Centers for Disease Control and Prevention Immunization Safety Office Update

Advisory Commission on Childhood Vaccines (ACCV)
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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 October 2019 Advisory Committee on Immunization Practice meeting*

- Selected publications

*https://www.cdc.gov/vaccines/acip/meetings/downloads/agenda-archive/agenda-2019-10-508.pdf

Pertussis Vaccines

ACIP Update – Pertussis-Containing Vaccines

- **Background**
  - FDA label change
    - Sanofi's Tdap product (Adacel)
      - 2nd dose of Adacel may be administered ≥8 years after the first dose of Tdap
      - Wound management: 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 but limited data on safety of multiple doses

ACIP Update – Pertussis-Containing Vaccines

- **Safety of closely spaced (≤ 12months) Tdap vaccines in the catch-up immunization schedule published studies)**

Studies	Design	Setting	N	Findings
Theeten H, et al. Current Medical Research and Opinion. 2007;23:11,2729-2739	RCT comparing: -Tdap x 3 -Tdap-IPV, Td, Td -Td x 3	Europe	460	No differences in reactogenicity between Tdap vs Td
Fortner K, et al. Reactogenicity and immunogenicity of Tdap in pregnant and non-pregnant women. Vaccine. 2018 Oct 8;36(42):6354-6360	Cohort retrospective no comparison	USA	8[1]	No severe local or systemic reactions

RCT: Randomized clinical trial; [1] Number with closely spaced Tdap (≤ 12 months)

ACIP Update – Pertussis-Containing Vaccines

- **Safety of closely spaced (≤ 12months) Tdap vaccines in the catch-up immunization schedule (unpublished studies)**
  - Vaccine Adverse Event Reporting System (VAERS) review
    - 88 reports of closely spaced doses
    - 21 (24%) described an adverse event; local reactions were most commonly reported (n=8)
  - Vaccine Safety Datalink (VSD)
    - Among subjects who received a Tdap dose ≤12 months compared to Td, no increased rates of adverse events were observed
    - Among 187 women in the VSD who received multiple Tdap doses in the same pregnancy, one presented with limb pain and limb swelling 7 days after vaccination (unclear if related)

Conclusions

- Published data on closely spaced (≤12 months) Tdap doses shows no increase in adverse events when Tdap or Td was administered as a second or third dose
  - Regimens similar to the current and proposed catch-up schedule did not show differences in reactogenicity
- Unpublished data of closely spaced Tdap doses shows no unusual or increased reporting of any adverse event
- While safety data on multiple Tdap doses is limited, review of published and unpublished safety data is reassuring

ACIP Update – Pertussis-Containing Vaccines Recommendations*

- **Decennial Td booster**
  - To ensure continued protection against tetanus and diphtheria, booster doses of either **Td or Tdap** should be administered every 10 years throughout life

- **Tetanus prophylaxis in the setting of wound prophylaxis**
  - For nonpregnant persons with documentation of previous vaccination with Tdap, **either Td or Tdap** should be used if a tetanus toxoid–containing vaccine is indicated

- Additional doses of the catch-up schedule for persons ≥ 7 years
  - **Either Td or Tdap** should be used

* All recommendations approved by ACIP are provisional until they are approved by the CDC director and published in *MMWR*.

Childhood Immunization Schedule

ACIP Update – Childhood Immunization Schedules

- **Introduction**
  - ACIP approval of the proposed schedules is required prior to publication in *MMWR* Feb 2020
  - AAP[1], AAFP[2], ACOG[3], and ACNM[4] also approve the proposed schedules prior to the 2020 publications
  - Annual schedules reflect recommendations already approved by ACIP
    - New policies are not established in the proposed schedules

1. AAP - American Academy of Pediatrics
2. AAFP - American Academy of Family Physicians
3. ACOG - American College of Obstetricians and Gynecologists
4. ACNM - American College of Nurse Midwives

