MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)

SEPTEMBER 18-19, 2025
MEETING SUMMARY

Trade names are used for identification purposes only and do not indicate endorsement.

THURSDAY: SEPTEMBER 18, 2025

WELCOME AND ROLL CALL

Call to Order/Roll Call

Dr. Mina Zadeh, ACIP Executive Secretary, CDC, convened the meeting at 10:00 a.m. on September 18, 2025, and welcomed participants to the September 18–19 session of the Advisory Committee on Immunization Practices (ACIP). She provided general logistical information and noted that presentation slides were available on the ACIP website. Dr. Zadeh reviewed the public comment process, explaining that two oral comment sessions were scheduled, with 19 speakers selected in advance through a blinded lottery, and that written comments were accepted through regulations.gov (Docket No. CDC-2025-0454). She reaffirmed ACIP's commitment to transparency and reviewed conflict of interest policies, noting that members must disclose relevant conflicts and may receive limited waivers for activities that enhance expertise but may not vote on related matters.

Dr. Zadeh then conducted the roll call and introduced five new ACIP members appointed for the September 2025 meeting: Dr. Catherine M. Stein, Dr. Evelyn Griffin, Dr. Hilary Blackburn, Dr. Kirk Milhoan, and Dr. Raymond Pollak. A complete list of Members, Ex Officio members, and Liaison Representatives is provided in the appendices at the end of this summary document. While no conflicts of interest were identified for the first day of the meeting, Dr. Robert Malone abstained from the MMRV votes due to existing legal agreements.

UPDATE ON WORK GROUPS

Dr. Kulldorff provided an update on the current work groups, noting that several are actively engaged in ongoing scientific discussions and analyses, with some scheduled to present their deliberations during this session. He announced the formation of two new work groups: one focused on vaccines in pregnant women and another on the childhood and adolescent vaccine schedule.

He explained that most existing work groups focus on individual vaccines or related vaccine groups. The new group will examine interaction effects and optimal sequencing within the broader vaccine schedule. Dr. Kulldorff emphasized the importance of careful consideration when evaluating vaccines during pregnancy due to potential risks, such as birth defects. He concluded by noting that findings from these new work groups will be presented at future ACIP meetings.

MEASLES, MUMPS, RUBELLA, AND VARICELLA (MMRV) VACCINE

Introduction
Dr. Martin Kulldorff (ACIP Chair)

Dr. Martin Kulldorff, Chair of the ACIP, opened the session by introducing the MMRV (measles, mumps, rubella, varicella) vaccine. He noted that the vaccine combines protection against four diseases in a single injection, developed to replace two separate shots (MMR and varicella), thereby reducing the number of needles children receive.

Note: Text enclosed in [brackets] was added following the meeting, per the presenter's request.

Background on MMRV

Dr. Arjun Srinivasan (CDC/NCIRD)

Dr. Arjun Srinivasan (CDC/NCIRD) provided background information on the measles, mumps, rubella, and varicella (MMRV) vaccine. He reviewed the significant health burden of these diseases in the United States (U.S.) before vaccine introduction. During the 1964 to 1965 rubella epidemic, approximately 11,000 pregnant women lost their babies, 2,100 newborns died, and 20,000 were born with congenital rubella syndrome, which can cause deafness, heart defects, and developmental delays. Before the measles vaccine, an estimated 48,000 hospitalizations and 400 to 500 deaths occurred each year due to measles. Mumps was the leading cause of viral encephalitis and sudden-onset deafness before the introduction of vaccination. In the early 1990s, varicella caused between 10,500 and 13,500 hospitalizations annually, along with 100 to 150 deaths.

The introduction of vaccines to protect against these diseases, in the form of monovalent vaccines and combination vaccines such as MMR (measles, mumps, rubella) and MMRV (measles, mumps, rubella, varicella), coupled with achieving and maintaining coverage rates above 90%, led to dramatic reductions in disease burden in the U.S. These efforts resulted in the elimination of endemic measles in 2000, elimination of endemic rubella in 2004, a 99% decline in mump cases by the early 2000s, and a 97% decline in varicella incidence by 2019.

