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

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

Period of review: 16/12/2019 – 6/05/2020

Contents

1 Advisory Committee on Immunization Practices (ACIP), USA

1.1 ACIP meeting: 26-27 February 2020

Agenda and presentation slides of this meeting:

- https://www.cdc.gov/vaccines/acip/meetings/slides-2020-02.html
- Full minutes of the February 2020 meeting are pending. Therefore, this summary has been developed from the presentation slides and video recordings.

Ebola vaccines

- November 2019, rVSVΔG-ZEBOV-GP vaccine (ERVEBO®, Merck) granted EU-wide conditional marketing authorisation. Vaccine indicated for immunisation of individuals 18 years of age or older to protect against Ebola virus disease caused by Ebola virus (species *Zaire ebolavirus*)
- December 19, 2019, US FDA approved rVSVΔG-ZEBOV-GP vaccine (ERVEBO®, Merck) for individuals 18 years or older for prevention of Ebola Virus Disease (EVD)
- February 12, 2020, World Health Organization's Emergency Committee unanimously agreed that the ongoing EVD outbreak in eastern Democratic Republic of Congo still constitutes a "Public Health Emergency of International Concern" (PHEIC)
- Three U.S. populations at highest risk for potential occupational exposure to Ebola virus for whom potential policy options are most urgent (broad definition):
  - Individuals responding to an outbreak of EVD due to Ebola virus
  - Individuals who work as laboratorians and support staff biosafety-level 4 (BSL-4) facilities that handle replication-competent Ebola virus
  - Healthcare personnel at federally designated Ebola Treatment Centers involved in the care and transport of confirmed EVD patients
- Additional U.S. populations with potential risk for occupational exposure include:
  - Healthcare personnel at state/jurisdictionally designated Ebola Treatment Centers
  - Healthcare personnel at Ebola Assessment Hospitals
  - Healthcare personnel at Frontline facilities

Healthcare personnel in this context has been specifically defined:
https://www.cdc.gov/infectioncontrol/guidelines/health-carepersonnel/index.html

<u>rVSVΔG-ZEBOV-GP vaccine</u>

- Live-attenuated recombinant vesicular stomatitis virus vaccine
- Initially developed by Public Health Agency Canada and New Link Genetics; Merck holds intellectual rights
- Protects only against Ebola virus (species *Zaire ebolavirus*)
- Safety:
  - Mild to moderate transient reactogenicity commonly reported within 24-48 hours of vaccination; resolved within 7 days: injection site pain, swelling, erythema, fever/subjective fever, muscle aches, malaise, headache
  - Arthralgia and arthritis reported in some vaccines
  - Vaccine-related SAEs are rare
- Immunogenicity:
  - No immune correlate for protection
  - Protective effect conferred by immunisation likely a combination of innate and adaptive immune response activation
  - As measured by ELISA, EBOV-GP-specific IgG antibodies begin to rise 14 days and can persist through 24 months post-vaccination
- rVSVΔG-ZEBOV-GP vaccine use in outbreak settings: Ca Suffit
  - Phase 3, cluster-randomised, open-label ring vaccination
  - Took place in Guinea, at a time when the EVD outbreak was waning
    - Ring vaccination design chosen in part to generate robust data on vaccine efficacy in the setting of a waning outbreak
  - Defined a cluster around a confirmed case of EVD
  - Primary outcome: Incidence of EVD with onset 10 days or more from randomization
- Ca Suffit: "Interim"
  - Clusters randomised to immediate vaccination or delayed vaccination (21 days after randomisation
  - Vaccine efficacy: 100% (95% CI: 74.7–100, p=0.0036)

- Ca Suffit: "Final"
  - July 2015, randomisation discontinued at the recommendation of the data and safety monitoring board, all subsequent clusters offered immediate vaccination
  - Reported vaccine efficacy for randomised and non-randomised clusters
  - Vaccine efficacy: 100% (95% CI: 68.9–100, p=0.0045)
- rVSVΔG-ZEBOV-GP vaccine use in outbreak settings: DRC
  - Ring vaccination started 1 week after the outbreak declared
  - Ring strategy has evolved over time, >200,000 vaccinated

Influenza vaccines

- Interim estimates of 2019–20 seasonal influenza vaccine effectiveness against medically attended influenza from the US Flu VE Network Summary**:**
  - Interim results for indicate vaccination reduced medically attended illness due to any influenza virus type by 45% (CI: 36 to 53) based on enrollment through January 25, 2020
    - 55% (CI: 42 to 65) VE against any influenza in children 6 months – 17 years
  - Vaccination provided 50% (CI: 39 to 59) protection against predominant influenza B/Victoria virus (clade V1A.3)
  - Overall effectiveness against H1N1pdm09 = 37% (CI: 19 to 52)
    - H1N1pdm09 circulation has increased since January 2020 – increased enrollment will improve precision of age-specific estimates

<u>Safety of adjuvanted versus high-dose inactivated influenza vaccines in older adults: preliminary safety results: ClinicalTrials.gov Identifier NCT03183908</u>

- Study design and participants:
  - Design: Randomised, blinded clinical trial of aIIV3 versus HD-IIV3 during the 2017–2018 and 2018–2019 influenza seasons
  - Setting: Duke University (2017–2019), Boston University (2017–2019), Cincinnati Children's Hospital Medical Center (2018–2019)
  - Participants: Community-dwelling volunteers aged ≥65 years and not immunosuppressed, cognitively intact, no co-vaccination, no influenza vaccine contraindications (goal to enroll ≥20% aged ≥80 years)
  - Intervention: Randomised 1:1 to 0.5 ml IM dose of aIIV3 or HD-IIV3 [Stratified by age group (65–79) and (≥80) years]
- Health-Related Quality of Life (HRQOL) Assessments
  - EuroQOL-5 dimensions-5 levels: EQ-5D-5L
  - EuroQol-Visual Analogue Scale: EQ-VAS
- Results:
  - Primary outcome (1) results: injection-site pain
    - Moderate-severe pain difference for aIIV3minus HD-IIV3= -2.7% 95% CI (–5.8% to 0.36%)
    - Upper limit of the 95% CI of the difference for aIIV3 minus HD-IIV3 was 0.36% and the non-inferiority margin was 5%
    - The proportion of participants with moderate-severe injection-site pain after aIIV3 was non-inferior (not higher) than the proportion after HD-IIV3
  - Primary outcome (2) results: SAEs and AECI
    - No SAE found to be related to vaccination
    - No significant difference in proportion of SAEs between vaccine groups
  - Secondary outcome (1) results: proportions of moderate-severe local reactions
    - No local reactions led to a medical visit
    - Non-inferiority criteria for 'tenderness' was not met for aIIV3
  - Secondary outcome (2) results: EQ-5D-5L and EQ-VAS between group analysis change in score From Day 1 Pre-vaccination to Day 3 Post-vaccination
    - EQ-5D-5L: No significance between group difference: aIIV3 -0.05 vs. HD-IIV3 -0.05, p=0.74
    - EQ-VAS: No significance between group difference: aIIV3 -2.22 vs. HD-IIV3 -2.45, p=0.79
- Summary:
  - The proportion of participants with moderate-severe injection-site pain was not higher after aIIV3 than HD-IIV3
  - There were no vaccine-related SAE
  - The short-term post-vaccination HRQOL was not affected by either vaccine.
  - The safety findings in our study were consistent with prelicensure data for aIIV3 and HD-IIV3.
  - From the standpoint of safety, either vaccine is an acceptable option for the prevention of influenza in older adults.

Rabies vaccine

Vaccines licensed in U.S.

- Imovax®: IM Human diploid cell vaccine (HDCV) Sanofi Pasteur
- RabAvert®: IM Purified chick embryo cell vaccine (PCECV) GlaxoSmithKline (In future: Bavarian Nordic)

Vaccine safety:

- Vaccine Adverse Event Reporting System (VAERS) safety data for HDCV; Imovax (Moro PL, et al PLoSNeglTrop Dis. 2016 Jul13;10(7):e0004846)
  - VAERS received 1,666 reports following HDCV (1/1/1990-12/31/2019)
    - 1,571 (94.3%) were non-serious
  - Systemic reactions were observed
    - Headache (18.8%), pyrexia (18.1%) and nausea (17.1%)
  - Angioedema rarely reported
  - Findings are consistent with pre-licensure and post-marketing studies
- VAERS safety data for PCECV; RabAvert (Moro PL et al. Travel Med Infect Dis. 2019 May-Jun;29:80-81)
  - VAERS received 739 reports following PCEC
    - 686 (92.8%) were non-serious
  - Most common systemic reactions observed were headache (19.5%), pyrexia (18.5%), nausea (18.1%)
  - Findings consistent with findings of pre-licensure studies and a previous evaluation of PCECV vaccine in VAERS during 1997-2005
- Safety data from 25 trials published since 2008 ACIP recommendations
  - Publications involved comparison of
    - New vaccine and one of the 2 US vaccines
    - Intradermal administration and intramuscular
    - Co-administration with other vaccines (e.g., Japanese Encephalitis vaccine)
    - Varying schedules
    - Use in pregnant persons and children
  - Safety findings
    - Similar to that of VAERS data and package insert - unchanged and favorable safety profile

Rabies PrEP

- Recommendations for PrEP vary depending on level of risk to unrecognized exposures: continuous, highest risk, frequent, infrequent, rare
- Proposed PrEP clinical guidance changes:
  - Laboratorians in the highest risk category
  - Disease biogeography determines whether animal care professionals, others who handle terrestrial reservoir species are listed in “Frequent” or Infrequent” Risk categories
  - Moved spelunkers / cavers from “Frequent” to “Infrequent” risk category
  - Added “short-term / volunteer hands-on animal care workers where increased risk is expected for short time periods”
  - Rephrased guidance for travellers which will align with CDC Traveler’s health destination pages and 2022 Yellow Book
- Vaccination route:
  - WHO recommends ID because dose and cost-sparing
  - US rabies vaccines not licensed for ID use
- Current ACIP PrEP schedule:
  - IM [0, 7, 21/28 days] for Continuous, Frequent, and Infrequent Risk Categories
  - No PrEP for Rare Risk Category
- Frequency of antibody checking:
  - Every 6 months for continuous, every 2 years for frequent, no titer checks for Infrequent
  - Booster is recommended if titer is below minimum acceptable antibody level (complete virus neutralization at a 1:5 serum dilution by the rapid fluorescent focus inhibition test.
  - Rabies antibody titer is used as an indicator of adequate immune response to vaccine
  - However, an acceptable titer is not an indication of protection; it is used as a surrogate
    - Person with a low titer may still be immune
    - Person may mount anamnestic response if exposed
  - Titer higher than the minimum acceptable antibody level needed for persons involved in some activities; example, handling rabies virus

    - That is because these persons (e.g., laboratorians) have a risk for unrecognized exposure to high titer viruses
    - Out of caution, higher titers are the target
- WG is evaluating
    - where vaccine series could be different depending on risk category, data for 2 dose IM series, booster for those at higher risk for rabies, whether frequency of titre check should be different depending on risk exposure category

CDC Rabies PreEP Systematic Review

- Review of immunologic response to rabies PreEP
    - Primary response, duration of immunity and booster response
- Started 2017, updated through 2019
- Review question
    - Population: persons at risk of rabies exposure
    - Interventions: 1) persons receiving alternate rabies vaccination schedules using modern cell culture vaccines; 2) persons receiving rabies vaccination by alternate routes using modern cell culture vaccines (i.e. ID)
    - Comparison: persons receiving ACIP recommended rabies pre-exposure prophylaxis regimen by the IM route using modern cell culture vaccines
    - Outcomes: Rabies neutralising antibodies reported as IU/mL 1-3 weeks after primary vaccination, 1-year post vaccination, and after booster

Results of systematic review:

- Primary seroconversion of ACIP recommended schedule:
    - Day 0,7,21/28 schedule well established with broad evidence base
      - Recommended schedule for >40 years
      - High (>97%) seroconversion (>0.5IU/mL) regardless of vaccine or administration route
- Primary titre response of ACIP recommended schedule:
    - Heterogeneity between studies higher for GMT
    - IM produces significantly higher GMT (not clinically significant)
    - Primary IM GMT >13.99 IU/mL (lowest 95% CI)
    - Primary ID GMT >4.50 IU/mL (lowest 95% CI)
- Rabies PrEP 2 dose, 1week schedule (day 0 and 7), intra-muscular:
    - Comparable primary GMT titer response to 3-dose schedule
    - Limited number of studies, but similar heterogeneity as observed in 3-dose ACIP meta-analysis
    - High seroconversion rate (SCR) (98%) achieved 7–14 days after second dose (day 7)
    - SCR consistent across studies (little heterogeneity)
    - 30–60 days post vaccination:
        - No significant difference in SCR between 3-dose and 2-dose schedules
        - Limited number of 2-dose studies with small cohort sizes
- 1-year immunogenicity and response to booster
    - Lower GMT in 2 dose (day 0,7) recipients
        - not significantly different from 3 dose recipients
    - Anamnestic response observed post booster in both 2 and 3 dose cohorts
        - GMT in 3 dose recipients significantly higher
    - Lower SCR proportion (59%) of 2 dose (day 0,7) recipients with adequate titer at 1 year
    - Anamnestic response post booster
        - All recipients achieve adequate antibody level, no significant difference IN SCR between groups

Summary of systematic review:

- 2-dose (day 0,7) schedule study summary
    - Soentjens et al (n=183) ID
        - Pre-booster (1–3 years post vaccination): 2-dose ID GMT (3.4 IU/mL) was significantly higher compared to 3-dose ID (2.0 IU/mL)
        - 100% of both groups had an adequate titer (>0.5 IU/mL) after booster
    - Endy et al (n=22) IM/ID
        - Compared to 3-dose IM series, no significant difference observed in the GMT at day 365 for 2-dose IM or 2-dose ID
        - 40–50% of 2-dose recipients had a titer of >0.5 IU/mL at day 365
        - 100% of recipients had an adequate titer after receiving booster at 1 year
- Duration and kinetics of antibody response
    - Most studies evaluated 3 dose (day 0,7,21/28) schedule (IM and ID)
    - Rapid decay during first 6 months post vaccination