ACIP Update - 2020 Child and Adolescent Immunization Schedule Update

2020 Child and Adolescent Schedule revisions

- Influenza vaccination (June 2019)
  - 2019–20 influenza vaccine recommendations
- Hepatitis A vaccination (June 2019)
  - Recommendation for routine catch-up vaccination for all children and adolescents aged 2 through 18 years
- Meningococcal B vaccination (June 2019)
  - Recommendation for booster doses for those ≥ 10 years and at increased risk of infection
- Tdap vaccination (October 2019)
  - Vaccination of persons who received Tdap at 7–10 years of age
- Edits to tables and notes of other vaccines as needed for clarity

Influenza Vaccines

ACIP Update – Influenza Vaccines

- **Influenza surveillance update**
  - Influenza activity remains low in the United States overall
  - Numbers are small, but so far, influenza A(H3N2) viruses are predominant in the US overall but this varies by region
    - Too early to tell what viruses will be predominant for the season
  - While the 2 of the 4 vaccine components were updated for the Southern Hemisphere, the components selected for the 2019-20 Northern Hemisphere vaccine, at this time, look appropriate for our season

ACIP Update-Influenza Vaccines for Older Adults

- Planned Systematic Review or Meta-analysis to answer this question
  - Do the relative benefits and harms of HD-IIV, aIIV, and RIV as compared with one another and with other influenza vaccines favor the use of these vaccines over others for persons aged 65 years and older?
    - Outcomes to be evaluated:
      - Efficacy/effectiveness
      - Safety
        - » Systemic and injection site adverse events
        - » Serious adverse events
        - » Guillain-Barré syndrome
        - » Severe hypersensitivity or anaphylaxis

HD- IIV-= high dose inactivated influenza vaccine **aIIV3**=adjuvanted trivalent inactivated influenza vaccine **RIV** = recombinant influenza vaccine