In the U.S., two options are available for measles, mumps, rubella, and varicella vaccination: the combination MMRV vaccine or MMR plus varicella vaccine. The routine schedule consists of two doses, administered at 12–15 months and 4–6 years. The MMRV vaccine available in the US, ProQuad, manufactured by Merck, was licensed by the FDA in September 2005 based on the non-inferior immunogenicity of its components compared with the simultaneous administration of the MMR and varicella vaccines. Efficacy of the individual components had already been established in clinical studies of the monovalent vaccines. At the time of MMRV licensure, disease burden in the U.S. was too low to perform efficacy-based clinical trials for the MMRV vaccine, so immunobridging trials were used to support approval. [Of note, immunobridging trials is an established approach for the development of vaccines.]

Immunogenicity after the first dose of MMRV was compared with that of MMR plus varicella vaccine in children aged 12–23 months in four randomized clinical trials. A total of 5,446 children received MMRV and 238 received MMR plus varicella at separate injection sites. In these studies, seroconversion rates and geometric mean titers were similar between groups and met the pre-established criteria for non-inferiority. Immunogenicity after the second dose in children aged 4–6 years was assessed in one randomized clinical trial, where 399 children received MMRV, 205 received MMR plus placebo, and 195 received MMR plus varicella. The findings also met the pre-established criteria for non-inferiority. As noted in the 2008 and 2009 reviews by the ACIP Vaccine Work Group, safety after MMRV was compared with MMR plus varicella. Based on the demonstrated non-inferior immunogenicity, vaccine effectiveness was assumed to be equal.

Upon licensure in September 2005 for children aged 12 months through 12 years, MMRV was preferred over the separate administration of MMR and varicella vaccines, consistent with the ACIP's preference at the time for combination vaccines. In February 2008, preliminary post-licensure safety findings from two studies identified an increased risk of febrile seizures after the first dose of MMRV, leading ACIP to remove its preference for MMRV over separate administration of MMR and varicella for both the first and second doses. After further review of safety data, consideration of the benefits of one fewer injection with MMRV, analysis of febrile

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seizure epidemiology, input from parents and providers, and consultation with ethics experts, the ACIP issued updated recommendations in June 2009.

These recommendations remain current and state that for the first dose of measles, mumps, rubella, and varicella vaccination at age 12–47 months, either MMR plus varicella or MMRV may be used. Providers who consider administering MMRV should discuss the benefits and risks of both options with parents and caregivers. At the time of publication, CDC implementation guidance recommended that, unless a parent or caregiver specifically preferred MMRV, the first dose in this age group should be administered as separate MMR and varicella vaccines. For the first dose at age 48 months or older and for the second dose at any age through 12 years, MMRV is generally preferred over separate administration of MMR and varicella vaccines.

No post-licensure vaccine effectiveness estimates are available for MMRV used in the U.S., as measles and rubella have been eliminated, and mumps and varicella remain at very low levels. There are not enough cases or outbreaks among children in the U.S. to assess vaccine effectiveness. However, those vaccinated with either MMRV or MMR plus varicella continue to have very low rates of measles, mumps, rubella, and varicella. To date, CDC has received no reports suggesting lower effectiveness of MMRV compared with the separate component vaccines, consistent with the immunogenicity results observed in clinical trials.

In terms of utilization, MMRV accounts for 15% of first-dose measles, mumps, rubella, and varicella vaccination among children aged 19–35 months. In most states, the use of MMRV for the first dose ranges from about 10% to under 20%, based on the first and third quartiles. Among children aged 4–6 years, MMRV accounts for 75% of second-dose vaccination.

Dr. Srinivasan concluded that the MMRV vaccine is one of two options for vaccination of U.S. children against measles, mumps, rubella, and varicella. As ACIP assessed in 2008 and 2009, given the balance of risks and benefits of a first dose of MMRV compared with a first dose of MMR plus varicella, and the importance of individual values and preferences in weighing these risks and benefits, maximizing choice remains an important ethical principle. Decisions should be made on a case-by-case basis by providers, parents, or caregivers. The two vaccination options, MMRV or separate injections of MMR and varicella, are considered equivalent in terms of protection. Under current recommendations, most MMRV use in the U.S. is among children aged 4–6 years for the second dose. Overall, vaccination for measles, mumps, rubella, and varicella has resulted in a reduction of at least 97% in all four diseases compared to the pre-vaccine era.

Discussion

Dr. Milhoan requested clarification on the adjuvant content, specifically comparing the amount in the MMRV vaccine with that of administering MMR and varicella separately, and whether the adjuvant is similar or different between these options.
Dr. Oliver, NCIRD SME, clarified that neither the MMRV vaccine nor the separately administered MMR plus varicella vaccines contain an adjuvant.

