pneumonia Etiology study, March 2016–March 2018: cases of Native American adults hospitalised at 5 hospitals with CAP compared with age-matched controls
    - Pneumococcus was detected in 91 (26%) of 348 cases of CAP identified by chest x-ray
    - Serotype data were available for 72 cases (79%) – 22 (31%) were PCV13-type of which majority were type 3 (4 were other PCV13-types); 13 (62%) of 21 with vaccination status available had received PPV23 followed by PCV13
  - Pneumococcus remains an important cause of CAP among Native American adults, with non-PCV13 serotypes and serotype 3 predominating
- Evidence presented at this meeting on the incidence of pneumococcal pneumonia and evaluation of racial disparities in pneumococcal disease will be included in the Evidence to Recommendations Framework for the ongoing review of the PCV13 recommendation for adults ≥65 years; GRADE summary to be finalised by February 2019 meeting.

Vaccine supply

- Hepatitis A vaccine supply has increased by both GSK and Merck, following outbreaks and shortage in 2017
- Merck not currently distributing adult hepatitis B vaccine through the end of 2018 and has limited supply of paediatric hepatitis B vaccine; GSK has sufficient supply during this period

1.2 Newly published or updated recommendations

1.2.1 ACIP recommendations for the use of quadrivalent live attenuated influenza vaccine (LAIV4) – United States, 2018–19 influenza season

- Published MMWR 8 June 2018 – https://www.cdc.gov/mmwr/volumes/67/wr/mm6722a5.htm
- The following recommendations are new or updated:
  - Providers may choose to administer any licensed, age-appropriate influenza vaccine (IIV, RIV or LAIV4); there is no preference for any influenza vaccine product

1.2.2 Prevention and control of seasonal influenza vaccines: recommendations of the ACIP, United States, 2018–19 influenza season

- Published MMWR 24 August 2018 – https://www.cdc.gov/mmwr/volumes/67/rr/rr6703a1.htm
- The following recommendations are new or updated:
  - Updated for the recommended 2018–19 strains
  - LAIV4 is an option for those for whom it is appropriate; there is no preference for any age-appropriate influenza vaccine
  - Persons with a history of egg allergy of any severity may receive any licensed, recommended and age-appropriate influenza vaccine (IIV, RIV4 or LAIV4)
  - New regulatory actions:
    - Afluria Quad approved for ages ≥5 years (previously ≥18 years)
    - Fluarix Quadrivalent approved for ages ≥6 months (previously ≥3 years)

2 Immunisation Advisory Centre (IMAC), New Zealand

2.1 PTAC Considerations

- A meeting was held on 3–4 May 2018 – https://www.pharmac.govt.nz/assets/ptac-minutes-2018-6.pdf
  - There were no vaccine-specific considerations at this meeting.
- Meeting held on 9–10 August 2018 – minutes not yet published; however, there were no vaccine-specific considerations listed on the meeting agenda

2.2 Other updates

- Antigen literature review for the NZ National Immunisation Schedule, 2018: Meningococcal
  - 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/AcRev2018_meningococcal_0.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 2014 to March 2018 on the use of meningococcal vaccines and their role in prevention of IMD.