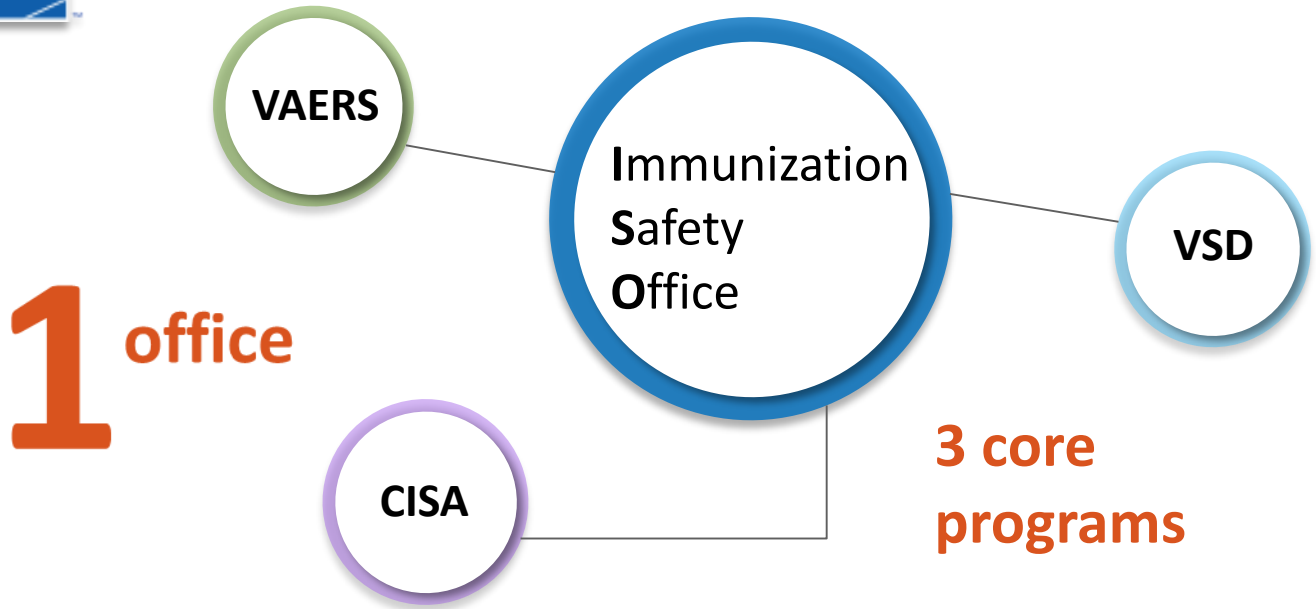
Measles Outbreak

ACIP Update-Measles Outbreak in New York 2018-19

- Causes
  - Global increase
  - Importation of Cases
  - Vaccine hesitancy and targeted anti-vaccine activity
- Most cases in Orthodox Jewish Communities (has no religious prohibition again vaccination)
  - No deaths or encephalitis
  - 28 cases of pneumonia
  - 28 hospitalizations
- Lessons learned
  - Need for vigilance regarding vaccine hesitancy and partnerships
  - June 2019: law passed to remove non-medical exemptions
  - School audits: focus on school and day care compliance

Overview of CDC Vaccine Safety Monitoring Systems

CDC vaccine safety monitoring



1 office

3 core programs

VAERS Vaccine Adverse Event Reporting System
CISA Clinical Immunization Safety Assessment Project
VSD Vaccine Safety Datalink

Communication and response to inquiries is cross-cutting function

ACIP Update-Overview of CDC's Vaccine Safety Monitoring Systems

- Vaccine Adverse Event Reporting System (VAERS)
  - CDC and FDA collaboration
  - Frontline spontaneous reporting system to detect potential safety signals

- Vaccine Safety Datalink (VSD)
  - CDC and 8 integrated health care systems collaboration
  - Large linked database system used for active surveillance and research with >12 million members

- Clinical Immunization Safety Assessment (CISA) Project
  - CDC and 7 academic centers collaboration
  - Expert collaboration that conducts individual clinical vaccine safety assessments and clinical research

Recent Publications

Recent Publication

- Moro PL, Haber P, McNeil MM. **Challenges in evaluating post-licensure vaccine safety: observations from the Centers for Disease Control and Prevention.** *Expert Rev Vaccines*. 2019 Oct;18(10):1091-1101.
  - Summary - We discuss selected challenges for conducting pharmacovigilance and epidemiologic studies of AEs after vaccination in the United States using the post-licensure safety surveillance infrastructure of the Centers for Disease Control and Prevention (CDC). The availability of specific post-licensure surveillance systems to monitor and study AEs after vaccination, such as the Vaccine Adverse Event Reporting System, the Vaccine Safety Datalink, and the Clinical Immunization Safety Assessment Project, each with its unique set of strengths and limitations, provide a harmonized and supportive approach to meet several of these barriers.
  - Available at https://www.ncbi.nlm.nih.gov/pubmed/31580725

Recent Publication

- McNeil MM, Paradowska-Stankiewicz I, Miller ER, Marquez PL, Seshadri S, Collins Jr LC, Cano MV. **Adverse events following adenovirus type 4 and type 7 vaccine, live, oral in the Vaccine Adverse Event Reporting System (VAERS), United States, October 2011–July 2018**. Vaccine 2019 Sep 20.
  - Summary-In March 2011, FDA licensed adenovirus type 4 and type 7 vaccine, live, oral (Barr Labs, Inc.) for use in military personnel 17 through 50 years of age. We investigated reports in VAERS October 2011 through July 2018. During the analytic period, VAERS received 100 reports following adenovirus vaccination; 39 (39%) were classified as serious and one death was reported. The most frequently reported serious AEs were Guillain Barré syndrome (GBS) (n = 12) and anaphylaxis (n = 8). Reports documented concurrent receipt of multiple other vaccines (95%) and penicillin G (IM Pen G) or other antibiotics. Conclusions: The reporting rate for serious AEs was higher than with other vaccines administered in the comparison military recruit population (39% vs 18%); however, we identified no unexpected or concerning pattern of adenovirus vaccine AEs. Co-administration of vaccines and IM Pen G may have contributed to the GBS and anaphylaxis outcomes.
  - Available at https://www.ncbi.nlm.nih.gov/pubmed/31548014