Dr. Hibbeln inquired about the overall risk-benefit balance, noting that the benefits were described extensively and that febrile seizures were identified as a potential risk. He requested an assessment of the magnitude of harm from febrile seizures and other side effects in relation to the benefits at both the individual and population levels.

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Dr. Srinivasan stated that Dr. Su would present the risk profile in the following presentation.

Dr. Malone disclosed that, due to his prior service as an expert witness in litigation involving vaccines, which granted him access to internal manufacturer communications under a legal agreement, he is bound not to conduct research on or offer opinions about these products. He clarified that he will not vote on this topic and has no opinion to provide due to the pre-existing legal agreement.

Dr. Pebsworth requested clarification on the varicella antigen amount in the two vaccination options: MMRV versus separate MMR plus varicella, and whether the amounts differ.

Dr. Marin, NCIRD SME, clarified that the measles, mumps, and rubella components are the same in MMR and MMRV. The varicella component in MMRV utilizes the same virus strain as the single-antigen varicella vaccine, but at a higher potency, approximately 3.99 log10 PFU, compared to about 3.13 log10 PFU in the single-antigen product, or roughly sevenfold higher. The viruses themselves are identical across products; the difference is potency.

Dr. Levi asked whether there is a biological or clinical rationale for the higher varicella antigen amount in MMRV compared with separate administration of MMR plus varicella, and why more is needed when included in the combination vaccine.

Dr. Marin explained that initial manufacturer trials using the same varicella potency as the single-antigen vaccine within MMRV produced a suboptimal immunologic response to the varicella component. Manufacturers then tested higher varicella potencies and selected the current formulation as the best balance of immunogenicity and adverse events. Evidence reviewed in 2008–2009 suggested potential interference between the measles and varicella viruses when combined in the same vaccine, resulting in a stronger measles response (with more fever and a measles-like rash) and a weaker varicella response than with a single-antigen varicella vaccine. Increasing the varicella potency in MMRV was intended to achieve an immune response comparable to that of the single-antigen varicella vaccine.

Dr. Levi asked whether there is a clearly understood biological mechanism that explains why different vaccine formulations and combinations produce different immune responses, beyond the outcomes observed.

Dr. Kulldorff shared that the manufacturer will provide more information on this topic later in the meeting.

Dr. Blackburn requested clarification on immunogenicity following the first dose of the MMR vaccine. She noted that most children develop protective antibodies after the initial dose and asked for the scientific basis for recommending a routine second dose. She wondered whether the second dose primarily addresses primary vaccine failure, waning immunity, or both, and whether antibody titers could be used to verify response after the first dose, rather than universally administering a second dose.

Dr. Oliver stated that antibody titers are one component of the protective response and are higher after two doses. She noted that the second dose, particularly for measles, helps identify and protect children who did not mount a protective response to the first dose, addressing primary vaccine failure. Two doses are recommended because this schedule has been used in many efficacy studies and provides additional overall protection.

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Dr. Blackburn requested percentages.

Dr. Oliver referenced slide 15 in the presentation, which showed seropositivity rates, percent fold rise in antibody titers, and geometric mean titers across multiple doses for ProQuad (MMRV), with MMR plus Varivax shown at the bottom of each group as the separate-vaccine comparator.

Dr. Milhoan inquired whether data are available on the serologic response after the primary first dose, noting that the presented results reflect responses after the second dose, and requested seroconversion or seropositivity data following the first dose.

Dr. Oliver shared that the data can be found on slide 13.

Dr. Meissner emphasized that while recent attention has focused on measles vaccination, rubella vaccination is equally critical. He noted that the last rubella pandemic in the U.S. occurred in 1964–1965, resulting in approximately 11,000 fetal deaths and 20,000 infants born with congenital rubella syndrome, a severe condition associated with congenital heart disease, developmental delay, and eye problems. He added that in 1969, Dr. Stanley Plotkin and colleagues at the Wistar Institute developed the rubella vaccine, which has been highly effective. In recent years, the U.S. has typically seen fewer than five cases of congenital rubella annually, primarily among women born in countries without rubella vaccination programs. He underscored the importance of ensuring every child is vaccinated against measles, mumps, rubella, and varicella.

Dr. Meissner thanked the chair and expressed appreciation for the participation of professional societies focused on infectious diseases and vaccines. He stated that the American Academy of Pediatrics' non-participation in these discussions is a mistake and expressed concern that continued absence could diminish the Academy's influence.