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

3.1 JCVI meeting: 6 June 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.

Influenza – update on 2017–18 season

- The activity of the 2017–18 season was characterised as moderate based on GP ILI consultations
  - Rates of consultation were highest in the older age groups and lowest in children.
- Rates of laboratory-confirmed influenza hospitalisations and ICU admissions were very high with peak levels being observed since 2010–11; a higher burden was observed in older age groups.
- All-cause excess mortality was at similar levels to that seen in 2016–17 but not as high as that in 2014–15.
- A large proportion of cases was due to influenza B; B viruses were dominated by B/Yamagata lineage which was well matched in the quadrivalent vaccine but was not in the 2017–18 trivalent vaccine.
- A/H3N2 viruses were mainly of the 3C2a1b haemagglutinin genetic group early in the season (up to November), but were then dominated by circulation of 3C2a2.
- Vaccine uptake was generally higher across all groups compared with previous seasons.
- Regarding vaccine effectiveness:
  - For all ages the overall VE against influenza was modest
  - VE against A/H3N2 was low; VE against A/H1N1 and B was higher than against A/H3N2
  - VE against B was low likely because most adults would have received TIV which did not contain the B strain that predominated in the 2017–18 season
  - The overall effectiveness of LAIV in the paediatric program was moderate: VE against A/H3N2 was not significant, but VE was significant against A/H1N1 and B.

- Potential reasons for low VE against A/H3N2 may have been genetic evolution of the circulating strain with emergency of 3C2a2 group, problems with egg adaptation and immunosenescence in older adults.
- Enhanced vaccines will be available for those aged over 65 years in future seasons: MF59 adjuvanted TIV (aTIV) to be available in 2018–19 season and high-dose TIV in 2019–20. QIV will be available for those in an at-risk group aged <65 years for the 2018–19 season.

Influenza – other items

- Cost-effectiveness analysis of vaccines for use in the 65+ program
  - The analysis examined the likely impact of immunisation in those aged ≥65 years with QIV, aTIV and TIV-HD (UK currently uses TIV in older adults)
  - Sensitivity analysis suggested that for QIV most of the uncertainty was around the additional B strain, and for the high-dose and aTIVs uncertainty was around the potential efficacy against A/H3N2 strain
  - Evidence indicated superior efficacy for aTIV and TIV-HD compared with standard dose products
  - Overall the results indicated a similar willingness to pay for the high-dose and adjuvanted influenza vaccines as that for the standard dose vaccine. The willingness to pay was higher for high-dose and adjuvanted vaccines compared with quadrivalent standard dose vaccine.
  - It was noted that aTIV would be the vaccine of choice in 2018–19 and that TIV-HD may be available in 2019–20. It was agreed that both these vaccines were suitable for the 65+ program and preferable to standard dose TIV and QIV, and close scrutiny of the program and vaccine effectiveness should be maintained.
- Pandemic-specific vaccine strategy
  - The current advance purchase agreement is for an MF59 monovalent vaccine produced using egg-based technology; this vaccine is not currently licensed for use in children
  - A biphasic approach would be used:
    - the vaccine is produced in <4 months for early use of the vaccine to reduce impact before the peak of the epidemic; vaccine will be produced using newly licensed technologies or those currently in the late stages of development
    - the second phase would be a sustained response with higher volumes of vaccine being produced using current technologies

Herpes zoster vaccination

- Noted that at the previous JCVI meeting that the new shingle vaccine, Shingrix, had good efficacy and would be a suitable vaccine for those eligible for the current program but contraindicated for receipt of Zostavax
- Economic analysis showed that a program using Shingrix in 70- to 79-year olds is highly likely to be cost-effective. The analysis was done as an incremental analysis to the current program and incorporated the use of two doses and administration cost. Further modelling on the optimal age for Shingrix is planned.
- JCVI agreed that use of Shingrix in 70- to 79-year olds is effective and cost-effective, and should be considered for use in the national program in the UK
- Use of vaccine for immunocompromised individuals outside the national program will be at the discretion of specialist clinical groups. Guidance on definitions of ‘immunocompromised’ is required to ensure consistency of approach across clinical specialisms.