Recent Publication

- Christianson MS, Wodi P, Talaat K, Halsey N. **Primary ovarian insufficiency and human papilloma virus vaccines: A review of the current evidence**. *Am J Obstet Gynecol*. 2019 Aug 31.
  - Summary: Human papilloma virus is the primary causative agent for cervical cancer, and vaccination is the primary means of preventing anogenital cancers caused by human papilloma virus infection. Despite the availability for over a decade, coverage rates lag behind the other vaccines. Public concerns regarding safety of the vaccines have been identified as an important barrier to vaccination, including that the vaccine causes primary ovarian insufficiency. Health care providers should address concerns by acknowledging the case reports but noting the lack of association found in a recently published epidemiologic study of approximately 60,000 females. Current evidence is insufficient to suggest or support a causal relationship between human papilloma virus vaccination and primary ovarian insufficiency.
  - Available at https://www.ncbi.nlm.nih.gov/pubmed/31479634

Recent Publication

- Grohskopf LA, Alyanak E, Broder KR, Walter EB, Fry AM, Jernigan DB. **Prevention and control of seasonal influenza with vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2019–20 Influenza Season.** Recommendations and Reports. *MMWR*. August 23, 2019 / 68(3);1–21. (Influenza ACIP MMWR)
  - Summary
    - This report updates the 2018–19 recommendations of the Advisory Committee on Immunization Practices (ACIP) regarding the use of seasonal influenza vaccines in the United States (MMWR Recomm Rep 2018;67[No. RR-3]). Routine annual influenza vaccination is recommended for all persons aged ≥6 months who do not have contraindications. A licensed, recommended, and age-appropriate vaccine should be used. Inactivated influenza vaccines (IIVs), recombinant influenza vaccine (RIV), and live attenuated influenza vaccine (LAIV) are expected to be available for the 2019–20 season. Standard-dose, unadjuvanted, inactivated influenza vaccines will be available in quadrivalent formulations (IIV4s). High-dose (HD-IIV3) and adjuvanted (aIIV3) inactivated influenza vaccines will be available in trivalent formulations. Recombinant (RIV4) and live attenuated influenza vaccine (LAIV4) will be available in quadrivalent formulations. Recombinant (RIV4) and live attenuated influenza vaccine (LAIV4) will be available in quadrivalent formulations.
  - Available at https://www.cdc.gov/mmwr/volumes/68/rr/rr6803a1.htm

Recent Publication

- Donahue JG, Kieke BA, King JP, Mascola MA, Shimabukuro TT, DeStefano F, Hanson KE, McClure DL, Olaiya O, Glanz JM, Hechter RC, Irving SA, Jackson LA, Klein NP, Naleway AL, Weintraub ES, Belongia EA. **Inactivated influenza vaccine and spontaneous abortion in the Vaccine Safety Datalink in 2012-13, 2013-14, and 2014-15**. *Vaccine*. 2019 Sep 17.
  - Conclusions: During these seasons we found no association between IIV and SAB, including among women vaccinated in the previous season. These findings lend support to current recommendations for influenza vaccination at any time during pregnancy, including the first trimester.
  - Available at https://www.ncbi.nlm.nih.gov/pubmed/?term=Inactivated+influenza+vaccine+and+spontaneous+abortion+in+the+Vaccine+Safety+Datalink+in+2012-13%2C+2013-14%2C+and+2014-15

Recent Publication

- Groom HC, Smith N, Irving SA, Koppolu P, Vazquez-Benitez G, Kharbanda EO, Daley MF, Donahue JG, Getahun D, Jackson LA, Klein NP, McCarthy NL, Nordin JD, Panagiotakopoulos L, Naleway AL. **Uptake and safety of hepatitis A vaccination during pregnancy: A Vaccine Safety Datalink study.** *Vaccine* Volume 37, Issue 44, 16 October 2019, Pages 6648-6655.
  - Conclusions: The rate of maternal HepA vaccination was low and rarely due to documented risk factors for vaccination. HepA vaccination during pregnancy was not associated with an increased risk for a range of adverse events examined among pregnancies resulting in live births, but an identified association between maternal HepA and SGA infant outcomes, while likely due to unmeasured confounding, warrants further exploration.
  - Available at https://www.sciencedirect.com/science/article/pii/S0264410X19312526