Febrile Seizures following Measles, Mumps, Rubella, and Varicella (MMRV) vaccine
Dr. John Su (CDC/NCEZID)

Dr. John Su (CDC/NCEZID) presented on febrile seizures following Measles, Mumps, Rubella, and Varicella (MMRV) vaccine. The ACIP chair requested that the Immunization Safety Office present an analysis of febrile seizures following the administration of MMRV compared with the simultaneous administration of separate MMR and varicella vaccines, with results stratified by two age groups: 1–2 and 4–6 years. The presentation should draw on data from randomized clinical trials and from the Vaccine Safety Datalink (VSD) project.

Dr. Su recapped that MMRV was licensed in the U.S. in 2005. Interim recommendations in 2008 removed the preferential recommendation for MMRV, and updated recommendations were issued in June 2009. Between February 2008 and June 2009, the MMRV Vaccine Safety Work Group reviewed multiple data sources, including two post-licensure studies from Merck and analyses from the Vaccine Safety Datalink (VSD). In brief, the 2009 updates stated that unless a parent or caregiver prefers MMRV, the first dose for children aged 12–47 months should be administered as separate MMR and varicella vaccines, while MMRV remains generally preferred for the second dose. Additional details can be found in the May 2010 issue of the MMWR Recommendations and Reports.

Background on the MMRV vaccine and febrile seizures was provided. Combination vaccines, like MMRV, reduce the number of injections a child receives and can improve vaccine

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compliance and coverage. MMRV is licensed for children aged 12 months–12 years. The routine schedule recommends two doses: the first at 12–15 months of age and the second at 4–6 years of age. ProQuad is the MMRV product licensed for use in the U.S.

Febrile seizures are seizures that occur in children who have a fever. By age 5 years, 2–4% of children have had at least one. They occur primarily between 6 months and 5 years of age, with a peak between 14 and 18 months of age. Although distressing, most febrile seizures are short (less than 15 minutes) and resolve without complications. They most commonly accompany fevers from routine childhood illnesses such as middle ear infections, viral upper respiratory infections, and roseola. Still, they can occur with any condition that causes fever, including those that follow vaccination. A family history of febrile seizures increases risk.

Pre-licensure studies of MMRV among children aged 12–23 months found that fever and measles-like rash were reported significantly more often during the 0–42 days after vaccination in children who received a first dose of MMRV than in those who received separate first doses of MMR and varicella at the same visit. Fever occurred in 21.5% of MMRV recipients versus 14.9% of recipients of separate MMR and varicella (risk difference 6.6%; 95% CI, 4.6%–8.5%). Considering these findings, CDC and Merck initiated post-licensure studies to evaluate whether an increased risk of febrile seizures might be associated with the first dose of MMRV.

Analyses of postvaccination intervals from a Vaccine Safety Datalink (VSD) study and a Merck-sponsored study, conducted primarily among children aged 12–23 months, used different populations and methods. Yet, both found significant associations in the first two weeks after vaccination. The VSD study, after medical record review, confirmed an increased risk of febrile seizures during days 7–10 after MMRV compared with MMR plus varicella, with an attributable risk of 4.3 per 10,000 doses and a relative risk of 2.0 (95% CI, 1.4–2.9). The Merck-sponsored study also observed an increased risk during days 5–12 after MMRV, with an attributable risk of 1.3 per 10,000 doses administered during 0–30 days postvaccination; the relative risk was 1.1 with a non-significant confidence interval.

An analysis of VSD outpatient visits for fever among children aged 12–23 months from 2000 to 2008 revealed that fever visits increased after any measles-containing vaccine during days 7–10 postvaccination, with the greatest increase following MMRV. Temporal scan statistics identified significant clustering on days 7–10 for all measles-containing vaccines ($p < 0.001$), while no temporal clustering of fever visits was observed after varicella vaccination alone.

An analysis of the number of seizures after vaccination among children aged 12–23 months (2000–2008) revealed peaks on days 7–10 following any measles-containing vaccine, with the highest counts occurring after MMRV vaccination. Temporal scan statistics indicated significant clustering on days 8–10 after MMRV (relative risk 7.6; p=0.001), days 7–10 after MMR plus varicella given at the same visit (relative risk 4.0; p=0.001), and days 7–11 after MMR alone (relative risk 3.7; p=0.001). No seizure peak or significant temporal clustering was observed after varicella vaccination alone.