- Slows to plateau between 6 months to 1 year
- Decay more rapid when administered by ID route
    - ID >1.5 times more likely to not have an adequate titer at 1-2 years post vaccination

- Post booster response typically greater than primary response
    - Decay slower after booster
    - Studies: Banga et al. Vaccine. 2014; 32:979, Brown et al. Vaccine. 2008; 26:3909, Mansfield et al. Vaccine. 2016; 34:5959, Strady et al. JID. 1998; 177:1290

Dengue vaccine

Dengue vaccine knowledge and attitudes in Puerto Rico survey:

- Summary of results presented

WHO Global Recommendations on Dengue Vaccination

- Dengue is a global public health priority: in 2019, WHO had listed dengue among the 10 biggest public health threats for the year.
- Current vaccine CYD-TDV has shortcomings but offers significant clinical benefit in seropositive target population
- Diagnostic tests for prior dengue infection key considerations: Rodríguez-Barraquer et al, Lancet ID 2019
    - Safety: high specificity and low cross-reactivity to minimise false positives
        - Of particular importance in low-moderate transmission settings and setting with other circulating flaviviruses
    - Public health benefit: high sensitivity to minimise number of individuals omitted from vaccination
        - Consideration to increase effectiveness of programmes
- Estimation of the proportion of vaccine-induced cases of hospitalised dengue –based on CYD15 data: Flasche et al, Wellcome Open Research 2019
    - Assumptions: seroprevalence in the population 85% (from RCT); relative risks in the Philippines school vaccination programme are similar to those observed in the Phase 3 trial CYD15, and irrespective if either 1, 2 or 3 doses of vaccine had been administered.
    - Estimation: Over the 5 years following vaccination in the Philippines, for each precipitated dengue hospitalisation in dengue-naïve vaccinees, CYD-TDV will likely have averted about 18 dengue hospitalisations among seropositive vaccines and about 10 severe dengue cases among seropositive vaccines.
- Concluding remarks:
    - Any use of the vaccine must be accompanied with a risk minimisation strategy: pre-vaccination screening is the method of choice to mininise risk
    - Rapid diagnostic test characteristics must be assessed in context of the epidemiological setting
    - Significant investments are needed in relation programmatic implementation, monitoring and communication – failure to do so can has dramatic consequences for public health confidence.

Polio

- Background:
    - 7+ years have passed without detection of wild poliovirus type 3 (WPV3)
    - WPV3 eradicated on 17 October 2019
    - 3+ years have passed with detection of any wild poliovirus in Africa
    - IPV supplies are now sufficient for routine immunization, and catch-up of missed cohorts is in progress
    - EURO, PAHO, SEARO remain polio-free (incl. type 2 circulating vaccine-derived poliovirus [cVDPV2])
    - Wild type 1 cases increased from 33 cases in 2018 to 173 cases in 2019
    - The Taliban ban on house-to-house vaccination in Afghanistan is severely affecting the ability of the program to carry out campaigns
    - In Pakistan, a new government is starting to provide national leadership –but >6 months passed in 2nd half of 2019 without large-scale vaccination campaigns and wild polio cases surged
    - AFRO, EMRO and WPRO battle outbreaks of cVDPV2
- Preventing cVDPV2:
    - OPV polioviruses in areas with low polio vaccine coverage can rarely mutate during prolonged circulation and become vaccine-derived polioviruses (VDPVs) able to spread and cause paralysis (circulating VDPVs, cVDPV)
    - 700 paralytic cases due to type 2 cVPDV polioviruses confirmed during 2001–2015

    - Prompted strategic decision to withdraw OPV2 use in all routine and supplementary immunization activities
    - IPV complements trivalent oral polio vaccine (tOPV) by increasing immunity to all three types of polioviruses, prepares for withdrawal of all OPV
    - By switching to IPV, it will:
        - provide protection against paralysis from type 2 polioviruses (in those reached and who seroconvert)
        - in previous OPV2 recipients, IPV will boost intestinal immunity to infections with type 2 polioviruses
        - strategic use of IPV in response to type 2 poliovirus outbreaks alongside monovalent OPV 2 (mOPV2) will increase population protection from paralysis
- Challenge:
    - The program is battling many outbreaks of cVDPV2 in Sub-Saharan Africa and at risk of re-establishing poliovirus type 2 endemicity in Africa
    - Detection of cVDPV2 outbreaks in Asia (China, Pakistan and the Philippines) may herald a global emerging problem
    - Limited supply in global mOPV2 stockpile requires balancing use with availability of new shipments
- Way forward:
    - Prevent cVDPV2 spread into new geographies
        - rapid deployment of mOPV2
        - revised strategy guidance for control of cVDPV2 finalized in January 2020
        - increase scope and quality of mOPV2 SIAs with surge in technical support
    - Accelerate development & regulatory review & use of novel OPV2 - Emergency Use Listing (EUL)
- novel OPV2 (nOPV2)
    - nOPV2 is a genetic modification of the existing OPV type 2
    - The modifications made are designed to improve genetic stability of OPV
    - This will in turn decrease the risk of seeding new cVDPVs and the risk of VAPP when deployed for cVDPV2 outbreak response
    - Owner: WHO Essential Medicine Department (EMP, PQ)
        - goal: make “experimental” health products available for emergency response
        - Products listed under EUL so far: 0
        - Eligibility criteria nOPV2: poliovirus spread is a Public Health Emergency of International Concern (PHEIC)
        - Fastest way to obtain regulatory review and approval
- Ramp-up of nOPV2 clinical development and production to align with EUL approval
    - Feb 2020 EUL submission:
        - Immunogenicity and safety of all ages
        - shredding adults and 1–5 year olds
        - genetic stability: adults
    - March 2020 EUL Submission
        - Genetic stability: 1-5year olds
    - July 2020 EUL submission
        - Updated stability data

1.2 Newly published or updated recommendations

Use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccines: recommendations of the Advisory Committee on Immunization Practices

- Published in MMWR 24 January 2020 – https://www.cdc.gov/mmwr/volumes/69/wr/mm6903a5.htm
- This report updates the 2005 recommendations from the CDC Advisory Committee on Immunization Practices (ACIP) regarding use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) and tetanus and diphtheria toxoids (Td) vaccine in the United States
- In 2013, a routine second dose of Tdap was not recommended. In 2019, it was again concluded that due to the higher cost of Tdap relative to Td and uncertainty about the impact that receipt of multiple Tdap doses would have on pertussis control and transmission, there continues to be insufficient evidence to preferentially recommend that Tdap replace Td. However, the safety profile and evidence of widespread use of Tdap in place of Td, either Tdap or Td was recommended in situations where previously only Td vaccine was recommended. **It is recommended that either Td or Tdap be used for the 10-year Td**

booster, tetanus prophylaxis for wound management, and for additional required doses in the catch-up immunisation schedule if a person has received at least 1 Tdap dose.

- Rationale:
  - Allowing either Tdap or Td to be used in situations where Td only was previously recommended increases provider point-of- care flexibility.
  - Repeat doses of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine at 5- and 10-year intervals are safe and immunogenic.

Use of Anthrax Vaccine in the United States: Recommendations of the Advisory Committee on Immunization Practices

- Published in MMWR 13 December 2019 – https://www.cdc.gov/mmwr/volumes/68/rr/pdfs/rr6804a1-H.pdf
- This reports updates the 2009 recommendations from the CDC Advisory Committee on Immunization Practices (ACIP) regarding use of anthrax vaccine in the United States
- Recommendations for Prevention of Anthrax Among Persons with Potential Risk for Exposure (PrEP) include:
  - A booster dose of Anthrax vaccine adsorbed (AVA) for PrEP is recommended to be given every 3 years instead of annually to persons who are not at high risk **and for those who might be at high risk in the future (e.g., persons involved in emergency response activities),** for exposure to *B. anthracis* who have previously completed the 3-dose primary (0, 1, and 6 months) and the initial 2-dose boosters (12 and 18 months) AVA series and want to maintain protection.
  - After completing the initial 3-dose priming and booster series, **persons who have not received a booster dose in the last 12 months and need to enter an area where *B. anthracis* is suspected to be present in the environment or be in use should be given an IM booster dose and then either wait 2 weeks to enter the high-risk area or, if required to enter immediately, take PEP-Abx for 2 weeks.** While in a high-risk area, a booster dose should be given within 1 year of the last booster dose.
    - Persons who are exposed to aerosolized *B. anthracis* spores but have not completed the initial priming and booster series for AVA should receive additional AVA doses and antimicrobial postexposure prophylaxis (PEP-Abx). The number of vaccine doses and duration of PEP-Abx will vary in a manner commensurate with the number of previously received doses.

- Recommendations for Prevention of Anthrax Among Persons with Suspected or Known Exposure (PEP) were also made.

1.3 Newly published or updated recommendations – not yet published

ACIP approved the following recommendations by majority vote at its February 2020 meeting. These recommendations have been adopted by the CDC Director and will become official once published in MMWR. Information available on https://www.cdc.gov/vaccines/acip/recommendations.html

- Pre-exposure vaccination with rVSVΔG-ZEBOV-GP vaccine is recommended for adults 18 years of age or older in the United States population who are at potential risk of exposure to Ebola vaccine (species *Zaire ebolavirus*) because they:
  - Are responding to an outbreak of Ebola virus disease; or
  - Work as healthcare personnel at a federally-designated Ebola Treatment Center in the United States; or
  - Work as laboratorians or other staff at biosafety-level 4 facilities in the United States.

2 Immunisation Advisory Centre (IMAC), New Zealand

2.1 PTAC Considerations

Meeting on 14–15 November 2019 –https://www.pharmac.govt.nz/assets/ptac-record-2019-11.pdf
There were no vaccine-specific considerations at this meeting

2.2 Immunisation Subcommittee Meeting: 15 October 2019

- Minutes of the meeting - https://www.pharmac.govt.nz/assets/ptac-immunisation-subcommittee-record-2019-10.pdf

Therapeutic group review

- Human papillomavirus vaccine (Gardasil 9):
  - Noted that supply issues during 2017 and 2018 had an impact on the distribution patterns of the HPV vaccine - supply to school-based programmes was prioritised over that period. No further supply disruptions occurred in 2019.
  - Noted that from 1 August 2019 funding was approved for widened access to HPV vaccine with bevacizumab for recurrent respiratory papillomatosis. This is a small group and is not expected to have a significant impact on HPV vaccine usage.
- Adult diphtheria and tetanus vaccine:
  - Noted that ADT Booster will be delisted from 1 October 2020 and the eligibility criteria will be added to those for Boostrix.
- Hepatitis B recombinant vaccine:
  - HBvaxPRO will be delisted from 1 October 2020 and Engerix B will have sole supply status.
- Measles, mumps and rubella vaccine:
  - Noted that there was a spike in MMR vaccine usage in March 2019 as a result of the Canterbury measles outbreak. While the Canterbury response used approximately 30,000 doses in March, there was also a large increase in vaccine usage across the country. Noted that an additional supply of 40,000 doses of MMRII brand vaccine was sourced but not used for the Canterbury outbreak - it was instead used between June and September 2019 for the Auckland measles outbreak.
- Meningococcal conjugate vaccines:
  - Noted that while usage of MenACWY vaccine is typically between 100 and 150 doses per month, there was a spike in distribution in December 2018 for the Northland MenW outbreak response.
- Pneumococcal conjugate vaccine:
  - Noted that the Immunisation Advisory Centre pneumococcal antigen review considered that if New Zealand moved from a 3+1 to a 2+1 pneumococcal dose schedule, infant born before 35 weeks gestation may be at increased risk from pneumococcal disease. The Subcommittee considered that it could be assumed that there would be no maternal antibody protection for infants born before 28 weeks, but it is not clear if there is a difference in maternal antibody protection for infants born between 28 and 35 weeks. The Subcommittee considered that there was only a small additional health need which there was no need to address, given their indirect protection.
- Influenza vaccine:
  - The Subcommittee noted that funded influenza vaccine distribution was slowly increasing year on year since 2017, but private influenza vaccine distribution had increased notably year on year since 2017. Total influenza vaccine distribution for 2019 had already exceeded the 2018 total by May. The Subcommittee noted the funded influenza vaccine coverage in 2019 to date was low for children aged 0–4 years and pregnant women (4% and 25%, respectively).

Influenza vaccine application

Application:

- Funding application from the Pharmaceutical Society for pharmacist vaccinators to be able to administer influenza vaccine to patients with serious mental health conditions or addiction.

Recommendation:

- Recommended that application for pharmacist influenza vaccination of people with serious mental health conditions or addiction be declined.

Discussion:

- Application did not extensively define "serious mental health conditions" but used a proxy of people who are prescribed clozapine.
- Subcommittee noted that people with serious mental health conditions or addiction are not currently eligible for funded influenza vaccination in the community, although patients in long-stay inpatient mental health care units are eligible due to increased risk of infection.

- The Subcommittee noted patients are very engaged with community pharmacy, but less likely to be engaged with their GP as they would typically be managed by secondary services.
- The Subcommittee considered that there was insufficient evidence demonstrating people with schizophrenia or addiction are at increased risk of influenza and that there was insufficient evidence that this group would be more likely to be vaccinated in a pharmacy than general practice.

Pneumococcal polysaccharide vaccine for CLL/SLL patients' application

Application:

- The Subcommittee considered a clinician funding application to widen access to PPV23 vaccine for patients with untreated chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL).

Recommendation:

- The Subcommittee recommended that the application to widen access to PPV23 vaccine for patients with untreated CLL/SLL be declined.