Thank you

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

Extra Slides

Updates in ACIP Recommendations: 2020 Adult Immunization Schedule

- Hepatitis A vaccination
  - Living with HIV as an indication
- HPV vaccination
  - 2 or 3 doses for men through age 26 depending on age at initial vaccination
  - Shared clinical decision-making for persons aged 27–45 years
- MMR vaccination in HCW
- Pneumococcal vaccination
  - Shared clinical decision-making for immunocompetent persons aged ≥65 years
- Meningococcal B vaccination
  - Shared clinical decision-making for persons aged 19–23 years
- Tdap vaccination
  - Tdap may be used any time Td is indicated
- Varicella vaccination
  - Indications for adults with HIV infection

ACIP Update-Influenza Vaccines

- Quadrivalent Influenza Vaccine-High Dose (QIV-HD) Phase 3 Safety and Immunogenicity Study*
  - Evaluated the safety and immunogenicity of QIV-HD as compared to TIV-HD
  - The safety component evaluated 1777 QIV-HD recipients compared to 893 TIV-HD recipients
  - Results
    - While higher percentages for some solicited reactions were observed for QIV-HD, the overall reactogenicity profile was comparable to TIV-HD with similar rates of unsolicited events, AEs leading to study discontinuation, SAEs, fatal SAEs, and AEs of special interest.
    - QIV-HD was non-inferior to TIV-HD by GMTs and seroconversion rates for all 4 strains.
    - QIV-HD induced an immune response superior to that induced by the TIV-HD that did not contain the corresponding B strain.

*Presented by Sanofi Pasteur

ACIP Update-Rabies

- Rabies in humans
  - Nearly always fatal after onset of clinical signs
  - Transmitted from infected mammals by bite, scratch, or exposure to saliva or neural tissue
  - Not transmitted by exposures to blood, urine, or feces of infected animals
  - Incubation period weeks to months
  - ~2-4 US cases per year
- Prevention of human rabies
  - Primary prevention
    - Avoiding animal exposures, vaccinating domestic and wild animals
  - Secondary prevention
    - Pre-exposure prophylaxis (PrEP)
      - Vaccine series
    - Post-exposure prophylaxis (PEP)
      - Washing wound with soap and water, rabies immune globulin, vaccine series
  - 50,000 people receive rabies PEP/year in U.S. & ~5000 animals test positive for rabies/year

ACIP Update-Rabies Vaccines and Human Immunoglobulins Licensed in U.S.

Biologic	Product Name	Manufacturer	Licensed for Administration
Human diploid cell vaccine (HDCV)	Imovax	Sanofi Pasteur	Intramuscularly
Purified chick embryo cell vaccine (PCECV)	RabAvert	GlaxoSmithKline (In future: Bavarian Nordic)	Intramuscularly

Human immune globulin	Imogam®	Sanofi Pasteur	Intramuscularly and Infiltrated around wound
	Kedrab™	Biopharma and Kamada Ltd	Intramuscularly and Infiltrated around wound
	HyperRab™ S/D and HyperRab	Grifols	Intramuscularly and Infiltrated around wound

ACIP Update -Rabies Pre-exposure Prophylaxis (PrEP) Schedule and Serologic Monitoring of High-risk Populations

- Status quo
  - 3-dose, 3-4 week schedule [0,7, 21 or 28]
  - Serological monitoring and boosters based on risk category
- Should a 2-dose, 1-week schedule [0,7] for rabies PrEP be recommended?
  - Recommended routes of administration
  - Special populations
    - High risk categories: booster/serological monitoring?
    - Immunocompromised: alternate schedules/serological monitoring?
- All rabies vaccines are FDA approved as 3-dose series for PreEP