A review of the biomedical literature on post-licensure febrile seizures following MMR or varicella vaccination identified one study showing a significant increase in febrile seizures during days 8–14 after MMR compared with unvaccinated children, corresponding to approximately one additional febrile seizure per 3,000–4,000 children vaccinated. No increased risk of febrile seizure was observed among children aged 12–23 months after varicella vaccination during the 0–30 days postvaccination.

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A 2015 systematic review and meta-analysis assessed the risk of febrile seizures following MMRV vaccination, including studies that used Priorix Tetra (MMRV) or ProQuad (MMRV). The analysis included both clinical trials and post-marketing observations, with some studies enrolling children as young as 9 months. Clinical trial data showed no significant differences in febrile seizure incidence between MMRV and MMR, with or without varicella, after any dose across multiple risk windows. Additionally, concomitant administration of MMRV with other pediatric vaccines was not a significant predictor of febrile seizures. In post-marketing analyses, an approximate twofold increase in risk of seizure or febrile seizure was observed during days 7–10 or 5–12 after MMRV vaccination in children aged 10–24 months.

A 2021 Cochrane review examined the use of MMRV in children, including five cohort studies, four of which evaluated first-dose vaccination only. Overall, there was a significant increase in febrile seizure risk among children receiving MMRV compared with separate MMR and varicella during the 0–42 days postvaccination and during days 7–10. In brand-stratified analyses, a cohort study of Priorix Tetra reported non-significant findings for febrile seizure risk compared with separate MMR and varicella vaccines, including in post hoc analyses. The four other cohort studies, which evaluated ProQuad, showed a significantly increased risk during the 0–42-day and 7–10-day postvaccination windows.

Dr. Su summarized that post-licensure studies assessed febrile seizures in children aged 12–23 months who received a first dose of MMRV compared with children who received a first dose of MMR and varicella at the same visit. Despite differences in methods, populations of children, and MMRV formulations, the findings were consistent across all studies. Studies identified an increased risk of febrile seizures during the 1–2 weeks after the first dose of MMRV compared with the first dose of MMR plus varicella; outside that period, risks were similar between the two options.

MMRV is licensed as a two-dose series, with the routine second dose at ages 4–6 years. The risk of febrile seizures is lower in children aged 4–6 years than in those aged 12–15 months. In Merck pre-licensure trials, fever rates were lower after a second dose of MMRV in children aged 15–31 months than after the first dose. Among children aged 4–6 years, fever rates were similar after receiving a second dose of MMRV and after receiving a second dose of MMR plus varicella, both administered at the same visit.

Merck-sponsored studies among children aged 4–6 years observed no febrile seizures in either of the comparison arms. In a VSD post-licensure study, very few seizures were identified by ICD-9 codes after measles-containing vaccines, with no significant differences during days 7–10 or 0–42 after MMRV, MMR plus varicella, or MMR alone. However, rates were numerically higher after MMRV. Electronic medical record review of the four events coded as seizures, 7–10 days after MMRV, found two afebrile seizures, one indeterminate event, and one confirmed febrile seizure. The resulting occurrence of febrile seizure 7–10 days after a second dose of MMRV was 1 per 86,750 doses (about 1.2 per 100,000), with the upper 95% confidence limit corresponding to no more than 1 per 15,570 doses (about 6.4 per 100,000). Similarly, for MMR plus varicella given the same day, the upper 95% confidence limit corresponded to no more than one febrile seizure per 18,282 doses.

The systematic review published in 2015 examined febrile seizure incidence and risk after the second MMRV dose. Pre-licensure data showed no statistically significant differences between children who received MMRV alone and those who received MMRV with one or more other pediatric vaccines at the same visit. Likewise, there were no significant differences between children who received MMRV plus other pediatric vaccines and those who received other

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pediatric vaccines without MMRV. The systematic review also summarized a post-licensure VSD study concluding that, among children aged 4–6 years, neither MMRV nor same-day separate MMR and varicella vaccination was associated with an increased risk of febrile seizures.

Dr. Su summarized that among children aged 4–6 years, the data do not suggest an increased risk of febrile seizures after a second dose of MMRV compared with a second dose of MMR plus varicella given at the same visit. In conclusion, there is a small increased risk of febrile seizures after the first dose of measles-containing vaccines (MMR and MMRV), with the risk slightly higher after MMRV. Studies have shown a small increased risk during days 5–12 after the first MMR dose; no increased risk has been observed after the varicella vaccine alone. There is no increased risk of febrile seizures after MMRV in children aged 4–6 years.

