Centers for Disease Control and Prevention Immunization Safety Office Update

Advisory Commission on Childhood Vaccines (ACCV)
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A. Patricia Wodi, MD
Immunization Safety Office
Centers for Disease Control and Prevention (CDC)

Disclaimer

- The findings and conclusions in this presentation are those of the author and do not necessarily represent the official position of CDC

- The use of product trade names is for identification purposes only

Topics

- Presentations at June 2019 Advisory Committee on Immunization Practice meeting*

- Selected publications

*https://www.cdc.gov/vaccines/acip/meetings/downloads/agenda-archive/agenda-2019-06-508.pdf

Human Papillomavirus Vaccine

ACIP Update – Human Papillomavirus (HPV) Vaccine

Key Agenda Topics

- **9vHPV (Gardasil 9) Immunogenicity and Safety Trial in Mid-Adult Females**
  - 9vHPV is highly immunogenic and well tolerated in women aged 27-45 years
    - >99% seroconversion rate for 9 HPV types
- **Overview of Health Economic Models for HPV Vaccination of Mid-Adults**
- **Evidence to Recommendations (EtR) Framework**
- **Work Group Considerations and Proposed Policy Options**

ACIP Update – Human Papillomavirus Vaccine Recommendations

- **Catch-up vaccination through age 26 years***
  - Catch-up vaccination for persons who are not adequately vaccinated through age 26 years (harmonization of recommendation for males and females)

- **Vaccination of adults aged 27 years and older**
  - 27–45 years: HPV vaccination based on shared clinical decision making for individuals who are not adequately vaccinated
  - > 45 years: Vaccine not licensed in this age group

*Replaces wording for special populations through age 26 years such as men who have sex with men, transgender persons and people with immunocompromising conditions

Hepatitis A Vaccines

ACIP Update –Hepatitis A Vaccines

Key Agenda Topics

- **Introduction**
  - Hepatitis A outbreak in United States 2016 to present
    - Cases 20,512; Hospitalizations 11,776 (57%); Deaths 194
  - Hepatitis A infection in pregnancy
    - Associated with gestational complications but infants generally healthy

- **Hepatitis A vaccine and Pregnancy (Safety)**
  - No increased risk of maternal or infant mortality after hepatitis A vaccination in pregnancy
  - Vaccine Adverse Event Reporting System[1] : no concerning pattern of adverse events
  - Vaccine safety datalink: a potential signal for small for gestational age (SGA) births (preliminary results)

1. Moro PL, Museru OI, Niu M, et al. Reports to the Vaccine Adverse Event Reporting System after hepatitis A and hepatitis AB vaccines in pregnant women. Am J ObstetGynecol2014;210:561.e1-6.

ACIP Update – Hepatitis A Vaccine Recommendations

- **Children and Adolescents aged 2 -18 years**
  - Routinely receive hepatitis A vaccine at any age if they have not been previously vaccinated (i.e., children and adolescents are recommended for catch-up vaccination)
- **Persons with HIV**
  - All persons with HIV aged ≥1 year should be routinely vaccinated with hepatitis A vaccine

ACIP Update – ACIP Hepatitis A Updated Statements

- **Pregnant women**
  - Recommends hepatitis A vaccination for pregnant women who are identified as being at risk for hepatitis A infection during pregnancy or having a severe outcome from hepatitis A infection
  - Pregnant women who are not vaccinated against hepatitis A virus during pregnancy should be counseled concerning other methods to prevent hepatitis A infection
- **Persons with clotting-factor disorders**
  - No longer a specific risk of hepatitis A infection
  - Persons with clotting factor disorders removed from consideration as part of a high risk population for whom hepatitis A vaccination is specifically recommended
- **Full updated ACIP statement**
  - ACIP affirms the updated statement “Prevention of Hepatitis A Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices”

Meningococcal Vaccines

ACIP Update – Meningococcal B (MenB)Vaccines

Key Agenda Topics

- **Review of Immunogenicity and persistence data**
  - Work Group interpretation
    - 1-2 years following primary MenB vaccination, booster vaccination is indicated in persons who remain at increased risk
    - Antibody persistence of a MenB booster dose is likely at least 2-3 years in healthy adolescents and adults