Discussion:

- The Subcommittee noted that PCV13 and PPV23 are currently listed in the Pharmaceutical Schedule for children up to the age of 59 months as well as for high-risk individuals. PCV13 is funded for pre- or post-haematopoietic stem cell transplant (HSCT) or chemotherapy, but PPV23 is only currently funded post-HSCT or chemotherapy. The Subcommittee considered that current funding criteria for PCV13 would mean that all CLL/SLL patients would be eligible for PCV13.
- The Subcommittee considered a randomised controlled trial by the Swedish CLL Group (Svensson et al. Vaccine 2018;36:3701-7). The trial demonstrated a better immune response to PCV13 than PPV23 in 10/12 serotypes one month after vaccination and in 5/12 serotypes six months after vaccination. The authors proposed that PCV13 should be administered as early as possible during the course of the disease, with PPV23 eight weeks later.
- The Subcommittee considered a review of infectious complications in patients with CLL (Morrison VA. Clin Lymphoma Myeloma 2009;9:365-70). The review noted that CLL/SLL patients have an elevated risk of pneumococcal disease. The review noted that conjugated vaccines would be more likely to give better responses than polysaccharide vaccines.
- The Subcommittee considered that the evidence for benefit from vaccination with PCV13 followed by PPV23 was of poor quality and low strength, consisting of small observational studies and international guideline recommendations.
- The Subcommittee considered that the above Svensson et al. 2018 trial demonstrated a good immune response to PCV13, but did not provide evidence of additional benefit for subsequent vaccination with PPV23.
- The Subcommittee considered that there is no evidence for a benefit from vaccination with PPV23 in addition to PCV13 in untreated CLL/SLL.

Additional 15-month pertussis dose for childhood schedule

Application:

- The Subcommittee considered a Ministry of Health review of the evidence regarding the addition of a pertussis-containing vaccine in the second year of life to the Pharmaceutical Schedule.

Recommendation:

- The Subcommittee recommended that the Ministry of Health should prioritise improving maternal pertussis vaccination coverage over the possible introduction of an additional pertussis-containing dose in the second year of life.

Discussion:

- The Subcommittee considered the EPIC study reporting pertussis vaccine effectiveness (VE) for New Zealand. The Subcommittee noted that VE against pertussis hospitalisation was 93% (95% CI 87-96) following three doses in infants aged 5-11 months who receive three doses compared to zero doses. The protection was sustained through the children's fourth birthdays (VE $\geq$ 91%). VE against non-hospitalised pertussis was also sustained after three doses, from 86% (95% CI: 80–90) among 5–11 month olds to 84% (95% CI: 80–88) among 3-year olds (Radke et al. Vaccine 2017;35:177-83).
- The Subcommittee noted that a WHO position paper reported that a number of countries have experienced a resurgence in pertussis while using an aP vaccine (Australia, Portugal, the USA and the UK), although New Zealand has not experienced the same resurgence.
- The Subcommittee considered that while notifications show a regular pattern of pertussis epidemics every 4 to 5 years, hospitalisations of children under 1 year of age are relatively consistent. The Subcommittee considered that there was no evidence of waning of pertussis vaccine effectiveness by 4 years of age in New Zealand.
- The Subcommittee considered a systematic review of 40 studies examining possible blunting of the infant's immune response to vaccination caused by maternal vaccination during pregnancy. The

Subcommittee noted that although there was some documentation of blunting of immune responses to some antigens in neonates born to women vaccinated during pregnancy, there was no apparent effect on vaccine efficacy (Switzer et al. Infect Dis Ther. 2019;8:499-541), and that although maternal blunting of the neonate antibodies may occur, it has not been shown to be of clinical significance.

- The Subcommittee noted that coverage for maternal pertussis vaccination in pregnancy is still low at approximately 25%, compared with the UK which has coverage of approximately 70%.
- The Subcommittee considered that there was a clear to priority to improve maternal pertussis coverage to protect infants under 3 months of age, rather than providing an additional pertussis booster dose in the second year of life.

2.3 Other updates

Measles in New Zealand

- https://www.immune.org.nz/hot-topic/measles-overseas-and-new-zealand
- Last updated 24 February 2020 (4.30PM)
- Measles cases have tapered off significantly (9 cases in January and 1 case in February as at 21 February 2020)
- Outbreak national priorities for MMR vaccination are removed
- Ordering MMR vaccine has reverted to the normal ordering process from ProPharma
- In Auckland metropolitan DHBs only: MMR0 (MMR vaccination before the scheduled 15 month dose) ceases but MMR1 remains at 12 months of age

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

3.1 JCVI Meeting: 4-5 February 2020

- Agenda and draft minutes – https://app.box.com/s/iddfb4ppwkmtjusir2tc/file/636396626894

This summary was based on the draft minutes only

I. **Immunisation Schedule**

- 2018, GSK decided to cease the manufacture and supply of Menitorix® from late 2020. Need to consider changes to the UK program to mitigate the loss of Menitorix®.
- PHE outlined four potential strategies (these options only covered currently available vaccines).
    - Option A - Replace Hib/MenC with single Hib and single MenC
    - Option B - Replace Hib with DTaP/IPV/Hib/HepB and give separate MenC
    - Option C - Keep single Hib and move MenC dose to infancy
    - Option D - Combination of B and C changes
- The Committee noted that GPs might be able to combine single antigen vaccines into one injection before administration.

Coverage-related issues due to potential schedule changes:

- Data analysed to inform considerations if the age of primary vaccination impacted coverage. Two analyses, the first looking at 3-dose specific coverage of Bexsero (MenB) in 2019 and the second on different ages of vaccination administration against coverage from 2017 to 2019. Results indicate duration between administering vaccine and measuring coverage had no significant impact on uptake and drop in coverage as age of administration increased.
- Impact on bringing forward the 3 years 4 months vaccines to 18 months – data reviewed from measles outbreaks between 2011 and 2018, in response MMR2 was introduced earlier than the recommended interval; and 2012 data showed there had been a significant improvement in coverage (3.3%) of 2 doses of MMR by age 5.
- Analysis on the impact of an additional 18 months dose visit on the coverage of all vaccines given in early life concluded the early MMR schedule had no significant impact on the rest of the schedule.
- concurrency of doses and acceptability of multiple vaccines – 2016–17 London data on the proportion of infants receiving 4 concurrent doses (at the 8-week visit) among those who received all 4 doses of vaccine, and how doses were staggered among those not receiving four concurrent doses were reviewed.

Analysis indicated that 96.7% received all 4 doses concurrently, 2.5% 3 doses were given concurrently and 1 dose separately.

- In summary, the earlier a vaccine was scheduled, the higher the coverage achieved (consistent across vaccines) and was not a function of the time between vaccine administration. Small delays in vaccination could, however, result in a significant drop in coverage. The offering of pre-school vaccines earlier resulted in an increase in coverage and adding a visit at 18 months would not negatively impact on coverage for vaccines delivered before or after this appointment. Most infants received up to four doses concurrently.
- Committee noted: It was considered that moving the second dose of MMR to a younger age was likely to have a positive impact on coverage and that four concurrent doses seemed acceptable. An early second dose of MMR would also provide an opportunity to offer catch up for other infant vaccines, as well as initiation of MMR for unvaccinated individuals.

Acceptability and parental attitudes: impact of possible changes to the infant schedule.

- 2019 survey: 33% indicated that they thought babies were given too many injections at one time; roughly the same numbers thought children were immunised against too many diseases at one time.
- 2018 survey: parents were asked if they would accept an added varicella vaccine (separate injection) alongside other vaccines at 12 months of age, meaning 5 injections in total. 58% of parents indicated they would be likely to have their child vaccinated, although the perceived seriousness of varicella was low in around 75% of responders. Combined varicella vaccine with MMR and 60% indicated they were likely to have their child vaccinated; however, meningitis was perceived as very serious.
- Committee noted: members questioned if there was any evidence around the acceptability of 4 or 5 injections, and if this was a significant issue. PHE noted there was no evidence of an actual limit.

Hib considerations: issues associated with maintaining *Haemophilus influenzae* type b (Hib) protection.

- Prior to routine immunisation, Hib was responsible for almost all invasive Hib infections, particularly in young children. Vaccination has led to declines across all age groups. Hib vaccination program (including catch up) in England led to substantial reduction in disease.
- Early 2000s resurgence in Hib disease, which was associated with increased carriage in 1- to 3-year olds. The routine vaccination with three infant doses allowed carriage to return.
- Booster dose at 12 months of age was introduced in 2006, and Hib disease considered to be under control in England with current 3+1 schedule. 90% of infants protected by the three-dose infant schedule; 80% of children have protective levels of antibody 4 years post the 12-month booster.
- Comparing Hib-TT and Hib-OMP vaccine responses indicated a higher response to the primary series with Hib-OMP, but lower responses post booster. Recent studies with more recent combination vaccines potentially allowed for the possibility of a 2+1 schedule.
- Studies indicated that the post-booster response increased when there was a longer time period between the primary series and the booster dose, although this was also confounded by the age at the time of the booster dose. Rapid waning of antibody levels after primary immunisation indicated that infants were protected by population level immunity and this could potentially allow the option of delaying the Hib booster from the current offer at 12 months of age, to 18 months of age, which was considered likely to maintain disease control, as long as high vaccine coverage was achieved for the booster.
- Committee noted:
    - Many countries used combination vaccines with Hib in 2+1 and 3+1 schedules and had good control of Hib disease. Hib-OMP not been widely used in national programs for sufficient time to have evidence of disease control. Hib/MenC boosted Hib-OMP primed infants very well. No data on Hib-TT in a hexavalent product boosting Hib-OMP primed infants.
    - Members questioned whether Hib vaccination only in the second year of life would be sufficient to provide herd protection for infants. No combination vaccines available, suitable for the UK infant schedule, that did not include Hib. Members expressed some caution regarding the impact of moving the booster dose to later in the second year of life, especially given the success of the current Hib schedule. It was considered that the schedule for pertussis, which was also in the combination vaccines suitable for the infant schedule, would be a more important consideration.
    - The Committee noted that there were no data on the persistence of Hib following a 2+1 schedule. Study being undertaken through National Immunisation Schedule Evaluation Consortium (NISEC) on concomitant administration of Hib-OMP hexavalent vaccine and 4CMenB, given the potential interactions between the Neisseria components (OMP and 4CMenB). Results start to be available from the end of 2020.

Meningococcal considerations: issues associated with maintaining meningococcal protection

- Could the UK move to a single dose of MenACWY in adolescence and if not what would be an appropriate priming schedule; should MenC or Men ACWY vaccine be used.

- How would a primary conjugate vaccine schedule impact the 4CMenB program? Since introduction in 1999 MenC program has changed, including a reduction in the number of doses in the infant schedule. 2016, last infant dose of MenC vaccine was removed.
- Only 1 MenC conjugate vaccine available in the UK (long-term availability questionable). Two MenACWY conjugate vaccines were available, one with a tetanus conjugate (MenACWY-TT vaccine licenced for use in infants) and one with CRM197 conjugate. Another MenACWY conjugate vaccine licensure process in Europe.
- IMD control in 2018–2019 was as good as it ever had been. Meningococcal conjugate vaccines elicited a strong response when given from 3 years of age. Both 4CMenB and the adolescent MenACWY vaccination programs had a substantial impact on MenW IMD in those under 5 years of age between 2015–16 and 2018–19.
- To consider alternate IMD schedules, mathematical models need updating.
- 2015–16 to 2018–19 data indicate largest burden of disease in those <4 years of age was seen in <1 year of age. Fewer MenW IMD cases expected in this age group, due to the accruing impact of the adolescent MenACWY program. MenC infant cases still being seen.
- Rapid decline in SBA titres after priming and booster doses of MenC conjugate vaccines. Higher SBA titres seen after 12-months dose in those primed, compared with those who were not.
- Adolescent-only program: easy to implement. Younger children and infants were being indirectly protected through the MenACWY adolescent program and were being directly protected against MenW through the 4CMenB program.
- Teenage-only program: would not provide broader direct protection in toddlers and pre-schoolers and would provide less resilience against the future introduction of virulent strains, and consideration would need to be given to the optimal timing of a MenC/MenACWY conjugate vaccine in the first year of life, particularly around waning, epidemiology, age dependent responses to vaccine, number of injections and conjugate options.
- Committee noted:
    - New work may be undertaken (modelling, a review of data from infant/toddler MenACWY studies, and immunogenicity and safety studies). Meningococcal conjugate vaccine considered more appropriate for infancy, rather than at 12 months, given the current profile of IMD cases and the potential impact of the 4CMenB booster dose at 12 months of age on MenW and MenC IMD.
    - Moving to adolescent-only meningococcal conjugate schedule would require very good coverage to ensure adequate population-level protection.
    - Availability of data on maternal meningococcal conjugate immunisation providing protection in the first few weeks of life. Study on MenA vaccination in progress.
    - Questioned if removal of all doses prior to the adolescent dose would have an impact on immunogenicity of the adolescent dose.
    - Members questioned whether the current 12-month dose offered household protection to younger infants. It was noted that very few cases were now part of household clusters, which would make assessing this very difficult.
    - Members concluded that modelling of infant doses of MenACWY should be undertaken to examine the potential benefits of infant dose(s) of MenACWY vaccine and their timing.

<u>Pertussis considerations:</u>

- Issues associated with maintaining pertussis protection and maternal vaccination.
    - 1957: whole-cell (wP) pertussis vaccine introduced. Concerns in 1970s led to fall in coverage of 30%, leading to large epidemics in 1970–80s. Accelerated schedule introduced: 8, 12, and 16 weeks. Disease rates fell.
    - 2001: acellular pertussis (aP) vaccine was introduced for the pre-school booster; 2004: aP vaccine was introduced in to the infant primary schedule; 2012: maternal program with aP vaccine was introduced
    - 2004 to 2014: infant schedule used a five-component aP vaccine (5aP); 2014 to 2017 both three component aP (3aP) and 5ap vaccines were used; 2017 only 3aP vaccines had been used in the infant schedule.
    - Maternal program introduced in response to the increase in infant cases, had had a significant impact on infant cases of pertussis, but pertussis levels in the population had remained at elevated levels since 2011.
    - 2018 saw the lowest recorded levels of pertussis in infants. 2012 there were 14 pertussis disease associated deaths. Since introduction of the maternal pertussis vaccination program in 2012, 18/20 infant deaths were born to mothers who were not vaccinated, and 2 born to mothers were vaccinated very close to delivery.