Discussion

Dr. Kulldorff asked whether vaccine coverage rates are influenced more by the reduced number of injections with combination vaccines or by concerns arising from adverse reactions that may spread through families and communities. He requested studies that quantify both effects and indicate which has the greater impact on coverage.

Dr. Srinivasan acknowledged the question, noted that subject matter experts could better address the effects of vaccine coverage, and requested the backup slide on the parent and provider survey to inform the discussion.

Dr. Oliver reported that the National Immunization Survey Child COVID module, published in 2024, asked parents to consider routine childhood vaccines (measles, polio, tetanus) and indicate overall hesitancy. Only 14% of parents of children aged 6 months–4 years expressed hesitancy toward these routine vaccines.

Dr. Kulldorff asked whether the 14% hesitancy figure referred specifically to parents whose child had experienced a febrile seizure or to the broader survey population.

Dr. Oliver clarified that the 2024 National Immunization Survey Child COVID module was a random-digit-dial survey of the general parent population, not specifically parents of children who had experienced febrile seizures.

Dr. Kulldorff asked how a febrile seizure attributed to MMRV, compared with MMR plus varicella, affects parents' willingness to continue vaccinating the child, vaccinate younger siblings, and recommend vaccination within their social circles. He asked whether such events reduce coverage and whether any studies quantify these effects relative to the coverage gains from fewer injections with combination vaccines, and which effect is larger.

Dr. Oliver referenced background slide 27 from the MMRV presentation and noted that there are no survey data specifically of parents whose children previously had febrile seizures. She explained that during the 2008–2009 Work Group discussions, a parent survey of mothers found that approximately 33% would be resistant to MMRV, about 25% were neutral, and around 40% would accept it. She emphasized that the most effective conversations about vaccination risks and side effects occur between the pediatrician and the parent, and that parents should be offered a choice between MMRV and separate MMR plus varicella. The CDC recommends that pediatricians include these risks in counseling and help families weigh the benefits and risks for the specific child and situation.

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Dr. Kulldorff acknowledged that there are no data available and that it is difficult to quantify how much vaccine hesitancy might increase because of additional febrile seizures.

Dr. Meissner noted that the discussion mirrors debate from about 15 years ago and was one of the few times the ACIP and the American Academy of Pediatrics (AAP) diverged, with the AAP not expressing a preference for the 12–15 months dose, while the ACIP allowed the use of separate MMR plus varicella. He added that a busy pediatric practice might see about one additional febrile seizure after MMRV at 12–15 months compared with separate vaccines. He asked Drs. Su and Oliver to confirm that febrile seizures after MMR alone at 12–15 months occur at roughly 1 per 3,000 doses and that MMRV increases the risk about twofold.

Dr. Su confirmed that prior studies show an additional risk of about one febrile seizure per 3,000–4,000 children after MMR and that a twofold increase in risk with MMRV compared with separate MMR plus varicella is correct.
Dr. Meissner asked to confirm that more than 95% of febrile seizures occur before age 4, with only a small percentage occurring after age four from any cause.

Dr. Su noted that febrile seizures after age five are rare.

Dr. Levi proposed that existing records could quantify downstream effects of febrile seizures on vaccine uptake, since diagnoses identify which children experienced a seizure and immunization records show subsequent vaccinations. He cautioned that the lower observed risk after the second dose might reflect selection bias if children who reacted strongly to the first dose delayed or skipped the second dose. He also questioned the field's limited mechanistic understanding, noting that a higher varicella antigen dose in MMRV may provoke a stronger immune response in some children. He asked whether children who experience febrile seizures have been evaluated for distinctive immune responses or biomarkers to clarify the underlying mechanisms, emphasizing that safety assessment should extend beyond symptoms to a biological explanation.

Dr. Pollak echoed concerns about limited mechanistic understanding and noted that very young children may have heightened IL-1–mediated fever responses. He asked whether cytokine levels were measured in febrile children and whether cytokine gene polymorphisms or other genetic predispositions were assessed. He cautioned that second-dose findings may reflect selection bias if pediatricians avoid revaccinating children with a history of febrile seizures. He recommended that guidance address how to manage vaccination schedules for children who have had prior febrile seizures.