ACIP Update- Ebola Outbreak, Democratic Republic of Congo

- Ongoing outbreak of Ebola virus disease (EVD) in North Kivu Province in Eastern Democratic Republic of Congo
- Case Counts as of September 29, 2019
  - >3000 cases; >2000 deaths
  - 165 healthcare workers infected
- EVD is a deadly disease caused by infection with one of 6 viruses within the genus *Ebolavirus*, family *Filoviridae*
  - Ebola virus (species *Zaire ebolavirus*) responsible for the current outbreak, untreated mortality rate of 70-90%
  - Natural reservoir unknown, likely bats
  - Person to person transmission, present in all body fluids including from dead bodies
  - Within one year of discharge, Ebola survivors have 5-fold greater mortality than the general population (may be due to renal disease)

ACIP Update- Ebola Virus Disease in the United States

- 11 individuals treated for EVD in the United States
  - All associated with 2014-2016 West Africa EVD outbreak
  - 2/11 (18%) died
- 1 imported case of EVD generated 2 secondary cases in the U.S.
  - Both secondary cases were nurses
- Populations at Risk for EVD in the United States
  - Laboratory personnel who directly handle cultures/diagnostic samples/animals contaminated or infected with replication-competent Ebola virus
  - Healthcare workers at U.S. Special Pathogen Treatment Centers caring for an EVD patient
  - Personnel responding to EVD outbreaks

ACIP Update- Ebola Vaccine

- Recombinant Vesicular Stomatitis Virus-Based Ebola Virus Vaccine (rVSVΔG-ZEBOV-GP)
  - Live-attenuated recombinant vesicular stomatitis virus vaccine
  - Initially developed by Public Health Agency Canada and New Link Genetics
  - Merck currently holds intellectual rights
  - Phase 1,2,3 clinical trials include >16,000 subjects
- WG Interpretation of MERCK Data
  - Encouraging evidence for effectiveness in prevention of EVD when administered in an outbreak setting using a ring-vaccination strategy
  - Acceptable safety profile
  - Arthritis was an adverse event in a subset of study participants (Europe, U.S.)
  - No known immune correlate for protection
  - EBOV-GP specific IgG antibodies can persist in vaccinees up to 24 months

ACIP Update- Ebola Vaccine- (rVSVΔG-ZEBOV-GP, LIVE ATTENUATED) V920 Overall Safety Conclusions to Date*

- Safety data in healthy, non-pregnant adults suggest an acceptable safety profile that in the context of demonstrated efficacy supports a positive benefit-risk ratio
  - Is generally well tolerated in healthy, non-pregnant subjects 18 years of age and older
  - Few vaccine-related serious adverse events reported to date
  - Injection-site reactions very common; generally mild to moderate in intensity and of short duration
  - Systemic AEs reported more commonly in vaccinated subjects than placebo/comparator subjects include: headache, pyrexia, fatigue, myalgia, arthralgia, arthritis, chills, sweats (hyperhidrosis), nausea, abdominal pain, and rash
  - Majority of joint events were mild to moderate intensity and resolved in days (arthralgia) to weeks (arthritis), however a few subjects reported arthritis of prolonged duration and/or recurrences/sequelae
  - Skin and mucosal-related AEs including rash (with and without vesicles) and mouth ulcers have been observed, generally mild to moderate intensity and short duration
  - Vaccine virus shedding not frequent in adults, more frequent in children; secondary transmission not yet evaluated

*Data presented by Merck

ACIP Update- Ebola Vaccine

- Vaccine Safety Discussion Points
  - Virus dissemination and replication (skin, joints) can occur and persist for up to 2-3 weeks after vaccination
    - Seeding of rVSV-ZEBOV into joints as demonstrated by detection of rVSV DNA in synovial fluid
    - Replicating rVSV-ZEBOV recovered from skin vesicles (culture)
  - Pathophysiology of chimeric rVSV-ZEBOV vaccine may include features attributable to both its VSV and ZEBOV glycoprotein components; may play a role in the development of arthralgia/arthritis
- Vote on policy options, pending vaccine licensure, February 2020
  - Potential for an emergency meeting in the event the vaccine is not licensed by February 2020