- From evidence at that time, it was clear that moving to an accelerated schedule had improved coverage (~6%).
- Protection for infants from the maternal program was unlikely to persist beyond 16 weeks, and there was clear additional protection from the third dose of pertussis in infancy.
- Vaccine effectiveness derived from 2004–2009 data found single dose VE:62%, 2 doses VE:85%; 3 doses VE: 95%.
- The impact of the change from an extended to an accelerated schedule was also seen in surveillance data, with declines in cases in older infants.
- It was considered that moving to a prolonged schedule risked an increase in infant pertussis cases, both due to the delay in protection from the third dose and due to the risk of decline in overall coverage. Prolonged schedule might however mitigate the impact of blunting from the maternal program.
- Prolonged schedule beginning at 3 months of age would leave infants of unvaccinated mothers at risk of severe pertussis/death; modelling predictions indicated increased activity observed from 2012 was likely to persist.
- Prolonged schedule offering the first two doses of DTaP/IPV/Hib/HepB one month apart was likely to have a detrimental impact on protection against Hib.
- Booster dose (introduced 2001) was prompted by concerns around early waning of protection from the accelerated schedule, considered to provide substantial additional protection compared to 3 doses; use of aP vaccines had been associated with faster waning of protection post booster, and the average age of infection was reducing, with outbreaks in primary school being seen for the first time in England in 2019.
- Additional booster dose with DTaP/IPV/Hib/HepB at 12 or 18 months of age had been considered, could result in some reduction of disease in pre-school children and mitigate the blunting effects of maternal immunisation.
- A dose offered at 18 months of age would also offer the opportunity to schedule the second dose of MMR at an earlier age, and provide room in the schedule for additional vaccines, such as varicella (subject to future JCVI advice).
- Additional option with the addition of a dose of DTaP/IPV/Hib/HepB at 18 months of age, would be the removal of the pre-school booster dose of DTaP/IPV at 3 years and 4 months of age; however, WHO had issued a position paper in 2015, which concluded the use of aP vaccines in a 3-dose primary course, with a booster dose in the second year of life, may provide insufficient protection for children over 6 years of age, and therefore additional booster doses should be considered at the time of school entry; and consideration would also be needed on the implications of removing the pre-school booster dose on diphtheria and tetanus protection.

- On pertussis modelling, the Committee noted that:
  - The model was deterministic and has been developed to consider the drivers behind the pertussis resurgence since 2012. Replacing wP vaccine with aP vaccine was a likely cause of resurgence, and was associated with the shorter duration of protection seen from aP vaccines.
  - Adding a toddler booster was predicted to have little impact on cases among infants too young to be vaccinated. Model was used to examine the impact of removing the pre-school dose of aP vaccine, with either 12 or 18-month doses added to the schedule.
  - The model predicted a decrease in cases in those aged 1 to 2 years, but an increase in all other ages, particularly those aged 5 to 9 years. The impact was most evident in the first few years after the change, and returned towards baseline thereafter, apart from in children aged 1 to 2 years. The changes were more marked if the duration of aP protection was towards the lower end of the range modelled.
  - The model did not include the maternal program; additional work required to include the maternal program, to model the third infant dose at 11 months of age, and fitting to notification data up to 2019.
  - The Committee noted a substantial number of additional cases were predicted with the removal of the pre-school booster, in the short term, and that later removal of the pre-school booster could mitigate some of the cases seen.
- Impact of maternal vaccination on antibody responses in infants, the Committee noted that:
  - IMAP2 study was undertaken by the National Vaccine Evaluation Consortium (NVEC) - designed to look at whether the blunting effect of maternal immunisation on infant antibody responses was different depending on whether the mother received a 3aP or 5aP vaccine.
  - blunting of infants' pertussis responses to primary vaccination was seen, but little residual effects following the pre-school booster. PCV13 responses were generally lower post-primary, in infants of vaccinated mothers, but similar post-booster responses with seen when compared with infants of

unvaccinated mothers. The analysis indicated that the response to IPV in infants born to vaccinated mothers, was attenuated.
    - Another NVEC study DTaP/IPV/Hib/HepB (Infanrix-Hexa®) was given at 8, 12 and 16 weeks of age, with concomitant MenC-CRM, MenC-TT/Hib- TT or MenC-TT at 12 weeks of age.
    - Overall, significant impairment of infants' responses to IPV in those born to mothers who received an IPV-containing vaccine. This meant there was a potential susceptibility gap to all three polio virus types prior to the pre-school booster dose, as no polio booster was currently given in second year of life.
    - If DTaP/IPV/Hib/HepB vaccine was recommended in the second year of life, it would be important to check the post-booster pneumococcal conjugate vaccine response if DTaP/IPV/Hib/HepB vaccine was given before or concomitantly with pneumococcal conjugate vaccine (1+1), and this was also relevant to MenC-TT, MenACYW-TT or MenACWY-CRM vaccines; and two doses of Hib-TT hexavalent vaccine at one month apart were considered to produce inadequate Hib responses in first year of life.
- Would a pertussis-only vaccine become available in the UK market for the maternal program, noted limited opportunity for this and getting DTaP vaccine could be more likely.
- Members questioned whether the blunting effect would be amplified in subsequent pregnancies. This data had not been assessed, but it was noted that blunting was seen even in infants born to unvaccinated mothers who had higher polio antibody levels.
- Presentation on 3 studies comparing alternative pertussis vaccines, the Committee noted that:
    - Study 1 (Carvalho et al 2020): the data indicated that three doses of 3aP were more likely to be associated with disease than wP vaccine; a mixed schedule of wP and 3aP was also more likely to be associated with disease than wP only schedule; there was no difference between three doses of 5aP and wP; limited by the different follow-up periods and inability to directly compare 3aP and 5aP vaccines; the study suggested that the type of vaccine used in the primary course could be important, but there was little difference due to the booster given;
    - Study 2: compared 3aP and 5aP vaccines after the pre-school booster during an outbreak investigation in a school; the preliminary analysis from this study found no significant difference between the two preschool boosters (3aP and 5aP), and concluded that the relatively high proportion of unvaccinated/ partially vaccinated students may have contributed to the outbreak at the school;
    - Study 3: underway, aimed to directly compare the odds of disease where 3aP and 5aP vaccines were used in the primary course; preliminary findings indicated that there were statistically significantly reduced odds of pertussis among children receiving only 5aP compared with children only receiving 3aP in the primary course, but this required further investigation; the odds of pertussis among children that received a mixed 3aP/5aP schedule were not significantly different from those solely receiving 3aP; when assessing only mixed courses, there was no significant difference in the odds of pertussis in those receiving 5aP as the first dose compared with those receiving 3aP as the first dose.
- The Chair noted that while the findings suggested a potential benefit from 5aP vaccines, the findings could also be indicative of the characteristics of specific products and the interaction between products. The information provided therefore meant that studies were required using the vaccines likely to be used in the UK schedule in the future to better understand any potential benefits.
- Study 1 and 3, controls were not matched by location or other socio-economic proxies but were matched by month of birth.

<u>Discussion:</u>

- More modelling work required regarding alternative options for meningococcal protection; pertussis protection seen as complicated, and likely the most important factor when considering alternative schedules. Options presented set out choices for the use of the vaccines, but the exact timing of visits could be changed.
- The Committee reviewed a number of alternative schedules developed by Public Health England.
    - Option A: sustainability of vaccine supply was a key consideration, especially regarding the future availability of MenC and Hib vaccines. Agreed that schedules including a single MenC vaccine or a single Hib vaccine were not future-proof and should not be considered further.
    - Option B: noted that this required an additional visit at 18 months. Considered it might be possible to remove the pre-school booster of DTaP/IPV at 3 years and 4 months of age, either at the same time as the rest of the schedule changed or at a later point. Considered that there was the possibility that later removal of the pre-school DTaP/IPV could reduce the possibility of a short-term increase in pertussis cases.
- No significant concerns regarding duration of protection with moving the second dose of MMR to a younger age and noted that it would provide earlier protection from 2 doses of MMR and might improve

coverage. Keeping the pre-school booster of DTaP/IPV would also provide an additional opportunity to ensure two doses of MMR were provided.

- Noted that if use of varicella vaccine was advised, this could potentially be offered as MMRV or individual varicella vaccine at 18 months under Option B.
- Questioned the move of the Hib booster to 18 months, do countries offer Hib boosting at this age. Most countries that used a 3+1 Hib schedule boosted later, and it was countries which offered a 2+1 schedule were more likely to boost earlier (~12 months). Duration of protection for Hib after the dose at 4 months of age questioned (noted likely substantial population-level immunity from Hib vaccination); comments regarding the higher antibody levels seen with Hib-OMP vaccine; studies considered on the boosting of Hib-OMP hexavalent vaccines with Hib-TT hexavalent vaccines.
- Option B, concerns regarding pertussis control from the removal of a dose of DTaP/IPV/Hib/HepB at 16 weeks; SAGE strongly advised 3 doses of pertussis-containing vaccine in the first year of life. Concern raised - coverage of the 3rd dose DTaP/IPV/Hib/HepB when offered at 11 months of age.
- Studies of concomitant administration of Hib-OMP–containing hexavalent vaccine potentially important in understanding protection offered from the non-Hib components. NISEC study using Hib-OMP–containing hexavalent vaccine would provide absolute antibody levels for all antigens.
- Commented on cost inefficiency of single injection visits; potential for lower coverage with a dose at 11 months of age.
- Option B, concerns raised around protection afforded by 4CMenB vaccine with 4 weeks between primary doses in a 2+1 schedule; Benefits: removal of a GP visit; commented on the success of the 8-, 12-, 16-week schedule, concerns raised about stopping this; this model trusted, changing could raise concerns with parents.
- Options C and D discussed the impact of alternative schedules for MenC and MenACWY vaccines. Given the expression of NadA in MenW, 4CMenB would provide some protection against MenW IMD in infancy. However, it would be possible for circulating MenW strains to down regulate the expression of NadA, thereby removing MenW IMD protection from 4CMenB.
- MenW clones now circulating with reduced susceptibility to penicillin; modelling on meningococcal protection should include scenarios where 4CMenB did not provide protection against MenW IMD.
- Going forward, MenACWY should be the only conjugate vaccine considered in schedule.
- Commented that changes with Option B were minimal, additional appointment main dis-benefit (considered manageable). Concerns raised around parental acceptance of 2 appointments close together around 12 months of age, and that Option B did not have this feature.
- Commented it was considered that MenC/MenACWY was not required in the childhood schedule, under Option B, DTaP/IPV/Hib/HepB given at 18 months could be brought forward to 12 months.
- Questioned if improved coverage with maternal program could have implications for the choice of schedule regarding pertussis control; noted that maternal immunisation would have no impact on control in the second half of infancy.
- Agreed that good control of pertussis was crucially important, and the 8-, 12-, and 16-week doses of DTaP/IPV/Hib/HepB were considered optimal, compared with other options.
- It was noted that the Hib-OMP hexavalent vaccine provided higher Hib antibody titres, and this would potentially improve duration of protection, extending protection against Hib between the 16-week and 18-month doses in Option B.
- Concerns raised regarding resilience in the supply chain, preferable to have the option of more than 1 supplier, particularly regarding the hexavalent vaccines used in the program.
- Noted that under Option B, there were only 2 injected vaccines at 8, 12, and 16 weeks, this would allow room for additional vaccines (if/when they became available and advised by Committee).
- Noted that there were no data on concomitant administration of MenACWY vaccines with Hib-OMP hexavalent vaccine in infancy, and that this should be assessed in an appropriate clinical trial. A clinical trial to assess options for mixed prime and boost with Hib-OMP and Hib-TT hexavalent vaccines would be important. Commented that use of 2 different hexavalent vaccines at specific points in the schedule could prove difficult from an operational perspective.
- Important that attitudinal work to be undertaken on the schedules under consideration, even though evidence was available on an earlier second dose of MMR from London.
- Earlier second dose of MMR considered to have a positive effect on measles control, including through the potential for increased coverage; positive impact on sociodemographic inequalities.
- Considered that the pre-school booster dose of DTaP/IPV could potentially be offered at an older age, and possibly even through a school-based program. Concerns were raised regarding the use of injectable vaccines in the school setting, although it was noted that there was increasing use of injectable vaccines in the school setting for children who missed vaccines at an earlier age.

Conclusion:

- Agreed that use of single Hib and single MenC vaccines unlikely to be sustainable in the long term.
- Hib control was most likely to be sustained by the addition of a booster of DTaP/IPV/Hib/HepB in the second year of life (at 12 or 18 months of age). This would also mitigate the blunting of polio responses from the maternal program.
- The dose of DTaP/IPV/Hib/HepB in the second year of life could be combined with an early second dose of MMR if given at 18 months.
- A three-dose accelerated schedule of DTaP/IPV/Hib/HepB in infancy would be better for operational delivery and for achieving high coverage. Pertussis control in late infancy was also likely to be better with a three-dose accelerated primary schedule than a two dose or extended schedule.
- MenC and MenW control may be sustained by indirect protection from the teenage dose. Modelling should be undertaken to examine the potential benefits of a dose of MenACWY either at 12 weeks or 12 months of age. Led to shortlist of schedule options based on the current schedule, with removal of Hib/MenC, the addition of an appointment at 18 months where DTaP/IPV/Hib/HepB and the second dose of MMR would be offered; and consideration of MenACWY vaccine at 12 weeks or 12 months of age.
- Modelling on pertussis should be undertaken to examine the potential impact of maintaining DTaP/IPV as a pre-school booster.
- Questions remained regarding protection against Hib between the 16-week and 18-month doses of DTaP/IPV/Hib/HepB, and the Committee noted data on better primary responses with Hib-OMP hexavalent vaccine. It was considered that a study should be undertaken to examine boosting at 18 months of age with a Hib-TT hexavalent vaccine, following a primary course with Hib-OMP hexavalent vaccine vs a non-Hib-OMP vaccine. The immunogenicity of a single dose of MenACWY at 12 weeks of age should also be examined.

III. Matters arising

Varicella and Down Syndrome

- 'regulation 28 report' received regarding investigation of the death of a child (with Down syndrome) who had varicella infection at the time of death. Review of literature of whether Down syndrome was a risk factor for severe varicella infection and should vaccination be offered to this group. No evidence of an increased risk from varicella infection in those with Down syndrome. Noted that the Committee was considering routine varicella vaccination.
- Recognised that some children with Down syndrome had immunodeficiency (risk of infection). Green Book stated that children with Down syndrome were at particular risk from measles infection, and MMR vaccine should not be delayed or deferred in this group.