Dr. Kulldorff agreed with the point that existing medical and immunization records could quantify whether a febrile seizure affects subsequent vaccination for the child and younger siblings. He added that he was not aware of any analysis that has examined this to date, though the data likely exist to do so.

Dr. Milhoan emphasized that febrile seizures are diagnosed retrospectively and that, for families, a 15-minute seizure feels incredibly long. He noted that in his practice, families who have experienced a febrile seizure are often hesitant to proceed with the next vaccine, and he shares their caution. He asked whether fever from natural viral illness shares the exact mechanisms as vaccine-associated fever, highlighted that rising temperature lowers the seizure threshold in all people, and questioned whether the measles vaccine further lowers that threshold. He observed increased vaccine hesitancy among families and emphasized the

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importance of clearly communicating the risks and benefits of vaccination. He also asked whether there are long-term follow-up data on children who experienced a febrile seizure after the first dose.

Dr. Su stated that the request was to present data on the risk of febrile seizures and that he would need to review data regarding longer-term outcomes.

Dr. Stein asked how risks are communicated to parents and guardians in practice, noting that some evidence predated the guidelines and additional data have been published since. She wondered how parental choice is incorporated into those discussions.

Dr. Marin explained that one-pagers were developed to support risk communication: a provider one-pager in table format outlining risks, benefits, and their implications, and a parent one-pager noting the increased risk of febrile seizures with MMRV compared to MMR plus varicella. These materials were designed to help pediatricians discuss options in clear, understandable terms.

Dr. Oliver added that usage data indicate about 85% of children receive separate MMR plus varicella at the first visit, while roughly 15% receive MMRV. She noted this distribution likely reflects discussions between pediatricians and parents about risks and benefits.

Dr. Griffin inquired whether manufacturers or other groups are conducting studies on the educational performance of children following febrile seizures.

An NCIRD SME shared that the group is not currently doing any long-term studies on the topic.

Dr. Griffin noted that, since the product has been licensed since 2005, it would be helpful to reassure parents that studies on children's educational outcomes after febrile seizures have been conducted. She also asked whether any studies were tested against a trustworthy saline placebo.

Dr. Su said a follow-up would be necessary to answer the question definitively. Most available studies compare MMRV with MMR plus varicella.

Dr. Griffin argued that comparing MMRV with separate MMR plus varicella introduces confounding and makes risk interpretation difficult. She noted the usual rationale that vaccine versus saline placebo trials are considered unethical once a vaccine is deemed safe and effective. Still, she contended that, given current levels of parental non-vaccination by informed choice, an actual placebo-controlled study could be ethical. She suggested inviting parents who have already chosen not to vaccinate their children to participate, to enable a clearer assessment of the risks.

Dr. Marin explained that a placebo study would require a randomized controlled trial. Selecting only parents who avoid vaccination would introduce confounding, as their children may differ systematically (for example, prior adverse events). Participants cannot be chosen based on willingness to forgo vaccination; they must consent to random assignment to either the vaccine or control group.

Dr. Oliver added that in a randomized controlled trial, participants must have an equal likelihood of receiving either a placebo or a vaccine, and families must consent to the randomization process. Given the currently elevated measles activity, asking parents to accept a chance of a

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placebo, and therefore no protection against measles, mumps, rubella, or varicella, would be concerning.

Dr. Griffin thanked Dr. Oliver for her response and shared that, in today's environment, many parents are asking for more studies. She suggested that the public would welcome observational studies comparing vaccinated and unvaccinated children.

Dr. Kulldorff suggested that ethical randomized trials could be conducted by varying the timing of vaccination rather than withholding it, noting that countries recommend MMR at different ages. For example, children could be randomized to receive MMR at 12 months versus 18 months, allowing randomized designs without denying vaccination.

Dr. Blackburn asked why trials were designed with MMR and varicella given on the same day, noting that simultaneous administration might produce adverse event rates similar to MMRV. She suggested that separating MMR and varicella by at least 28 days could better distinguish differences in adverse reactions. She asked whether this approach had been considered, given that typical pediatric visits occur at 12, 15, 18, and 24 months of age.

Dr. Marin explained that trials were designed to compare MMRV with the same-day administration of separate MMR plus varicella, because MMRV is intended to replace two injections with one. The primary question was whether a single injection would provide comparable immunogenicity and an acceptable adverse event profile relative to administering both vaccines at the same visit. While some studies included arms with MMR alone or varicella alone, most focused on the two practical options parents and providers face. Spacing MMR and varicella across separate visits (for example, at 12 and 15 months) would not answer the substitution question because children would still receive two injections.