HPV vaccination

- The findings of updated modelling done by the University of Warwick to assess the cost-effectiveness of a boys' HPV vaccination program were considered (in lieu of a model by PHE which had been delayed)
- Under the standard methodology assumptions (£20k/QALY, 3.5% discount rate, incremental on the girls' program), extension of the program to adolescent boys was unlikely to be cost-effective
- A sensitivity analysis with a higher attributable fraction for oropharyngeal cancer made the vaccine more cost-effective but only at a very low, unrealistic vaccine price
- A sensitivity analysis using a lower discount rate (1.5%) showed a program to be cost-effective at a realistic price
- An additional scenario was considered comparing a gender-neutral program to no program, on the basis of equality; this was highly cost-effective
- Data were presented on schedules using 1 or 2 doses; however, 1-dose data are only available from opportunistic studies and will be considered in a few years when more robust data are available
- JCVI agreed that a 1.5% discount rate was appropriate in accordance with NICE Health Technology Assessment guidance which states that a 1.5% discount rate can be considered where the impact of a lifesaving intervention is sustained over a period of at least 30 years
- JCVI noted that the many of the benefits of an expanded program include reduction in cervical cancer in girls and genital warts in MSM
- Despite high coverage among girls, the changes in coverage in other countries in Europe were noted, and JCVI considered that a gender-neutral program was likely to be more robust with respect to potential short-term fluctuations in uptake
- Considerations on the basis of equality are not within the scope of JCVI's considerations as an expert scientific advisory committee; however, JCVI agreed that the findings of analysis with no program as the comparator should inform the government's decision
- It was noted that there could be additional economies of scale when procuring double the volume of stock and should be considered in the development of policy
- Overall JCVI agreed that this was a complex issue; cost-effectiveness under the standard economic methodology would not be cost-effective, but use of a 1.5% discount rate would make the program cost-effective

Pneumococcal vaccination

- Review of evidence by the Pneumococcal Sub-committee found the following:
  - Recent data indicated that serotypes 3 and 19A had predominated in most vaccine-type IPD cases in infants <2 years, with the majority of cases having been appropriately vaccinated for age
  - Immunogenicity data indicated that 2+1 and 1+1 schedules were broadly comparable in terms of immunogenicity (including serotypes 3 and 19A)
  - Models of schedules of 1+1, 0+1 and 2+0 indicated maintenance of herd protection with a 1+1 schedule, and that the effectiveness of the priming dose had little impact on findings given the level of herd protection seen in modelling of a 0+1 schedule
  - The model predicted a very small increase in IPD cases in <2 years and that any increase in non-invasive disease would be small; this increase would not cause considerable increase in antibiotic use or hospitalisation
- Consultation responses were discussed by the sub-committee:
  - Concerns had been raised about low vaccine coverage; however, the model had used a significantly lower coverage value than national data and was lower than the lower coverage by area in England and Wales
  - Only a small proportion of additional cases predicted would present as meningitis, which is rare and presents in about 5% of IPD cases

    - Robust surveillance would ensure that JCVI could react swiftly should it become necessary to reconsider the advice for a 1+1 schedule, which would not need a cost-effectiveness analysis
    - Given the very small increase in cases predicted, the extra dose in a 2+1 schedule was unlikely to represent a good use of public money
- The Pneumococcal sub-committee fully supported the advice of JCVI to move to a 1+1 schedule
- Epidemiology update: PHE presented on the impact of a 1+1 schedule on vaccine-type disease in the first year of life
    - In the past 5 years, there had been 85 vaccine-type IPD cases (17 cases/year on average) in those <2 years
    - Serotype 3 and 19A were responsible for most IPD cases
    - The majority of cases were in those who had been appropriately immunised for their age
- Adult vaccination:
    - Previous modelling of the use of PCV13 in adults was not cost-effective; given that serotypes 3 and 19A were not expected to decline in the way predicted for other serotypes, JCVI considered that no further review of PCV13 vaccination in the elderly was required at this time
    - Modelling would need to be reviewed for assessment of higher-valency pneumococcal vaccines in the pipeline once more information on the vaccines becomes available
    - The sub-committee considered that, although it was found to be not cost-effective in previous analyses in 2015, the use of PPV23 is likely to now be more cost-effective given that IPD from serotypes in PPV23 but not in PCV13 had increased considerably in adults. JCVI agreed that the sub-committee should consider this matter further.