DHSC Vaccine Strategy: Being prepared for clearance and publication, published in due course.

COVID-19:

- Vaccines in development, UK Government provided funding for research on a vaccine. The Immunisation Department in PHE had undertaken work on setting up surveillance systems and reviewing the first cases to assess transmission rates and factors which influenced transmission.
- The Coalition for Epidemic Preparedness and Innovation (CEPI) had put out a call for vaccine development (3 vaccines being reviewed, including a DNA and RNA vaccine and a protein vaccine). Also work to identify antiviral interventions underway.

IV. Yellow Fever

- MHRA update: 2 fatal adverse reactions in 2018–2019, in response a safety risk assessment conducted by the Committee on Human Medicines (CHM), one fatality due to inadvertent vaccination of a person contraindicated to receive the vaccine and the other in an otherwise apparently healthy individual over the age of 60 years.
- CHM has expert working group to review risks and benefits of vaccine. Recommendations published in November 2019, with no new risks identified. Recommendation to strengthen recommendations on existing contraindications, particularly the advice around those aged over 60 years of age and those with any history of thymectomy, incidental or otherwise. Vaccination was also not recommended in those with a family history of a severe adverse reaction to the vaccine.
- Over 60 years of age vaccination: only recommended for travel to countries where there was likely to be a significant and unavoidable risk of yellow fever infection. Put in place a standardised check list for risks and precautions at yellow fever centres.
- Recommendations were communicated through a joint letter from MHRA, PHE and NaTHnac and Health Protection Scotland and the Green Book chapter had been updated.

IV. Monkeypox and Ebola

- PHE guidance rapidly updated in response to a second incident of an importation of a case from Nigeria. Prior to this an incident occurred in 2018 involving 2 index cases in travellers returning from Nigeria with onward transmission resulting in a case in the UK in a healthcare setting. Expert working group convened to review pre- and post-exposure vaccination data from the first incident.
- Recommendation: those at risk (those working in high consequence infectious disease units) should have pre-exposure vaccination of 2 doses 28 days apart. Post-exposure vaccination recommended for those considered exposed, to be given as early as possible to attenuate potential disease progression. Healthcare professionals with likely ongoing future risk were recommended to complete the course with a second dose at least 28 days later.
- A policy document from DHSC on Ebola vaccination covering scenarios of potential risk to Ebola pre- and post-exposure (UK and abroad) linked to the ongoing outbreak in the Democratic Republic of the Congo. Agreed on current policy; however, more conservative than monkeypox guidance. Committee advised as there is a licensed vaccine with proven efficacy (the Merck rVSV-ZEBOV vaccine) it would be appropriate to update and further review the guidance.
- Supportive of a proposal from PHE for JCVI to convene a similar working group of ACDP and JCVI members and other experts to proactively consider other potential infectious disease threats, review potential vaccines in development and consider similar issues to those looked at in developing the monkeypox and Ebola guidance. This would enable PHE and JCVI to have a repository on the available evidence to hand with draft protocols, which could be used in the event of an incident. Further discussion needed.

VI. Influenza

- Influenza modelling update from PHE estimating incremental cost-effectiveness of QIVc compared with QIVe. Work done to quantify recent advice for a slight preference for the quadrivalent cell-based vaccine (QIVc) over egg-based quadrivalent inactivated vaccine (QIVe). Preference due to the potential advantage of QIVc in protecting against A(H3N2) in an egg adaptive season.
- The Committee noted that:
    - aim was to establish the cost threshold at which a QIVc program (in the high risk under 65 adults) would be cost-effective over QIVe;
    - results indicated that QIVc could be cost-effective relative to QIVe at the same price, but this was highly dependent on the rVE estimates; the higher the rVE the more cost-effective the vaccine would be; and the mean of the pooled estimates of the rVE of QIVc were approximately 7% (wide CIs; observational data from 1 season).
- Caveats to the work included that uncertainty was not fully embedded in the model as VE point estimates were used, old epidemiological and burden estimates used and the time series of 14 past influenza seasons only went up to 2008. PHE has plans to update the model, which would then be available for future considerations, including the planned review of the childhood program as well as the impact and cost-effectiveness assessments for new and existing influenza vaccines.
- longer-term effects of the childhood program were not well understood, including understanding the potential build-up of susceptible individuals in the population, due to incomplete coverage and cohorts leaving the program as they aged. The role of natural versus vaccine-induced immunity and the long-term effects of repeated vaccination with the live attenuated vaccine were also not well understood.
- 2019–20 influenza season update: started earlier (and lower) compared to recent years with community influenza activity starting towards the end of Nov/early Dec, outbreaks in schools reported (noted most of these occurred before vaccination had started owing to the delay in vaccine supply); A(H3N2) predominant subtype; moderate peak hospitalisation rates similar to 2018–19; lower ICU rates than 2018–19 season; 80% of H3 viruses genetically characterised were of the 3c3a clade (like the vaccine strain) and 20% were in the 3c2a clade (like the 2018/19 vaccine strain); influenza B and A (H1N1) influenza viruses detected were a close match to the relative vaccine strains both genetically and antigenically:
    - influenza vaccines used in the program for the 2019–20 season included the adjuvanted trivalent (aTIV) and QIVc for the elderly, QIVe and QIVc in at-risk 18- to 64-year olds, live attenuated influenza vaccine (LAIV) for 2- to 17-year olds and QIVe in under 2-year olds in risk groups or children contraindicated for LAIV;
    - rate of uptake in over 65s higher than in the 2018–19 season (delay in supply); update rates behind in 2018–19 rates but by January were approaching similar levels;
    - Vaccine effectiveness (VE): relatively modest, showed significant protective effect against all influenza (no quantitative data point provided) with a similar point estimate for AH3N2; VE point

estimates were slightly higher in 2- to 17-year olds and 18 to 64 years olds (wide CIs); insufficient data to stratify results by vaccine type, but in >65-year olds VE point estimates were lower.

- The committee noted:
  - Likely to be little more data to contribute to VE estimates, issue further complicated by the growing use of point of care testing in hospitals. Discussed need to expand the sentinel swabbing network to improve the sampling size and the power for calculating VE estimates and requested that this is discussed with DCMO. Swabbing rates to calculate VE low in over 65s.
  - Point of care tests could distinguish between A and B influenza types and some could distinguish H3 or H1 subtypes. If vaccination status recorded, results could be used to calculate VE. Hospital-based study was going through ethics approval to look at the potential for this. Future, GPs could adopt point of care testing.
  - Concern over attack rates in the cohorts of children leaving the program (after primary school), especially those in risk groups who would transition to receiving vaccination via GPs (needs monitoring).

VII. Tuberculosis and BCG vaccination

- October 2018: paper from the National Screening Committee (NSC), outlining intention to evaluate neonatal screening for severe combined immunodeficiency (SCID). JCVI had agreed with advice that it would be necessary to move the neonatal BCG program from birth to after SCID screening results were available, as vaccination before testing would not be acceptable. Deferring vaccination would require a change in delivery setting from secondary care to the community, concerns raised about the challenges and the risk of lower uptake.
- October 2019: indications that SCID screening was likely to remain cost-effective, even where there was a drop in coverage associated with a move of BCG vaccination to 4 weeks of age. Questions regarding modelling, presentation Feb 2020. Debate over achieving consent for vaccination before the results of screening were available would be challenging.

Epidemiology of tuberculosis in England: latest epidemiological information presented.

- In 2018, around 4,600 cases of TB in England (8.3/100,000), considered low incidence country; 40% reduction in cases since a peak of cases in 2011(similar decreases in UK and non-UK born children); majority of paediatric cases born in the UK; high proportion of paediatric cases were in those with Black African and Pakistani ethnicity; cases predominantly occur in large urban areas, rates above 40/100,000 in some areas; associated with deprivation.
- rate in children under 15 falling steadily (current rate 1.5/100,000); 75% of cases born outside of England; 5% of cases overall are in children under 15 years of age; 6.5% of young children had severe disease, with meningitis almost double the rate seen in adults; around 70% of notified cases in non–UK born young children had a history of vaccination;
- BCG vaccine, 60-80% protective efficacy against severe forms of TB in children, particularly meningitis; efficacy of BCG against meningitis and military tuberculosis estimated at between 73% and 77%; BCG probably protects against M tuberculosis infection and progression from infection to disease; duration of protection likely beyond 15 years;
- WHO recommended provision of BCG vaccine could be limited to neonates and infants in recognised high-risk groups for countries with low TB incidence; 2005, UK moved from an adolescent to a selective neonatal program, this has been associated with a reduced incidence of TB, although the strength of the evidence was weak; overall, around 2 to 3 cases of disseminated/meningeal TB/year in infants <1 year of age and 5 to 6 cases in the under <5 years age group.
- The confidence in notifications was questioned, PHE indicated that there was a good level of confidence in the system and notification data.

BCG program: Committee noted that:

- Current program was a selective, risk-based, targeting neonates born to parents or grandparents who were born in a country where the annual incidence of TB is 40/100,000 or higher, or who were living in a local authority where the annual incidence of TB was 40/100,000 or higher; 5 local authorities in London met the criteria for universal offer of BCG vaccination at birth.
- Aim: to protect infants from the most serious forms of TB
  - Big variations in commissioning and provision of the BCG program, including through maternity units, community clinics, TB clinics and other out-patient clinics.
  - a tri-partite project board had been convened to manage the change in the BCG program from birth to four weeks of age, and included representatives from NHS EI, PHE, DHSC, providers, commissioners, communications experts, and those involved in the SCID screening preparations;
  - 2019 mapping exercise indicated that BCG delivery was highly variable; high vaccination areas, common for delivery in maternity settings, believed this worked relatively well, but limited

supporting data; areas with few high-risk neonates, clinics run once every 2 weeks, with infants offered vaccination anywhere from 2 to 8 weeks of age; data are highly variable and there are local authorities where there are no data; most cases only the number of doses given is captured, as there is no denominator available; only 5 local authorities with a universal program can a denominator be used to estimate coverage; most recent available year ranged from 37-69%;
    - Current system was considered not optimal.

Tripartite project board:

- Move of BCG vaccination from birth to 4 weeks of age, the Committee noted that:
    - key risks: reduction in coverage due to the move away from vaccine delivery prior to discharge; new clinics set up would not be easily accessible
    - key actions to mitigate: development of a new service specification and a patient care pathway which would address limitations in the existing system; development of training/education materials for health professionals and parents; embedding robust systems to identify eligible individuals and enable a call-recall system to be established; the ability to accurately record denominator data for eligible infants; ensuring SCID results were made available to BCG immunisation providers; ensuring there was sufficient provider capacity and adequately trained staff to deliver the program to babies in the fourth week of life; and enablement calculation of BCG coverage and reliable reporting in all areas.

Statistical modelling of the move to a neonatal program: presentation from the University of Bristol describing modelling on the move to neonatal BCG vaccination from the adolescent program.

- Previous modelling on the change had shown a minimal impact of stopping the adolescent program; model recreated using updated parameters, data, parameter uncertainty and correcting an error in the original model. Conclusion, withdrawing universal vaccination at school age and targeting vaccination towards high-risk neonates was associated with reduced incidence of TB; and this was largely driven by reductions in the non–UK born, with cases increasing in the UK born.

Statistical modelling the impact in TB patients: impact of move from adolescent to neonatal vaccination

- Analysis indicated that BCG vaccination reduced all-cause mortality in TB cases, which supported findings in other settings, and the study could not be generalised outside of TB cases, and therefore benefits to the wider population could not be extrapolated.

Statistical modelling TB risk in at-risk groups:

- Enhanced Tuberculosis Surveillance System: extracted data on country of birth, year of diagnosis (2000–2014), gender, age, time since entry and world region. Conclusion, potential for the threshold for TB vaccination could be relaxed for the neonatal population, to infants born to parents from countries with an incidence of 100/100,000 cases or higher.
- Potential number of cases if threshold relaxed: this work still to be undertaken. Comments made regarding limitations in the original evidence on which the decision to move to neonatal vaccination had been made. Further cost-effectiveness work still to be undertaken. Comment on how transmission defined particularly as latent TB may not be identified but would still be a transmission, defined as cases with the same genotype, but this could also be due to importation of the same strain, latent TB would not be counted.
- Comments were made around whether Mantoux positivity would be a better way to assess transmission, noted that latent cases would not be infectious, and majority would not develop TB. Modelling would capture latent cases once completed, and age dependent progression from latency.

SCID screening and BCG vaccination: presentation from modellers from the University of Sheffield

- Commissioned by the NSC to look at the economics of including screening for SCID in the bloodspot screening program; work informed the NSC's decision making around SCID screening, and they had advised a pilot and evaluation for SCID screening covering around 60% of the population in England. Issue for live vaccines had been raised economic impacts of changes to the BCG program had been assessed.
- Modelling estimated that SCID screening would identify 17–18 cases, and prevent ~6 deaths annually (in pilot area); total cost ~£3m; cost per QALY ~£18,000
- 2 scenarios:
    - 1. BCG at birth with SCID screening: no marginal effect on the non-SCID population, early diagnosis would however lead to improved management of BCGosis;
    - 2. BCG at 4-6 weeks with SCID screening: possibly increase cases of TB, through a potential drop in coverage, but would avoid BCGosis in the SCID population;
- vaccination coverage ~43%; relative risk, developing pulmonary TB (0.44) and meningeal TB (0.26); model had a number of assumptions.