- **GRADE*, EtR**, and policy options for Meningococcal B vaccine booster doses**

- **Proposed recommendations for use of meningococcal vaccines**

*Grade = *Grading* of Recommendations, Assessment, Development and Evaluation

**EtR = Evidence to Recommendations

ACIP Update – Meningococcal B Vaccine Recommendations

- **Persons aged ≥10 years with complement deficiency, complement inhibitor use, asplenia or who are microbiologist**
  - MenB booster dose 1 year following completion of a MenB primary series, followed by MenB booster doses every 2-3 years thereafter, for as long as increased risk remains

- **Persons aged ≥10 years determined by public health officials to be at increased risk during an outbreak**
  - One-time MenB booster dose if it has been ≥1 year since completion of a MenB primary series
  - Booster dose interval of ≥6 months may be considered by public health officials depending on the specific outbreak, vaccination strategy, and projected duration of elevated risk

- **ACIP affirms the updated ACIP statement:** ACIP "Meningococcal Vaccination: Recommendations of the Advisory Committee on Immunization Practices"

Combination Vaccines

ACIP Update – Combination Vaccines

Key Agenda Topics

- **Summary and Relevant Evidence to Recommendation Information**
  - Pediatric Hexavalent Vaccine DTaP-IPV-Hib-HepB (Vaxelis)
    - Joint venture between Merck and Sanofi Pasteur
    - FDA approval Dec. 21, 2018 ; commercially available ~ 2021
    - Licensed for 2, 4, 6-month dose, but not birth dose
    - Safety
      - Higher rate of fever compared to pentavalent, but no increase in fever-related medical events
    - Immunogenicity non-inferiority criteria met except geometric mean concentration for one of:
      - 5 pertussis antigens (FHA) post-dose 3
      - 13 pneumococcal antigens (PN6B) post-dose 3 but it rarely cases disease in US children

ACIP Update – Combination Vaccines

- DTaP-IPV-Hib-HepB (Vaxelis) should be included as an option in the Vaccines for Children (VFC) Program for the infant series at 2, 4, and 6 months of age

- Future topic: Consider if the new pediatric hexavalent vaccine (DTaP-IPV-Hib-HepB) should be preferentially recommended for the American Indian/Alaskan Native (AI/AN) population
  - In the pre-vaccine era, Hib disease occurred at younger age among AI/AN population compared to general population in the United States
  - Hib PRP-OMP*-containing vaccines (i.e. Vaxelis) achieve protective immunity in majority of infants after 1st dose
  - Preferential recommendation would require future ACIP vote

*PRP-OMP: purified polyribosylribitol phosphate (PRP) capsular material from type b strains of *H. influenzae* type b covalently bound to the outer membrane protein complex (OMPC) of *Neisseria meningitidis* serogroup *B*

Influenza Vaccines

ACIP Update – Influenza Vaccines

Key Agenda Topics

- **2018-19 U.S. Influenza Activity**
  - Severity was classified as moderate
  - Two waves of influenza A viruses of similar magnitude: influenza A(H1N1)pdm09 wave and H3N2 wave
    - Majority of H3N2 viruses belonged to the 3C.3a genetic group, antigenically distinct from the 3C.2a genetic group
- **2018-19 Influenza Vaccine Effectiveness(VE)***
  - Overall VE was ~30% against influenza illness and hospitalizations
    - Likely prevented between ~40,000 to 90,000 hospitalizations based on previous seasons' estimates
    - Reduced A(H1N1)pdm09-associated outpatient influenza illness by 44% and hospitalizations by 48%-60%
    - No significant protection against H3N2 illnesses likely due to emergence of antigenically different A(H3N2) clade 3C.3a

*VE estimates are preliminary and will be updated when final data are available

ACIP Update – Influenza Vaccines

Key Agenda Topics

- **2018-19 Influenza Vaccine Safety**
  - Vaccine Adverse Event Reporting System (VAERS):
    - Vaccines monitored: IIV3, IIV4, HD-IIV3, ccIIV4, aIIV3, RIV4, and LAIV4
      - No data mining signals for Guillain-Barré syndrome (GBS), anaphylaxis, or febrile convulsion
      - No new safety concerns detected
    - Surveillance for 2019-2020 influenza season will include enhanced monitoring[1] for
      - aIIV3
      - RIV4
      - Pregnancy
      - Anaphylaxis in persons with a history of egg allergy