Coverage

- Measles outbreaks in the final quarter of 2017 in England and Wales were noted; they often occurred in under-vaccinated populations and young adults and were associated with importation

3.2 Newly published or updated statement/recommendations

3.2.1 Statement on HPV vaccination (conclusions on extending the HPV vaccination program to adolescent boys in the UK)

- Published July 2018 – https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/726319/JCVI_Statement_on_HPV_vaccination_2018.pdf
- Conclusions regarding key considerations and cost-effectiveness of a boys' HPV vaccination program are as summarised in the JCVI discussion above

3.2.2 Updated guidance on use of varicella zoster immunoglobulin (VZIG) – Green Book chapter 34

- Updated 10 July 2018 – https://www.gov.uk/government/publications/varicella-the-green-book-chapter-34
- In response to a significant shortage of VZIG because of manufacturing issues, VZIG will only be issued to susceptible pregnant women who have had a significant exposure to chickenpox or singles in the first 20 weeks of pregnancy. Pregnant women who are exposed after 20 weeks should be offered the oral anti-viral drug acyclovir (800mg 4 times a day from day 7–14).

3.2.3 Updated guidance on rabies pre-exposure and post-exposure prophylaxis – Green Book chapter 27

- Updated 10 July 2018 – https://www.gov.uk/government/publications/rabies-the-green-book-chapter-27
- Updates include:
    - Changes in definitions of exposures and animal and country risk

- Clarification of the groups who should receive rabies pre-exposure immunisation
- Post-exposure risk assessment including Composite Rabies Risk
- Reduction in the number of vaccine doses for immunocompetent individuals to 4
- Change to the recommendations on the use of human rabies immunoglobulin (HRIG)
- Guidance on the management of immunosuppressed individuals.

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4 National Advisory Committee on Immunization (NACI), Canada

A meeting was conducted on 6–7 June 2018 and 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

4.1.1 NACI literature review on the comparative effectiveness and immunogenicity of subunit and split virus inactivated influenza vaccines in adults 65 years of age and older

- Published May 2018 – http://publications.gc.ca/collections/collection_2018/aspc-phac/HP40-213-2018-eng.pdf
- A literature review was undertaken to examine the vaccine effectiveness and immunogenicity of unadjuvanted, standard dose subunit inactivated influenza vaccines compared to unadjuvanted, standard dose split virus inactivated influenza vaccines in adults aged ≥65 years.
- 8 included studies did not show statistically significant differences in vaccine effectiveness or immunogenicity.
- NACI concludes that there is insufficient evidence to determine the comparative vaccine effectiveness and immunogenicity of unadjuvanted subunit and split virus inactivated influenza vaccines in adults aged ≥65 years, and evidence is not sufficient to support specific recommendations on the differential use of these vaccines in older adults.

4.1.2 Updated recommendations on the use of herpes zoster vaccines

- Published 30 August 2018 – https://www.canada.ca/en/services/health/publications/healthy-living/updated-recommendations-use-herpes-zoster-vaccines.html
- The following notable recommendations are made:
  - Recombinant zoster vaccine (Shingrix®, HZ/su) should be offered to people aged ≥50 years without contraindications
  - HZ/su (2 doses) should be offered to people aged ≥50 years who have previously been vaccinated with live zoster vaccine (Zostavax®) at least one year after receiving live zoster vaccine
  - Live zoster vaccine may be considered for immunocompetent populations aged ≥50 years without contraindications when HZ/su is contraindicated, unavailable or inaccessible
  - HZ/su, but not live zoster vaccine, may be considered for use in immunocompromised adults aged ≥50 years.