- Model predicted an additional 15.5 (9.9-29) cases of non-disseminated/meningeal TB and 1.3 (0.76-3.2) additional cases of disseminated/meningeal TB in the 0-14 years population per year, from a reduction in BCG coverage.
- Limitations: lack of clarity in BCG coverage outside of areas with universal programs; the number of infants vaccinated post-discharge.
- Recent data indicated 60% of BCG vaccinations were provided after 2 weeks of age.
- No good data on economics of BCG vaccination in the UK; estimated ~40 QALYs could be lost from the changes to the BCG program, versus ~550 QALYs gained from SCID screening (all undiscounted); and discounting would increase the difference between the two estimates.
- Committee noted:
    - members questioned model sensitivity of the model to coverage loss (seen as the key driver of the results, and the move of vaccination to 4 weeks had no intrinsic impact on TB cases).
    - Considered that there would be disutility losses in those effectively treated for TB, although the disutility losses from disseminated/meningeal TB would be quite small given the number of additional cases predicted. Data on QALY losses were limited, data available from developing countries and may not translate to the UK setting.
    - Australian decision, not to move BCG from birth following introduction of SCID screening, had agreed that BCGosis was manageable if treated early.
    - Further considered that provision of information to parents around SCID screening could potentially lead to a reduction of coverage, with parents potentially declining BCG vaccination and choosing to wait until after results were available. In this circumstance, additional actions would be required to offer BCG at a later stage. It was considered there were also ethical issues, particularly around gaining consent for BCG vaccination before SCID screening results were available. Questions were also raised around legal liability.
    - Important to ensure that SCID screening results were available prior to the BCG appointment. Only around 250–300 would have a potential positive, and further testing would be undertaken on a same-day basis.
    - NHS has intentions for commissioning. Active work already underway to ensure there would be clinics ready for a potential start date of September 2020.

Conclusions

- The provision of BCG vaccination services in England was currently varied, with relatively poor coverage in some areas with a universal program. The understanding of coverage outside of areas offering universal vaccination was very limited, due to the difficulty in calculating the total number of infants eligible for vaccination. Need to substantially strengthen monitoring of the program, including improved identification and recording of infants eligible for vaccination.
- Impact of parents declining consent to vaccinate prior to screening results could have an impact on vaccine coverage, in the same way that a move to vaccination at 4 weeks of age.
- Committee reassured by work by NHS E and I and PHE to make a success of the change in delivery model and agreed that the move of BCG vaccination to 4 weeks of age should continue. Improvements to the program could include improved uptake, good quality data collection, end to the current mixed model of delivery and provide the ability to properly manage delivery of the program going forward. Monitoring and evaluation of the change was considered a very high priority by the Committee. Asked to actively review tuberculosis epidemiology following the change.

VIII. HPV vaccination

- In England: 1st dose given in year 8 (12 to 13 years of age) and the 2nd dose 6 to 12 months later (year 8 or 9). Delaying the 2nd dose by 3 years might miss children who left school early. Therefore, to adopt a delayed second dose schedule in England, the program would need to deliver the 1st dose a year earlier, in year 7 (11 to 12 years of age) and the 2nd dose in year 10 (14 to 15 years of age). The Committee agreed this option would need further consideration.
- The Committee received an update from Dr Kreimer on single-dose HPV vaccination covering:
    - post-hoc analyses of vaccine efficacy trials where some participants who were randomised to receive multi-dose regimens yet only received one dose. Non-randomised data from RCT trials provided good evidence of single-dose protection, long-term data continuing to accumulate.
    - Post-marketing phase VI studies from vaccine registries: provided useful information on the effectiveness of 1 dose but with important confounding limitations, including unknown HPV baseline status at time of vaccination, the population included women vaccinated outside of the routine cohorts and the characteristics of women often varied by the number of doses received. Systematic review (Markowitz et al. 2018) evidence showed a tendency for 1 dose recipients to be older and to initiate pap screening earlier, suggesting earlier sexual debut. Committee noted:

        - initial analysis of data on cervical abnormalities indicated that 1 dose was inferior to 3 doses with no significant effectiveness; using a 12-month buffer period to control for potential infection at time of vaccination improved the VE of 1 and 2 doses to protective and more in line with that of three doses; stratifying VE results by aged at HPV vaccination (< or >14 years, the routine cohort age) showed 1 dose to be significantly protective against anogenital warts; and stratifying by age and allowing for a 12 months buffer period resulted in a VE for one dose that was noninferior to that from three doses.
    - ongoing randomised control trials (RCT) trials on one dose: trials initiated with populations randomised to a single dose of HPV vaccine. A data package from mid to late 2020–21 should become available from some of the trials with final data coming later and the ESCUDDO non-inferiority data arriving in 2025.
        - population-based impact or effectiveness studies measuring HPV prevalence had been initiated in South Africa and Thailand among community groups receiving one or two doses of the bivalent and quadrivalent vaccines, respectively.
        - Committee noted: continuing post-hoc analyses of 2 RCTs suggest that HPV vaccines may generate long-term protection after a single dose; vaccine registry studies that control for bias support the possibility of substantial single-dose protection in national immunisation programs; and a series of efficacy, immunobridging and demonstration trials had been initiated that would provide increasingly robust data over the next 5+ years.
    - ongoing studies to generate vaccine effectiveness data:
        - No ongoing trials had boys participating, focus has been on prevention of cervical cancer as proof of principle; the view had been that an immunogenicity study in boys would be able to bridge to results observed in girls; previous trials using 2 doses in boys had shown a slightly better immune response compared with girls.
        - CVT follow-up would provide immunogenicity data 15 years following HPV vaccination (2023), and the IARC study would be approaching 10 to 11 years in the coming year and would have sufficient numbers to look at the impact of one dose on precancerous lesions;
        - remarkable persistence of antibody regardless of the number of doses and consideration was given to whether this might be due to a natural boosting effect (amnestic response); this was thought to be unlikely because HPV vaccine type prevalence or incidence rarely exceeded 5%, thus not everyone is boosted.
- Move to delaying a second dose would be challenging from an operational and implementation point of view and that ideally a move to a single dose was the best outcome, evidence permitting. At the same time moving back to 2 doses would be difficult if data came in later that supported this.
- Data in support of 1 dose presented showed a remarkable persistence of antibody; noted that the longest follow-up data available was for the adjuvanted bivalent vaccine from the CVT study. Committee considered that longer follow-up data were needed for the unadjuvanted quadrivalent vaccine from the IARC study to confirm sustained protection and antibody kinetics. Follow-up data for 10 to 11 years was expected in 2021 but might be available at the end 2020.
- The 9-valent vaccine might replace the quadrivalent vaccine in the UK program, therefore evidence would be needed that 1 dose of the 9-valent vaccine had similar immunogenic properties as for the quadrivalent vaccine HPV types and for five additional HPV vaccine types.
- The Committee agreed that a potential timeframe for the possible implementation of a move to one dose and the implications of this would require careful thought by PHE, NHSE and DHSC.

Conclusions

- The Committee supported advice from SAGE regarding the global vaccine shortage. Therefore, a move to 1 dose in the UK could have the potential added benefit of helping alleviate the global shortage. Committee agreed data presented was compelling in support of 1 dose and that it would be sensible to follow the relevant JCVI process for the consideration of this issue.

IX. MHRA yellow card report

- MHRA had not identified any new serious risks with any of the routine vaccinations; very few yellow card reports following extension of the HPV program to adolescent boys.
- Active surveillance in place for influenza vaccines new to the program, and observed vs. expected analyses had been undertaken; No new issues identified. This approach would be continued in future years. No new issues had been identified in the maternal pertussis vaccination program.

X. Coverage

- Latest coverage data from the 4 countries of the UK. The Committee noted that:
  - England: coverage data showed a continuing decrease in vaccine uptake; recent data included annual HPV data 1 dose (88%), 2 doses (84%); Prenatal pertussis vaccination levels had increased, although PPV annual data for >65 years was only 31%.
  - Scotland: change in service delivery model, with a phased approach building on a current trend with NHS boards rather than GPs taking on responsibility, so data sources are still settling down.
  - Wales: vaccine uptake levelled off, still concerns regarding MMR coverage; better coverage levels seen for the 2nd MMR dose (boosted by an audit, children wrongly categorised); concerns raised about shingles vaccine as poor coverage (30%) seen in 70-year olds.
  - Northern Ireland: slight improvements in coverage in 2nd quarter, coverage still below 95%; HPV uptake in girls increased to 84%; maternal pertussis only delivered in general practice, but plans to move the offer to maternity services; and shingles was currently given with flu, and there were efforts underway to try and separate them to improve coverage.

3.2 Newly published or updated statement/recommendations

3.2.1 Statement from JCVI on immunisation prioritisation

- Published 17 April 2020 - https://www.gov.uk/government/publications/jcvi-statement-on-immunisation-prioritisation/statement-from-jcvi-on-immunisation-prioritisation
- Statement expressed the need to maintain immunisation services during the COVID-19 pandemic
- The national immunisation programme is highly successful in reducing the incidence of serious and sometimes life-threatening diseases such as pneumococcal and meningococcal infections, whooping cough, diphtheria and measles. It is important to maintain the best possible vaccine uptake to prevent a resurgence of these infections.
- Most children suffer from a very minor illness with COVID-19. If immunisation services lapse, there will be consequential substantially increased risk to health from vaccine-preventable diseases.
- The statement expressed that if there is a high demand on services, it is important to prioritise time-sensitive vaccines for babies, children and pregnant women. JCVI recommended:
  - routine childhood immunisations (to include targeted neonatal hepatitis B and BCG), from birth up to and including vaccines offered to babies, infants and pre-school children including first and second MMR doses
  - pertussis vaccination in pregnancy
  - pneumococcal vaccination for those in risk groups from 2 to 64 years of age and those aged 65 years and over (subject to supplies of PPV23 and clinical prioritisation)
  - immunisation should proceed providing those attending for vaccination (including parents of babies) are well, are not displaying symptoms of COVID-19 or other infections and are not self-isolating because they are contacts of suspected COVID-19 cases.

3.2.2 Updated guidance for Measles – Green Book chapter 21

- Updated 31 December 2019 - https://www.gov.uk/government/publications/measles-the-green-book-chapter-21
- Revised to include the updated epidemiology to 2018, the administration of MMR and other live vaccines and recommended intervals, rare and serious events, and advice for pregnant women sections.

3.2.3 Updated guidance for Immunisation of individuals with underlying medical conditions – Green Book chapter 7

- Updated 10 January 2020 -https://www.gov.uk/government/publications/immunisation-of-individuals-with-underlying-medical-conditions-the-green-book-chapter-7
- Revised to include the updated recommendations on the schedule for immunising individuals with asplenia, splenic dysfunction or severe immunocompromise and advice regarding the removal of the recommendation for an additional Hib vaccine for children and adults with asplenia or splenic dysfunction.
- Some medical conditions increase the risk of complications from infectious diseases, and children and adults with such conditions should be immunised as a matter of priority. These groups may also require additional vaccinations or additional doses of vaccines to provide adequate protection.

3.2.4 Updated guidance for Pneumococcal – Green Book chapter 25

- Updated 13 January 2020 - https://www.gov.uk/government/publications/pneumococcal-the-green-book-chapter-25
- Revised and updated with the latest information for and data including the schedule with the changes to the routine infant programme. The recommendations for children and adults in clinical risk groups have been reviewed and simplified.

3.2.5 Updated guidance for Yellow Fever– Green Book chapter 35

- Updated 13 January 2020 - https://www.gov.uk/government/publications/yellow-fever-the-green-book-chapter-35
- Updated to reflect the recommendations of the Commission on Human Measures (CHM) to strengthen measures to minimise the potential risk of rare but serious and fatal adverse events associated with yellow fever vaccination (in those with weakened immune systems, those aged 60 years or older and anyone who has had their thymus removed).

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4 National Advisory Committee on Immunization (NACI), Canada

4.1 NACI Meetings

The most recent meeting was conducted on 5–6 February 2020 in Ottawa, Ontario; however, the summary of discussions has not yet been released. Summary of discussions was made available for the June and September 2019 meetings. Decisions and recommendations from these meetings are summarised below. https://www.canada.ca/en/public-health/services/immunization/national-advisory-committee-on-immunization-naci/meetings.html

4.1.1 5–6 June 2019 meeting; Ottawa, Ontario

- NACI approved the Standard Operating Procedure (SOP) for the systematic review of economic evaluations. This SOP outlines the best practices when conducting a systematic review of economic evaluations within NACI or by a contractor. This review will be used to inform NACI recommendations and will be published in the advisory committee statements.
- NACI approved the SOP for the reporting of economic evaluations. The purpose of the Reporting Guidelines is to provide guidance on how to report economic evaluations to NACI. It is to be used in house and by contractors.
- A discussion took place on the parameters around the "use" of or reliance on health economic evidence from industry, and acceptable extent of industry involvement in creating that evidence. Several options for a path forward were presented and discussed.
- A presentation was provided on the Canadian Pandemic Influenza Preparedness Plan and the Federal/Provincial/Territorial Public Health Response Plan for Biological Events. Members were informed of a Pandemic Influenza Exercise that the Center for Emergency Preparedness and Response is currently working on multi-phased exercise which will take place over the course of 18 months in 2019-2020 with the support of Centre for Immunization and Respiratory Infectious Diseases (CIRID). NACI was not part of the previous pandemic response, but NACI is now positioned to provide guidance going forward.
- NACI MMRV Working Group discussed upcoming Mumps Focus Statement which is to include programmatic recommendations that will support the provincial/territories' goal of controlling the scale of mumps outbreaks in Canada. An overview of the results of a survey to collect provincial and territorial data on the recent mumps outbreak activity was also presented.
- RSV Working Group update: An overview of safety evidence and economic evaluations for Palivizumab were presented, and NACI discussed approaches to integrate this evidence into the NACI statement under development.
- An update on the current Ebola outbreak (2018–19) in the Democratic Republic of Congo (DRC) was presented; this included information on the epidemiology, international response, immunisation, as well as the Canadian support.

- Ethics, Equity, Feasibility, Acceptability (EEFA) Framework: EEFA frameworks with a focus on acceptability. The presentation provided the acceptability matrix and the algorithm and key highlights from research conducted on acceptability of vaccines in Canada.
- EEFA: Systematic review on acceptability. Preliminary results from a systematic review of the factors that influence the acceptability of vaccines among Canadians was presented the University of Alberta contractor who conducted the review. The systematic review on vaccine acceptability will be published on NACI's website when completed.
- The objectives of the NACI EVD Vaccine Working Group and the critical path for the rapid development of interim guidance on the use of stockpiled EVD vaccine was provided. The findings of a rapid review on ring vaccination against EVD, as well as draft guidance considerations and options, were also presented.