[1]Includes clinical review of all reports and available medical records for the specific vaccines and outcomes and conditions specified

IIV3=trivalent inactivated influenza vaccine **IIV4**=quadrivalent inactivated influenza vaccine **HD- IIV3-**= high dose trivalent inactivated influenza vaccine **ccIIV4** = cell culture-based quadrivalent influenza vaccine **aIIV3**=adjuvanted trivalent inactivated influenza vaccine **RIV4 =** quadrivalent recombinant influenza vaccine **LAIV4** = quadrivalent live attenuated influenza vaccine

ACIP Update – Influenza Vaccines

Key Agenda Topics

- **2018-19 Influenza Vaccine Safety**
  - Vaccine Safety Datalink (VSD)/Food and Drug Administration (FDA)
    - Anaphylaxis: Statistical signals ruled out following IIV4 and ccIIV4
    - GBS after IIV3-HD
      - VSD: Statistical signal ruled out
      - FDA (preliminary): CMS data indicate that the risk, if any, is no greater than in some previous seasons and consistent with labeled risk of GBS
    - Bell's palsy: Elevated risk for Bell's palsy following ccIIV4 in 4-17 year olds (RR=3.0, 95% CI 0.31-28.8) --Based on a small number of cases and doses
    - Febrile seizure: Final self-controlled risk interval (SCRI) analysis of confirmed febrile seizure cases showed an elevated incidence rate ratio (IRR) in children aged 6-23 [IRR=2.41 (95% CI 1.12-5.18); AR=4.24] and 24-59 months [IRR=3.5 (95% CI 1.01-12.09); AR=1.8]

IIV3=trivalent inactivated influenza vaccine **IIV4**=quadrivalent inactivated influenza vaccine **HD- IIV3-**= high dose trivalent inactivated influenza vaccine **ccIIV4** = cell culture-based quadrivalent influenza vaccine **aIIV3**=adjuvanted trivalent inactivated influenza vaccine **RIV4** = quadrivalent recombinant influenza vaccine
LAIV4 = quadrivalent live attenuated influenza vaccine

ACIP Update – Influenza Vaccines

Key Agenda Topics

- **Recommended influenza vaccine strains for 2019-2020**
  - Trivalent Vaccines
    - A/Brisbane/02/2018 (H1N1)pdm09-like virus – updated
    - A/Kansas/14/2017 (H3N2)-like virus (3C.3a) – updated
    - B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage)
  - Quadrivalent Vaccines
    - Above three, plus B/Phuket/3073/2013-like virus (B/Yamagata/16/88 lineage)

- **ACIP affirms the updated statement:**

"Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices—United States, 2019–20 Influenza Season"

Pertussis Vaccines

ACIP Update – Pertussis Vaccines

Key Agenda Topics

- **Introduction**
  - FDA label change to Sanofi's Tdap product (Adacel)
    - Allows a second dose of Adacel may be administered ≥8 years after the first dose of Tdap
    - Wound management: A booster dose of Adacel may be administered if ≥5 years since previous receipt of a tetanus toxoid containing vaccine
  - No change to GSK's Tdap product (Boostrix)
  - Evidence that repeat Tdap vaccination is widespread

- **Evidence to Recommendations (EtR) Framework**

ACIP Update – Pertussis Vaccines

- **Proposed Policy Options: Questions to be addressed by ACIP**

1. Should the current recommendation that non-pregnant adults receive a single lifetime dose of Tdap with Td boosters every 10 years be changed to allow any Td-containing vaccine (Tdap or Td) to be used for the decennial Td booster?