4.1.3 Updated NACI recommendation for measles post-exposure prophylaxis

- Published 6 September 2018 – https://www.canada.ca/en/public-health/services/reports-publications/canada-communicable-disease-report-ccdr/monthly-issue/2018-44/issue-9-september-6-2018/article-7-naci-recommendation-pep.html

- NACI continues to recommend that susceptible immunocompetent individuals 6 months of age and older who are exposed to measles and who have no contraindications be given measles-mumps-rubella (MMR) vaccine within 72 hours of the exposure.
- NACI recommends that for susceptible infants younger than 6 months, if injection volume is not a major concern, intramuscular immunoglobulin (IMIg) should be provided at a concentration of 0.5 mL/kg, to a maximum dose of 15 mL administered over multiple injection sites.
- Susceptible infants aged 6 to 12 months who are identified after 72 hours and within six days of measles exposure should receive IMIg (0.5 mL/kg) if injection volume is not a major concern
- Additional recommendations for use of IMIg are provided.
- NACI does not recommend that susceptible immunocompetent individuals older than 12 months receive Ig PEP for measles exposure because of low risk of disease complications and the practical challenges of administration for case and contact management.

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5 Immunisation updates from the World Health Organization (WHO)

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

There has not been a SAGE meeting since its April 2018 meeting, which was covered in the previous NITAG report for ATAGI. SAGE will meet again in October 2018. A summary of position papers published since the last summary is below.

5.1.1 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.

5.1.2 Dengue vaccines: revised WHO position (September 2018)

http://apps.who.int/iris/bitstream/handle/10665/274315/WER9336.pdf?ua=1

WHO position

- CYD-TDV (Dengvaxia) has been shown in trials to be efficacious and safe in persons who have had a dengue virus infection in the past (seropositive individuals).

- CYD-TDV increases the risk of severe dengue in those who experience their first natural dengue infection after vaccination (individuals who were seronegative prior to vaccination).
- For countries considering vaccination as part of their dengue control program, pre-vaccination screening for past dengue infection is the recommended strategy.
- If pre-vaccination screening is not feasible, vaccination without individual screening could be considered in carefully selected areas with recent documentation of seroprevalence rates of at least 80% by the age of 9 years.
- Screening tests should be highly sensitive (to ensure a high proportion of seropositive persons are vaccinated) and highly sensitive (to avoid vaccinating truly seronegative persons).
- The vaccine should be used within its indicated age range, typically 9–45 years; the optimal age group to be targeted is the age before 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.
- CYD-TDV should not be considered as a tool for outbreak response.
- CYD-TDV is not recommended in pregnant and lactating women because of insufficient data on its use in this population; however, data on inadvertent administration have not identified a specific risk.
- CYD-TDV is contraindicated in immunocompromised individuals.
- In travelers who have already had a documented dengue illness or are seropositive, vaccination before travel to high dengue transmission settings could be considered.

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

- 6–7 June 2018, Geneva, Switzerland. Full meeting report available at: http://apps.who.int/iris/bitstream/handle/10665/273010/WER9329-30.pdf
- Pharmacovigilance in pilot use of malaria vaccine
  - In May 2018, the national regulatory authorities of Ghana, Kenya and Malawi granted special authorisation for use of the RTS,S malaria vaccine (Mosquirix™) in the planned pilot implementation program, which is expected to commence later in 2018.
  - Safety data will be derived from post-marketing monitoring of cohort events by the manufacturer, GSK, with detailed active follow-up, surveillance of mortality throughout the pilot area and surveillance of meningitis and cerebral malaria in sentinel hospitals in control and vaccine areas, active surveillance of adverse events of special interest (AESI), and pharmacovigilance through passive reports of adverse events following immunisation (AEFI) with all vaccines from each country.
- Safety of dengue vaccine in the Philippines
  - In April 2018, SAGE recommended that CYD-TDV (Dengvaxia®) not be administered to individuals who have not been previously infected with wild dengue virus, and advised that countries considering CYD-TDV vaccination as part of their dengue control program to include pre-vaccination screening. A revised position paper on dengue vaccine will be released in September 2018.
  - 14 fatal case reports in the Philippines were reviewed by the national AEFI committees and the Dengue Investigative Task Force (DITF) – 3 were classified as dengue shock syndrome, 6 with other clinical diagnoses, 3 as coincidental and 2 were unclassifiable. A further review of 12 cases (8 fatal and 4 non-fatal) by DITF found that most cases were indeterminate, coincidental or unclassifiable. In the absence of criteria for distinguishing vaccine failure from vaccine-related immune enhancement, individual cases cannot be attributed to one or the other.
  - GACVS maintained its earlier recommendation that CYD-TDV should not be administered to people who have not been previously infected with wild dengue virus.