4.1.2 25–26 September 2019 meeting; Ottawa, Ontario

- NACI reviewed and approved a template to standardise presentation of systematic reviews of economic evaluation literature.
- Economic process presentation: NACI support for multi-model comparisons where feasible, with the caveat that a more detailed approach be developed following consultation with the Public Health Agency of Canada (PHAC) Public Health Ethics Consultative Group. This approach may allow for submission of models from vaccine industry to be compared to independent academic models.
- NACI discussed a draft statement on mammalian cell-culture based influenza vaccines. The presentation included the methodology, results and conclusions of a systematic literature review on the efficacy, effectiveness, immunogenicity and safety. For a second review and approval in early 2020.
- NACI Mumps Working Group will refine the epidemiology section of the upcoming statement, and the revised draft Statement will be sent for review by provinces and territories in late 2019 for stakeholder input.
- High Consequence infectious disease working group workplan approach: NACI created a new Working Group for High-Consequence Infectious Diseases (HCID). Decided that Smallpox vaccine will be the next topic addressed by the new HCID WG.
- NACI was informed of recent activities and next steps in RSV vaccine readiness. In spring 2019 PHAC hosted an RSV vaccine readiness workshop with Canadian RSV and surveillance experts. This activity identified several information and evidence gaps in the Canadian context, and the results of the workshop are being prepared for publication. PHAC will update NACI as vaccine readiness and surveillance planning evolves

4.2 Newly published or updated statement/recommendations

4.2.1 An Advisory Committee Statement (ACS): The Use of Bivalent Factor H Binding Protein Meningococcal Serogroup B (MenB-fHBP) Vaccine for the Prevention of Meningococcal B Disease

Background:

- NACI released an ACS for the use of Bexsero® in 2014 - the vaccine is recommended for use in individuals at high risk of meningococcal disease and for use in controlling outbreaks and for close contacts of a case of IMD caused by serogroup B *Neisseria meningitidis.*
- There are currently no established national disease reduction targets or vaccination coverage goals for the prevention of invasive meningococcal serogroup B disease. There are also no publicly funded, routine meningococcal serogroup B immunisation programs in Canada.

Recommendations:

- **NACI recommends that the MenB-fHBP vaccine should not be offered in routine universal immunisation programs in Canada at this time due to insufficient evidence.**
    - The greatest incidence of serogroup B IMD is in children of an age for which the vaccine is not authorised for use. There are also only limited data on the persistence of the vaccine immune response and no data on the need for booster doses after the primary immunisation series. In addition, some caution may be required in extrapolating findings on the immune response generated by the vaccine against the breadth of strains covered in clinical trials to the Canadian context.

- **NACI recommends that a serogroup B meningococcal vaccine (MenB-fHBP or 4CMenB) should be offered in jurisdictions experiencing serogroup B meningococcal disease outbreaks**
- **NACI recommends that the MenB-fHBP vaccine may be considered as an option for use in individuals 10 years of age and older in such circumstances.**
    - There are no data on the effectiveness of the MenB-fHBP vaccine or its effect on meningococcal carriage or herd immunity. Previous experience with the use of conjugate serogroup C and serogroup B outer membrane vesicle vaccines against emerging hyperendemic and/or hypervirulent strains expressing homologous antigens to those present in a vaccine has been demonstrated to be an effective public health strategy for managing clonal IMD outbreaks.
- **NACI recommends that a serogroup B meningococcal vaccine (MenB-fHBP or 4CMenB) should be offered, in addition to chemoprophylaxis, for protection of individuals who are close contacts with a case of invasive meningococcal disease caused by serogroup B *Neisseria meningitidis*.**
- **NACI recommends that the MenB-fHBP vaccine may be considered as an option for use in individuals 10 years of age and older who are close contacts with a case of IMD caused by serogroup B *Neisseria meningitidis***
    - There are no data on the population-level effectiveness of the MenB-fHBP vaccine or its effectiveness in close contacts of a case of IMD caused by serogroup B *N. meningitidis*. Close contacts of individuals with meningococcal infections have an increased risk of developing IMD and should receive immunoprophylaxis in addition to chemoprophylaxis. Vaccination of close contacts should be carried out independent of tests of strain susceptibility to the vaccine to ensure there are no delays in contact management. NACI considered that for the individual, there is currently sufficient evidence that MenB-fHBP, when given according to the schedules used in clinical trials, is safe, immunogenic and may offer protection against a range of fHBP variants present in MenB strains causing IMD.
- **NACI recommends that a serogroup B meningococcal vaccine (MenB-fHBP or 4CMenB) should be offered for the active immunisation of individuals with underlying medical conditions that would put them at higher risk of meningococcal disease.**
- **NACI recommends that the MenB-fHBP vaccine may be considered as an option for use in high-risk individuals 10 years of age and older, in a 3-dose schedule (0, 1–2, 6 months), to reduce the risk of invasive serogroup B meningococcal disease.**
    - NACI considered that for the individual, there is currently sufficient evidence that the MenB-fHBP vaccine, when given according to the schedules used in clinical trials, is safe, immunogenic and may offer protection against a range of fHBP variants present in MenB strains causing IMD. However, the clinical trials identified in the literature recruited healthy adolescents and adults. There was insufficient evidence identified regarding the safety and immunogenicity of the vaccine in any individuals with underlying medical conditions that would result in a higher risk of IMD. However, this recommendation is consistent with NACI recommendations for other meningococcal vaccines and is based on expert opinion.
- **NACI recommends that the MenB-fHBP vaccine may be considered as an option for individuals 10-25 years of age who are not at higher risk of meningococcal disease than the general population, in a 2-dose schedule (0 and 6 months), to reduce the risk of invasive serogroup B meningococcal disease.**
    - NACI considered that for the individual, there is currently sufficient evidence that MenB-fHBP, when given according to the schedules used in clinical trials, is safe, immunogenic and may offer protection against a range of fHBP variants present in MenB strains causing IMD. However, there are limited data available on the persistence of immunogenicity elicited by the vaccine, and available data show protection declines rapidly 12 months after vaccination.

<u>Evidence gaps:</u>

- Evidence gaps regarding the MenB-fHBP vaccine also apply to meningococcal serogroup B vaccines in general
- Such as the effectiveness of the vaccine at the population level, the effect of immunization on carriage and herd immunity, the duration of protection, the need for booster doses, the potential coverage of

circulating meningococcal serogroup B strains in Canada, as well as the use of the vaccine in specific subpopulations (e.g., pregnant women, immunocompromised).

5 Immunisation updates from the World Health Organization (WHO)

5.1 Strategic Advisory Group of Experts (SAGE) on Immunization, WHO, 31 March–2 April 2020

- Virtual meeting via video conference. The highlights are available https://www.who.int/immunization/sage/meetings/2020/april/SAGE_Highlights_MarchApril_2020.pdf The full report with final recommendations will be published in the Weekly Epidemiological Record on 29 May 2020.)

Global and Regional Reports

- In the context of the COVID-19 pandemic and its impact on primary health and immunisation services across the world, SAGE stressed the imperative to explore innovative approaches and to seize opportunities that may emerge from this crisis to move the global immunisation agenda forward
- These opportunities include using subnational data to drive vaccination coverage, tailoring local immunisation programs, improving the design of clinics, accelerating the use of integrated campaigns and of life course immunization, addressing gender inequities, and overcoming fragmentation of vaccine-preventable disease surveillance.
- The regional reports confirmed the challenges that countries will experience to sustain immunisation activities in the current COVID-19 context. Furthermore, continued high numbers of measles cases and outbreaks were highlighted in various regions; these are likely to increase.
- SAGE was updated on key COVID-19 modelling results for transmissibility, serial interval, incubation period, severity of the disease, risk groups, asymptomatic infections and role of public health interventions and social measures.
- SAGE members stressed that safeguarding immunisation services was of critical importance during the current pandemic and adequate catch-up activities should be planned at this stage to ensure that children receive all their needed vaccines.
- Gavi expressed its concerns on the implications of COVID-19 on routine immunisation, with an anticipated plummet of routine immunisation coverage and emergence of outbreaks of VPD. Gavi outlined its engagement in response to the COVID-19 pandemic with providing immediate support to countries.

Update on COVID-19 vaccine

- SAGE acknowledged the unprecedent effort to develop a COVID-19 vaccine and requested that studies give due attention to vaccine performance in vulnerable populations and in low- and middle-income countries.
- SAGE commended the early collaboration with key technical partners on consideration of use scenarios, access, availability and supply.
- SAGE discussed the need to establish a SAGE Working Group on COVID-19 Vaccines to advise on strategies and use scenarios for investigational and licensed COVID vaccines.
- SAGE requested that the Working Group be constituted now to permit active involvement of SAGE in WHO processes to advise on product profile and target groups for vaccine evaluation.

Update on Ebola vaccine

- The Eastern Democratic Republic of Congo (DRC) Ebola outbreak is coming to an end with no new cases reported since 17 February 2020, and more than 320,000 individuals vaccinated.
- In a subsequent meeting, SAGE will discuss possible off-label recommendations for the licensed rVSV-ZEBOV vaccine to allow its appropriate use in future outbreaks.
- SAGE recommended that a comprehensive review be conducted of the recent experience of Ebola vaccine implementation and policy development during an outbreak response to inform future processes for the development of recommendations, the use and the monitoring of un-licensed vaccines in emergency situations.

Measles outbreak epidemiology and WHO coordination

- In the setting of the increased numbers of measles outbreaks throughout the world since 2019, SAGE expressed concern that the COVID-19 pandemic will further strain measles control efforts. Countries and

immunisation partners will need to re-double immunisation efforts, guided by the recently published "WHO Guiding principles for immunization activities during the COVID-19 pandemic".

- SAGE was updated on newsworthy or graded measles outbreaks (e.g. Democratic Republic of Congo, European region) as well as on success stories (e.g., China, Colombia) and the WHO global response, including advice from the Strategic Technical Advisory Group – Infectious Hazards (STAG-IH) of WHO, and the development of the Global Strategic Response Plan and other measures.
- An update on the ongoing measles and rubella policy and strategy work was provided, including the presentation of the Measles Eradication Feasibility Report to the Executive Board (EB) in February 2020 and World Health Assembly (WHA) in May 2020 with the Immunization Agenda 2030; the proposed M&E framework for measles and rubella; a benchmarking process to define an evidence based process to consider measles eradication; the Measles Rubella Strategic Framework.

Polio

- SAGE expressed concern about the continuing upsurge in wild poliovirus cases and by the inability of the polio eradication program to effectively control outbreaks of vaccine derived polioviruses in Africa and Asia.
- SAGE took note of the current reorientation of polio resources for country COVID-19 responses. In practice, this results in a halt of polio activities. The Global Polio Eradication Programme (GPEI) plans to monitor the COVID-19 situation and prepare scenarios for program restart vaccination activities.
- SAGE reconfirmed the prioritisation of available inactivated polio vaccine (IPV) supply for 2020:
  1. Routine immunisation
  2. Catch-up of missed children due to delayed introduction
  3. Supplemental immunisation activities (SIA) for endemic countries and high-risk areas, based on risk assessment
  4. Introduction of second dose of IPV into routine immunisation.

- However, for 2021, SAGE agreed that the introduction of a second dose of IPV into routine immunisation (currently 4th place) will be prioritised over IPV for SIAs for endemic countries and high-risk areas (currently 3rd place).
- In terms of tOPV, SAGE endorsed that tOPV may be made available to countries for cVDPV2 outbreak response in subnational areas where there is co-circulation or high risk of co-circulation of cVDPV2 with cVDPV1, cVDPV3 or wild type 1 poliovirus to avoid the need for dual mOPV2 and bOPV campaigns. Use of tOPV will require the same authorisations and restrictions as required for use of mOPV2.
- SAGE endorsed in principle criteria for initial nOPV2 use under emergency use listing (EUL) in cVDPV2 outbreak response and will continue to monitor and further review this in the future.
- In the current epidemiological context, SAGE expressed caution over regions or countries moving from bOPV to an IPV-only schedule as a general principle and recommended that instead these regions or countries take a gradual approach, first introducing a 2nd dose of IPV into routine immunisation.
- SAGE concluded that a key lesson from the switch is that the GPEI cannot plan for complete cessation of OPV with the tools and knowledge that are currently available.

Monitoring and Evaluation framework

- SAGE was presented with initial framework of the monitoring and evaluation and accountability (M&E/A) framework for the immunisation strategy for the new decade. The final framework is expected to be submitted to the WHO EB and WHA in 2021 for endorsement.
- SAGE supports the proposed IA2030 ME&A Framework principles as well as the approach to defining indicators and targets in a lean and action-oriented manner.

Global Vaccine Safety Blueprint 2.0

- SAGE acknowledged the significant progress made in strengthening the capacity of countries to address vaccine safety issues in all WHO regions since 2012 through the implementation of the Global Vaccine Safety Blueprint 1.0 (GVSB 1.0) and endorses the GVSB 2.0.
- To make GVSB 2.0 more aligned with the Immunization Agenda 2030, SAGE suggested that the country ownership and country driven aspects be incorporated into the document with an emphasis on a bottom-up approach to mirror the IA2030 philosophy.

5.2 Meeting of the Global Advisory Committee on Vaccine Safety (GACVS), 2–3 December 2020

- Published in WHO: Weekly epidemiology report 24 January 2020 – https://extranet.who.int/iris/restricted/bitstream/handle/10665/330607/WER9504-eng-fre.pdf?ua=1
- This report examined data on the safety of vaccines against rotavirus, Ebola virus and human papilloma viruses. It also reviewed 2 generic issues: updating of the global vaccine safety strategy and case reviews of communications on vaccine safety.

Risk of intussusception with RotaVac™ in India

- The purpose is to review data on the safety of RotaTeq™ vaccine in 5 sub-Saharan African countries and of RotaVac™ vaccine (RVV) in parts of India and to examine baseline data from a nationwide network in India of active surveillance for intussusception following vaccination.