2. Should any Td-containing vaccine (Tdap or Td) be allowed for tetanus prophylaxis in the setting of wound management?

3. Should the catch-up immunization schedule for Tdap/Td be changed for those ≥7 years of age?

Dengue Vaccine

ACIP Update – Dengue Fever

Key Agenda Topics

- **Dengue Epidemiology: estimated annual global burden**
  - 390 million infections; 96 million clinical infections
  - 500,000 hospitalizations; 20,000 deaths
  - Frequent/continuous infection risk in American Samoa, Puerto Rico, U.S. Virgin islands and some U.S.-affiliated Pacific Islands
    - Highest in 10-19 year old age group, but many cases occur in adults
  - Risk of severe dengue is greater after secondary infection

ACIP Update – Dengue Fever

Key Agenda Topics

- **Dengvaxia Phase III Clinical Trials and Long Term Follow Up**
  - FDA approval May 2019
  - Based on yellow fever 17-D backbone
  - Safety profile
    - Higher risk for severe dengue & hospitalization for dengue in seronegative subjects who receive the vaccine
      - Hazzard ratio for hospitalization 1.41
        - Cumulative incidence 1.57% in vaccinated, 1.09% in controls; attributable risk, 0.48%
  - Vaccine efficacy for seropositive subjects aged 9-16 years ~75% (60-85)
  - Vaccine is only for seropositive persons

ACIP Update – Dengue Fever

Key Agenda Topics

- **Work Group Considerations and Next Steps**
  - Should 3 doses (0,6,12 month schedule) of vaccine be administered routinely to persons aged 9-16 years with laboratory-confirmed previous dengue infection & living in endemic areas?
  - Available tests not designed or evaluated for detection of past dengue infection

Measles Outbreak

ACIP Update – Measles Outbreak

- Measles cases in 2019- United States
  - 1077 individual cases of measles confirmed in 28 states (Through 20 June2019)
  - Greatest number of cases reported in the United States since 1992 and since measles was declared eliminated in 2000
  - Measles outbreaks ongoing
    - New York State
      - Rockland County
      - Boroughs of Brooklyn and Queens
    - California
      - Butte County
    - Pennsylvania
      - Allegheny County
    - Washington
      - King County

ACIP Update – Measles Outbreak-CDC response

- Operating in Incident Management Structure (April 8)
  - >100 staff working on response
  - Update case counts and outbreak information weekly
  - Promote vaccination of travelers and prevention of importations
- Providing technical assistance to states reporting measles cases
  - Prevention and control
  - Case confirmation and genotyping
- Providing rapid, on-ground assistance when requested
  - >25 staff deployed
- Providing science-based information and targeted communications resources
- Establishing collaborations with key stakeholders in affected communities
  - Rabbis/Rabbinical organizations, healthcare providers, health centers, and summer camps
- MMWR publication: Increase in Measles Cases — United States, January 1–April 26, 2019. https://www.cdc.gov/mmwr/volumes/68/wr/mm6817e1.htm

ACIP Update – Measles Outbreak Summary

- United States remains in elimination status, although there are prolonged outbreaks in close-knit communities
- Vaccination coverage remains high, but communities with low vaccination coverage are at risk for outbreaks
- Increased global measles activity poses a risk of continuing importations

Recent Publications: Immunization Safety Office

Recent Publication

Publication	Summary
Hesse EM, Hibbs BF, Cano MV. ***Notes from the Field: Administration of expired injectable influenza vaccines reported to the Vaccine Adverse Event Reporting System - United States, July 2018-March 2019***. *MMWR* 2019 Jun 14;68(23):529-530. Available at https://www.cdc.gov/mmwr/volumes/68/wr/mm6823a3.htm?s_cid=mm6823a3_w	During the 2018-2019 flu season, VAERS received 125 reports (192 patients) following expired inactivated influenza vaccine (IIV); 169.1 million doses of seasonal flu vaccine were distributed. 70% were in high-risk groups for influenza (aged <5 yrs, >50 yrs, pregnant women). Reported adverse events were consistent with adverse events following administration of non-expired seasonal IIV, suggesting no additional safety issues associated with receipt of expired IIV.
DeStefano F, Bodenstab HM, Offit PA. **Principal controversies in vaccine safety in the United States.** *Clin Infect Dis*. 2019 Feb 12. Available at https://www.ncbi.nlm.nih.gov/pubmed/30753348	Summarized the key evidence on some of the main current U.S. vaccine safety controversies: 1) MMR vaccine and autism 2) Thimerosal, a mercury-based vaccine preservative, and the risk of neurodevelopmental disorders 3) Vaccine-induced Guillain-Barré Syndrome (GBS) 4) Vaccine-induced autoimmune diseases 5) Safety of HPV vaccine 6) Aluminum adjuvant-induced autoimmune diseases and other disorders 7) Too many vaccines given early in life predisposing children to health and developmental problems A possible small increased risk of GBS following influenza vaccination has been identified, but the magnitude of the increase is less than the risk of GBS following influenza infection. Otherwise, the biological and epidemiologic evidence does not support any of the reviewed vaccine safety concerns.