- The manufacturer provided post-marking updates: between December 2015 and March 2018, 1876 adverse events were reported to the manufacturer, mainly from Brazil and the Philippines. Fever, headache, dizziness, vomiting and rash were the most frequent. Of the 211serious AEFI reported, most were consistent with an underling infectious disease, including dengue fever.
- 87 cases of dengue infection (23 serologically confirmed) had been reported after vaccination with CYD-TDV. 14 were fatal. The interval between vaccination and disease onset was <6 months for all 9 cases for whom this information was known.
- GACVS examined the possible risk of viscerotropic or neurotropic disease associated with the yellow fever backbone of the CYD-TDV vaccine; non-clinical and clinical evaluations do not provide evidence of an association.

- Progress in the Global Vaccine Safety Initiative (GVSI)
  - An update on the progress in achieving its objects 6 years after the launch of GVSI was provided; the Blueprint (a framework of 8 objectives for enhancing global vaccine safety activities) vision of effective vaccine pharmacovigilance systems is progressively being established in all countries.
  - The concept of the Global Vaccine Safety Observatory was discussed – it was conceived as a clearinghouse for data on vaccine safety systems to assist member countries in achieving the Blueprint objectives. The expected outputs include presentation and analysis of relevant data, a website to provide indicators of vaccine safety capacity and links to relevant activities for vaccine vigilance, and an annual report.
  - With the Decade of Vaccines being completed by 2020, a new vaccine strategy is being developed; GACVS recommends close collaboration to ensure that the global vaccine safety strategy is well positioned in the new global approach to immunisation.
- Vaccine safety communication
  - A new GACVs subcommittee on vaccine safety communication has been established to integrate safety assessments with better capacity to communicate them
  - Two existing resources were highlighted: the new Council for International Organizations of Medical Sciences (CIOMS) Guide to Vaccine Safety Communication and the WHO Vaccination and Trust Library
- Vaccine Safety Net (VSN)
  - A WHO initiative to identify trustworthy information on vaccine safety and immunisation on the internet
  - New research opportunities, including the use of web analytics to document patterns of web-searching on specific vaccine safety issues, to monitor the effects of digital communication strategies in real time, to measure and track vaccine confidence and to provide resources in response to vaccine safety events
  - Preliminary results from the VSN web analytics project and plans for digital communication models for vaccine safety were presented

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

- 6–8 March 2018, Chamonix, France. Summary and conclusions available at: http://apps.who.int/iris/bitstream/handle/10665/272832/WER9324.pdf?ua=1&ua=1
- Rotavirus vaccine global research update: a collaboration of various partners reported on recommendations regarding methods for determining the age distribution of rotavirus disease, the efficacy of rotavirus vaccine and its waning efficacy and the benefit-risk of use of the vaccines. The recommendations are detailed in the summary report.
- HPV vaccine global research update:
  - Increasing the introduction and uptake of HPV vaccination is a priority for WHO. A template for improving vaccine acceptance and effectiveness of HPV vaccination programs was presented.