Evidence:

- self-controlled case series (SCCS) analysis found the incidence rate ratios for the first 7 days after doses 1, 2 and 3 as compared with the period from day 28 to 1 year of age were 0.83, 0.86 and 1.65, respectively, none of which was statistically significantly different from no association. Similarly, no significant difference was found for the 8- to 21-day risk window after vaccination
- The incidence of intussusception varies by population and infant age. The data did not indicate a significantly higher risk of intussusception during the post-vaccination risk periods than in the reference period for either of the vaccines (RotaTeq™ and RotaVac™).
- Baseline data from 2010 to 2017 were also presented from an Indian nationwide network of tertiary care hospitals in 18 states. Most of the data were from a period before introduction of RVV. Data on intussusception were collected for children aged <2 years. Over 75% of cases occurred before 12 months of age and the majority during the first 6 months. The numbers of cases were age-dependent, with a peak between 20 and 35 weeks of age. The baseline hospitalisation rates for intussusception (number of cases per 1,000 paediatric surgical admissions) differed by region, with the highest in southern states and the lowest in western India.

Recommendations:

- Continued monitoring of the risk for intussusception associated with RVVs and comparisons of products in the same risk window are recommended when new RVVs are introduced into new populations.
- India may consider pooled analysis of their intussusception data to increase analytical power, as common definitions and protocols have been used.

Safety of Ebola virus vaccines

- Safety profiles of rVSV-ZEBOV-GP vaccine and Ad26.ZEBOV/MVA-BN-Filo vaccine constructs are reassuring and they represent breakthroughs as medical countermeasures against EVD.
- It is recommended that safety reviews of additional vector-based Ebola virus vaccines should be based on the Brighton Collaboration vector template, as it offers a structured approach to evaluating safety.
- rVSV-ZEBOV vaccine (Merck)
    - rVSV-ZEBOV vaccine conditionally approved by the European Commission and prequalified by WHO to be used according to the SAGE recommendation for expanded access in a ring vaccination strategy.
    - An outbreak of EVD was reported on 1 August 2018 in the Democratic Republic of Congo (DRC), where 250,000 people received a single dose of the rVSV- ZEBOV-GP vaccine under the expanded access protocol, including pregnant women and infants <1 year of age. AEs reported within first 3 days post vaccination were mild (>90%). Solicited AEs were mostly mild to moderate for pregnant women.

- Limitations in follow up and data recording on safety due to large number of people vaccinated under challenging operational conditions. No new AEs and the safety data suggest that the vaccine is well tolerated by adults and children.
- Phase 1 of the study was conducted from August 2018 to June 2019, when people were given 5 x 107 plaque-forming units (PFU) of the vaccine. Phase 2 was conducted between June and September 2019, when people received 2 x 107 PFU, that is, an adjusted dose similar to that administered in a ring vaccination trial in Guinea in 2014–2015.
- Other WHO-sponsored studies: AEs 3 days post vaccination and in adults 15-21 days post vaccination in regions including Uganda, South Sudan, Rwanda were similar. Insufficient data on AEs in children aged 6–17 years during the 4–14 day and 15–21 day follow-up periods.

- Ad26.ZEBOV (Janssen Pharmaceutical) and MVA-BN-Filo vaccine (Bavarian Nordic)
  - Product characteristics and nonclinical and clinical data were reviewed in the context of the viral vector templates and clinical safety data presented by Janssen. Vaccine administration is in 2 doses. First dose consisting of Ad26.ZEBOV at 5 x 1010 virus particles, followed by a dose of MVA-BN-Filo at 1 x 108 infectious units 56 days later.
  - Vaccine safety is being evaluated in 12 ongoing and completed phase 1, 2 and 3 studies in Africa, Europe and the USA. Unblinded pooled data found that Solicited and unsolicited local and systemic AEs were mild to moderate, and of short duration. Incidence of grade 3 fever within 7 days of vaccination was low (1.4%). All serious AEs that occurred in children (2%) were infections or complications of malaria. No concern about safety was identified in children aged 1–17 years. In 66 unintended pregnancies, there was no apparent pattern of AEs and no safety concerns. The data presented suggest that the vaccine is well tolerated and does not raise any safety concerns but that the data for special populations and children are limited.
  - The standardised template was reviewed for the replication-incompetent Ad26 viral vector and the modified vaccinia Ankara (MVA) vector (developed by the Brighton Collaboration Viral Vector Vaccines Safety working group).
    - The Ad26. ZEBOV vaccine consists of the replication-incompetent (due to deletion of early region 1 and partial deletion of early region 3) Ad26 vector containing the glycoprotein gene of Ebola virus at the site of the E1 deletion. The Ad26 vector is not toxic in animal models and has limited biodistribution, as the vector is detected mainly at the injection site. Vaccines based on Ad26 platform administered to >8,000 participants had an acceptable safety profile and induced potent humoral and cellular immune responses.
    - The MVA-BN vector has 6 major deletions, including immune evasion genes, structural proteins and host interaction protein genes. Protein sequences for the glycoprotein from Ebola virus Mayinga, Sudan virus Gulu and Marburg virus Musoke and nucleoprotein from Tai-Forest virus were inserted into the MVA-BN non-coding regions. Safe when administered to the animal models studied, and it is not biodistributed. Recombinant MVA BN vaccines induce an immune response in individuals previously vaccinated against smallpox.
    - Has shown favourable safety profile and strong vaccinia-specific immune response in 22 completed clinical trials with backbone vector (>14,500 people both healthy and immunocompromised) and >20 trials with recombinant constructs.

Human papilloma virus vaccines and infertility

- Since 2006, post-licensure monitoring and research has been conducted for the 3 vaccines (bivalent by GlaxoSmithKline, quadrivalent and 9-valent by Merck and Co.), with over 160 studies completed. HPV vaccines were found to have a favourable safety profile, with no confirmed clinically serious signals about safety. Anaphylaxis and syncope are known AEs.
- Since 2012, individual case reports have linked vaccination against HPV with primary ovarian insufficiency (POI), defined as dysfunction or depletion of ovarian follicles, menopausal symptoms and reduced fertility before the age of 40. A systematic review was conducted, where 7 articled addressed HPV vaccination and POI and 2 articled assessed the association between HPV vaccination and the

ability to conceive. It was concluded that the evidence does not suggest a causal relationship between HPV vaccination and infertility.

- Three articles reported on cases of POI in six girls 8–24 months after they received the first dose of quadrivalent vaccine. A temporal association was found, but there was no evidence for a causal association nor for the involvement of a vaccine component in the pathogenic process or of autoimmune disease.

5.3 The Fourth meeting of the Global NITAG Network (GNN), 24-25 February 2020

- Meeting held in Atlanta, Georgia, USA
- Record of discussion located: http://www.nitag-resource.org/network/meetings/related

Monitoring NITAG performance

Highlights of participant discussion:

- Suggested changes/additions to six WHO/UNICEF JRF criteria:
  - Change number of annual meetings from 1 to 2-4.
  - Add written records of NITAG meetings.
  - Add core competencies in Evidence-based Decision Making (EBDM) of members and Secretariat.
  - Add existence of annual workplan and goals.
  - Add % of Gross Domestic Product (GDP) provided to NITAG (measures country ownership)
- Suggested indicators or approaches to evaluate NITAG recommendations:
  - Indicate the origin of a particular policy question (NITAG or MoH)
  - Develop a method to evaluate the EBDM process used for a recommendation on a scale from 0 to 5.
  - Indicate the type feedback from MoH after recommendation is submitted (written, approval, rejection, request for more information, etc.)
  - To evaluate output, indicate the quantity, quality and revisions of previous recommendations.
  - Note whether recommendations are implemented completely or partially
  - To evaluate outcome, report on vaccination coverage of recommended vaccines.
  - Indicate the role of NITAG in follow-up on the implementation of a recommendation.
- Suggest that conflict of interest guidance be broadened to political issues since it currently overemphasises financial conflicts.
- Measure collaborations with specialists to generate necessary evidence.
- Suggest each NITAG issue annual report with achievements, challenges, plans and share with neighbouring countries to enable coordination.
- Proposed action points:
  - Develop guidance on advocating with MoH for sustainable financing and resources.
  - Survey GNN members on how to revise the 6 criteria.

Vaccine hesitancy & creating demand for vaccination

Highlights of participant discussion:

- Mandatory vaccination for children entering schools and healthcare providers can backfire. Positive reinforcement and proactive information dissemination may be more helpful than vaccination mandates.
- Develop and implement strategies in LICs to talk with mothers at birth about the benefits of vaccination.
- Influence providers through medical education, incentives, and penalties to train and encourage them to promote vaccination.
- Educate children about the benefits of vaccination as a way to influence parents.
- Give positive reinforcement for people who get vaccinations.
- Data on vaccine hesitancy:
  - Need data on community concerns about vaccine safety to guide development of ways to address them.
  - Need record of parents' reasons for not vaccinating their children.
  - In Pakistan, 20% of non-acceptance is due to pain.

    - In UK, annual surveys show many do not believe in social media but trust the National Health Service
- Policy:
    - NITAGs should consider number of injection sites per immunisation visit and try to minimise them.
    - Emphasise to MoH the negative impact of stock-out on confidence in vaccination program
- Proposed action points:
    - Consider GNN/NITAG role in:
        - Development of recommendations to mitigate pain during vaccination to increase acceptance.
        - Advocating for better tracking and management of vaccine stocks.
        - Tailoring messages about vaccination to specific populations.
    - Develop guidelines on the role of NITAGs in addressing vaccine hesitancy and creating demand for vaccination

Data for action – VPD surveillance: where to start?

Highlights of participant discussion:

- Models can use remote sensing to measure population distribution.
- With unreliable data sources, modelers use an ensemble approach to aggregate estimates from multiple models.
- Barriers to accessing and using data
    - Lack of local data and lack of knowledge of how to use existing data.
    - Difficulty in getting government funding for vaccine preventable disease surveillance.
    - Finding and understanding health economics data.
- Proposed action points:
    - Consider twinning to help build capacity in data collection and analysis.

Case studies of latest recommendations

Highlights of participant discussion:

- Using GRADE allows transparency and reveals that recommendations are sometimes made on low-quality data.
- Twinning must account for time needed for well-developed NITAG to understand the level and needs of the supported country.
- Proposed action points:
    - Provide guidance on starting a twinning relationship, including who initiates, scope, etc.

Maturity model

Highlights of participant discussion:

- Mandates of NITAGs may differ and should be considered
- Model should be applicable also to very small countries
- Not every country needs to reach the highest maturity level
- Publicising maturity of a NITAG has implications for its credibility
- Could be used prior to a training to ensure approach is appropriate
- Proposed action points:
    - Survey all regions for feedback on maturity model

Off-label recommendations

Highlights of participant discussion:

- Decisions on off-label use depends on many different factors, including safety.
- MIC MoH worry about lawsuits after off-label use.
- Need for dialogue with regulatory agency to minimise need for off-label use. Regulatory agencies can ask for a blanket statement from manufacturer, e.g., vaccine should be given in accordance with official MoH recommendations.
- Can or should the WHO develop good regulatory practices for off-label vaccine recommendations?
- Proposed action points:
    - Identify solutions to bring together regulatory agencies, programs, manufacturers, and NITAGs
    - Look at WHO prequalification process as way to address off-label recommendations.
    - Provide information to GNN members on how lawsuits are addressed
    - Include a session on off-label recommendations as a standing item of GNN meetings.

Managing with little resources

Highlights of participant discussion:

- The greatest difficulty in resource-poor areas is the ability to have a scientific secretariat that can generate evidence-based recommendations.
- Funding from MoH after donor funding has ended requires NITAG advocacy.
- NITAGs need more access to health economics expertise.
- Funding shortfalls don't always compromise ability for NITAGs to meet, rather the impact of limited funding is felt elsewhere.
- Fruitful Scandinavian collaboration provides a promising model for resource-limited settings, e.g. many countries in Africa.
- Proposed action points:
    - Raise awareness and promote use of existing programs that provide access to high-impact journals for reference (e.g. Hinari)
    - Provide guidance on health economic analysis and interpretation.
    - Provide guidance on advocating to MoH for sustainable NITAG support.

NITAG evaluations

Highlights of participant discussion:

- Evaluations are best conducted in the local language. The comprehensive evaluation tool and the simplified one are currently only available in English, French and Spanish.
- Length of evaluation varies based on quantity of documents needed to review; 3-7 days.
- Evaluations are useful for learning strengths and envisioning what steps are needed for NITAG improvement.
- Evaluation sometimes show that a NITAG is not independent or systematic; or that it functions like an Interagency Coordination Committee (ICC).
- Lessons learned:
    - Country must have interest in evaluation and self-reflection
    - Evaluations can be conducted as self-evaluation, peer to peer, or facilitated by WHO RO.
    - The evaluation process includes desk review, interviews, group discussions, and then advocacy with the MoH regarding recommendations made for NITAG strengthening.
    - Process when conducting external evaluations should including sharing primary observations after evaluation is completed and before leaving, followed by development of a final report with feasible and achievable recommendations
- Proposed actions points:
    - Translate existing tools into more languages, e.g., Portuguese, Russian.
    - Find opportunities to follow up on evaluation results (e.g., via twinning relationships)
    - Develop an evaluator guide

5.4 Global immunisation news and other items and resources

- Latest news available here: https://www.who.int/immunization/newsroom/en/
- WHO Executive Board Delegates welcome the draft immunisation vision "Immunisation Agenda 2030" highlighting the urgency and the critical need to ensure a successor for the Global Vaccine Action Plan to maintain the momentum and sustain the gains in vaccines and immunisation over the next decade.
- Additionally, the World Health Organization's Executive Board formally agreed that the Defeating Meningitis by 2030 Global Roadmap should be brought before the World Health Assembly in May 2020.

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6 Other items

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

New/updated registrations for vaccines:
nil

7 Upcoming meetings and agendas

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

- 24–25 June 2020
- 28–29 October 2020

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

- 20–21 February 2020
- 21–22 May 2020
- 20–21 August 2020
- 12–13 November 2020

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 June and October

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

- 5–6 February 2020
- 10–11 June 2020
- 23–24 September 2020

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

- 6–8 October 2020
- 23–25 March 2021
- 5–7 October 2021
- 5–7 April 2022
- 4–6 October 2022

WHO-GACVS (https://www.who.int/vaccine_safety/committee/en/)

- 3–4 June 2020
- 2–3 December 2020
- 2–3 June 2021
- 1–2 December 2021