Recent Publication

Publication	Summary
Moro PL, Arana J, Marquez PL, Ng C, Barash F, Hibbs BF, Cano M. **Is there any harm in administering extra-doses of vaccine to a person? Excess doses of vaccine reported to the Vaccine Adverse Event Reporting System (VAERS), 2007-2017.** *Vaccine*. 2019 May 30. Available at https://www.ncbi.nlm.nih.gov/pubmed/31155414	More than three-fourths of reports of an excess dose of vaccine did not describe an adverse health event (AHE). Among reports where an AHE event was reported, no unexpected conditions or clustering of AEs were observed.
Edwards K, Hanquet G, Black S, Mignot E, Jankosky C, Shimabukuro T, Miller E, Nohynek H, Neels P. **Meeting report narcolepsy and pandemic influenza vaccination: What we know and what we need to know before the next pandemic? A report from the 2nd IABS meeting.** *Biologicals*. 2019 May 23. Available at https://www.ncbi.nlm.nih.gov/pubmed/31130313	Increased risk of narcolepsy was consistently observed after Pandemrix (AS03-adjuvanted) vaccine, but similar associations following Arepanrix (AS03-adjuvanted) or Focetria (MF59-adjuvanted) vaccines were not observed. Whether the differences are due to vaccine composition or other factors such as the timing of large-scale vaccination programs relative to H1N1pdm09 wild-type virus circulation in different geographic regions is not clear. Limitations of retrospective observational methodologies could also be contributing to some of the differences across studies.
Su JR, Moro PL, Ng CS, Lewis PW, Said MA, Cano MV. **Anaphylaxis after vaccination reported to the Vaccine Adverse Event Reporting System, 1990-2016.** *J Allergy Clin Immunol*. 2019 Apr;143(4):1465-1473. Available at https://www.ncbi.nlm.nih.gov/pubmed/30654049	Anaphylaxis after vaccination is rare in the United States and can occur among persons with no history of hypersensitivity. Most persons recover fully with treatment, but serious complications, including death, can occur.

Recent Publication

Publication	Summary
Klein NP, Goddard K, Lewis E, Ross P, Gee J, DeStefano F. Baxter R. **Long term risk of developing type 1 diabetes after HPV vaccination in males and females**. *Vaccine* 2019 Mar 28;37(14):1938-1944. Available at https://www.ncbi.nlm.nih.gov/pubmed/30827738	No increased risk for development of diabetes mellitus type 1 (DM1) following HPV vaccination. Study provides reassurance that during the 10-year time period after HPV vaccine was introduced, there was no substantial increased risk for DM1 following HPV vaccination.
Kochhar S, Edwards KM, Ropero Alvarez AM, Moro PL, Ortiz JR. **Introduction of new vaccines for immunization in pregnancy-Programmatic, regulatory, safety and ethical considerations**. *Vaccine* 2019 May 31;37(25):3267-3277. Available at https://www.ncbi.nlm.nih.gov/pubmed/31072733	Important pre-requisites for the successful introduction of new vaccines for immunization in pregnancy include political commitment and adequate financial resources: trained, committed and sufficient numbers of healthcare workers to deliver the vaccines; close integration of immunization programs with antenatal care and Maternal and Child Health services; adequate access to antenatal care by pregnant women in the country (especially in low and middle-income countries (LMIC)); and a high proportion of births occurring in health facilities (to ensure maternal and neonatal follow-up can be done). The framework needed to advance a vaccine program from product licensure to successful country-level implementation includes establishing and organizing evidence for anticipated vaccine program impact, developing supportive policies, and translating policies into local action.