IVIR-AC proposed criteria for select countries for pilot implementation and consideration of several issues in planning and community acceptance, including barriers to first vaccination and completion of series, limitations of vaccinating adolescents who have left school and opposition to vaccination.
    - Evidence from the consortium on evaluating use of HPV vaccine as a single dose and priorities for future research on this were discussed.
- WHO guide on standardisation of economic evaluations of immunisation: an update on the 2008 WHO Guide on standardisation of economic evaluations of immunisation programs was presented for comment.
- Malaria RTS,S policy decision-making framework and impact modelling: IVIR-AC provided feedback on the appropriate metric(s) for estimating a threshold for RTS,S vaccine coverage in modelling to predict impact and cost-effectiveness. The Committee proposed conducting analyses of impact of 3 doses versus no vaccination, 4 doses versus no vaccination and the incremental impact of the fourth dose.
- Measles: optimal intervals between supplementary immunisation activities (SIAs) and mortality model
    - The Measles and Rubella SAGE working group, with support from IVIR-AC, is reviewing guidance on SIA intervals for the October 2018 SAGE meeting.
    - An updated measles mortality model was presented. IVIR-AC proposed a direct comparison of the new mortality model with simulations of standardised incidence ratios.
- Global vaccine demand and acceptance: research update: The International Collaboration for Vaccine Acceptance Initiative (ICVA) is an open, international, multidisciplinary network of social and behavioural researchers linked to immunisation programs to address the demand for and acceptance of vaccines and vaccination. The ICVA presented its objectives and plans to the IVIR-AC for feedback. IVIR-AC will establish a working group to serve as a link between IVIR-AC and ICVA.
- Development of full public health value propositions for the new vaccines framework:
    - A scoping review of investment cases of vaccines was presented, followed by a presentation of work in progress on the economic accounting framework applied to vaccines and immunisation programs in collaboration with the WHO Health Governance Financing department.
    - A prototype decision support interface for country decision-makers to evaluate vaccine schedules was presented for feedback.
- Total system effectiveness: The Bill & Melinda Gates Foundation–funded pilot project on TSE was presented to IVIR-AC for feedback. The aim of the pilot project is to test “multi-criteria decision analysis” as a support for countries in choosing vaccine products and/or prioritising pathogens.
- Standardisation of vaccine delivery and operational costs: IVIR-AC has reviewed the micro-costing and planning tools supported by WHO to assist countries in estimating the cost of introducing and delivering new vaccines that often target populations who are not among the standard age groups of the Expanded Programme on Immunization. A plan to standardise delivery costs has been prepared.
- Another meeting of IVIR-AC was held in September 2018; a summary report is not yet available.

5.4 Meeting of the Technical Advisory Group on Immunization and Vaccine-preventable Diseases in the Western Pacific Region

- 19–22 June 2018, Manila, Philippines. http://www.wpro.who.int/immunization/meetings/2018/tag27/en/
- A summary report is not yet available

5.5 Global Immunization News and other items

- Available here: http://www.who.int/immunization/gin/en/
- WHO has released recommended standards for conducting surveillance for vaccine preventable diseases that countries should consider in establishing and improving existing VPD surveillance. Available at: http://www.who.int/immunization/monitoring_surveillance/burden/vpd/standards/en/

6 Other items

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

- New/updated registrations for vaccines:
  - Fluarix Tetra: updated 29 May 2018, eligibility extended to adults and children from 6 months of age
  - Nimenrix: updated 5 September 2018, eligibility extended to infants and adults >55 years of age
  - Bexsero: updated 12 September 2018, dose schedule for infants aged 2–5 months updated (both 3+1 and 2+1 schedules now approved)
- New Australian Public Assessment Reports (AusPARs) available for the following vaccines:
  - Fluzone High-Dose – 9 July 2018
  - Influvac Tetra – 23 August 2018
  - Trumenba – 27 August 2018

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7 Upcoming meetings and agendas

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

- 24–25 October 2018
- 27–28 February 2019

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

- 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 February 2019
- 5–6 June 2019

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

- 23–25 October 2018