Thank you

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

Extra Slides

Pneumococcal Vaccines

ACIP Update – Pneumococcal Vaccines

Key Agenda Topics

- **Introduction**
  - In 2014, ACIP recommended PCV13 in series with PPSV23 for adults ≥65 years old.
  - Recommendation was made with a commitment to re-evaluate this policy 4 years later and revise as needed
- **Considerations for PCV13 use among adults 65 years or older**
  - Should PCV13 be administered routinely to all immunocompetent adults aged ≥65 years in the context of indirect effects from pediatric PCV use experienced to date?
    - *Continuing* PCV13 vs *No longer* using PCV13
- **Summary of the Evidence to Recommendations (EtR) Framework**
- **Proposed policy options**

PCV13 = 13-valent pneumococcal conjugate vaccine PPSV23= 23-valent pneumococcal polysaccharide vaccine

ACIP Update – Pneumococcal Vaccines Recommendations for adults ≥ 65 years

- **Recommendations for PCV13**
  - Shared clinical decision making for adults ≥65 years who do not have an immunocompromising condition and who have not previously received PCV13

- **Recommendations for PPSV23**
  - All adults ≥ 65 years should receive a dose of PPSV23

Recombinant Zoster Vaccine

ACIP Update – Recombinant Zoster Vaccine (RZV)

Key Agenda Topics

- **Update: Safety Monitoring and Surveillance for Recombinant Zoster Vaccine (RZV)**
  - Vaccine Adverse Event Reporting System: No concerning patterns or findings of disproportional reporting for adverse health events
    - Generally consistent with the safety profile observed in pre-licensure clinical trials
    - Serious adverse events were rarely reported (2.7% of reports; similar to other vaccines given in same age group)
    - No empirical Bayesian data mining findings for any RZV-adverse event pairings except for "**Product administered to patient of inappropriate age**"

ACIP Update – Recombinant Zoster Vaccine (RZV)

Key Agenda Topics

- **Update: Safety Monitoring and Surveillance for Recombinant Zoster Vaccine (RZV)**
  - Vaccine Safety Datalink: Statistical signals detected in rapid cycle analysis using automated ICD-10/9 analysis for
    - Bell's palsy
      - » Not consistent across comparators
      - » Ongoing chart review/confirmation indicates 15 of 36 presumptive cases confirmed in 1-42 day risk window
    - Guillain-Barré syndrome (GBS)
      - » Included chart review of all potential GBS cases identified by ICD codes in current RZV and historical ZVL recipients
        - Confirmed cases RR=3.5 (95% CI 0.3, 47.8) based on 2 RZV and 2 ZVL confirmed cases
        - If the 'unconfirmed' GBS case in the ZVL comparator group is included as a true incident case, RR changes to RR=2.3 (95% CI 0.2, 20.2)

ACIP Update – Recombinant Zoster Vaccine (RZV)

Key Agenda Topics

- **Update: Safety Monitoring and Surveillance for Recombinant Zoster Vaccine (RZV)**
  - FDA Medicare data:
    - Elevated rate ratio for **GBS** detected in the FDA cohort analysis using automated ICD-10/9 analysis
      - » Rate ratio (95% CI) adjusted for age and sex: 2.34 (1.01, 5.41)
      - » Attributable risk (95% CI) (per million doses) adjusted for age and sex: 6.54 (-0.11, 13.9)
    - Additional analysis and chart review/confirmation pending

Post-licensure RZV Next Steps

- Bell's palsy
  - CDC will continue to monitor Bell's palsy in VSD
- GBS
  - Initial safety monitoring data so far are insufficient to conclude that a safety problem exists, but further evaluation and continued vigilance are warranted
    - CDC will continue to monitor GBS in VSD
    - FDA will continue charts review of GBS cases and will consider doing a chart confirmed self-controlled analysis

Rabies Vaccine

ACIP Update – Rabies Vaccine Work Group Purposes and Goals

- To provide a forum for discussion to update the 2008 and 2010 ACIP recommendations on human rabies prevention

- Members have been reviewing new and existing data and providing individual input on topics that may inform changes to recommendations

- Updated ACIP Guidelines expected to be completed in 2020 or 2021