Dr. Pebsworth inquired whether the MMR/MMRV Vaccine Information Statement states that a prior febrile seizure or any post-vaccination seizure constitutes a contraindication, noting that this relates to informed consent. She also referenced VSD findings that included both febrile and afebrile seizures and questioned whether the lack of statistical significance for second-dose events at ages 4–6 years might reflect selection bias. Additionally, she asked whether the assumption that febrile seizures are largely benign is clinically justified and whether a history of febrile seizures should be considered a contraindication to receiving the vaccine again.

Dr. Oliver noted that the MMRV Vaccine Information Statement advises parents to consult their health care provider if the child has a history of seizures or if a parent or sibling has a seizure history. She added that the FDA sets contraindications.

Dr. Marin added that the MMRV Vaccine Information Statement includes language under "Risks of a vaccine reaction", noting that seizures, often associated with fever, can occur after MMRV. The risk is higher with MMRV than with separate MMR and varicella when given as a first dose. The VIS advises that a health care provider can recommend the appropriate vaccines.

Dr. Meissner stated that febrile seizures occur in 3–5% of children, are familiar to pediatricians, and have an excellent prognosis. He emphasized that while the episodes are frightening for families, they are not associated with impaired neurocognitive development, school problems, or long-term performance issues. He noted that the practical question is whether to use MMRV or separate MMR plus varicella doses. Combination vaccines can improve completion rates by reducing the number of injections, whereas separating doses may reduce compliance. The argument against using MMRV at 12–15 months is a slight increase in febrile seizure risk. He

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supported the current ACIP wording, which allows parents to choose based on their preferences: those concerned about febrile seizures may select separate MMR and varicella vaccines. In contrast, those prioritizing fewer injections may choose MMRV. He added that about 85% of children currently receive separate MMR and varicella at the first visit and concluded that the existing guidance is appropriate.

Dr. Levi expressed unease about assumptions underlying current interpretations. He cautioned that febrile seizures after viral infection may differ biologically from those observed after vaccination and that measurement alone may obscure important mechanistic differences. He urged agencies to investigate mechanisms, including biomarkers, and to follow children who experience seizures over the long term. He noted that higher antigen content may be associated with more events and recommended that safety assessments extend beyond 30–40 days.

Dr. Meissner thanked Dr. Levi and responded that febrile seizures are well-defined: they occur in children, usually under 5 years (often under 4), are generalized rather than focal, last less than 15 minutes (typically a few minutes), and do not recur within 24 hours. He noted that most febrile seizures are not associated with vaccination and that the prognosis is excellent apart from the emotional impact on families. Given the limited resources and extensive pediatric experience with these events, he questioned whether investing heavily in additional studies on vaccine-associated febrile seizures would be the most effective use of effort.

Dr. Milhoan cautioned that heavy reliance on ICD codes can be problematic. As a practicing physician, he noted that selecting precise codes is often time-consuming and prohibitive, and retrospective analyses should account for this limitation. He emphasized the importance of “clean” data, suggesting a clear distinction between ICD-coded febrile seizures temporally related to vaccination and those not associated with vaccination. He urged researchers who use ICD-based datasets to acknowledge that these codes are imperfect and may not fully capture clinical reality.

Dr. Pebsworth thanked Dr. Meissner for his comments and clinical perspective; however, she noted a 2023 study on long-term neurodevelopmental outcomes of febrile seizures reporting clinical and animal evidence of potential adverse effects, including attention deficit hyperactivity disorder, increased susceptibility to epilepsy, hippocampal sclerosis, and cognitive decline in adulthood, while mechanisms remain unclear. She recommended adding this topic to a future agenda for safety review.

Rick Haupt, a Merck representative, noted that as a pediatrician, he witnessed fatal pneumococcal, Hib, and varicella infections before they became vaccine-preventable and emphasized the importance of not returning to that era. He stated that ProQuad (MMRV) has been rigorously evaluated in clinical trials and post-licensure studies, with findings shared with regulators, public health agencies, and medical societies, and published in journals. He reiterated that a slight increase in febrile seizures after the first dose was first reported in a 2009 observational study with Kaiser and has informed current recommendations: MMRV is preferred for the second dose, while separate MMR plus varicella is preferred for the first, with provider or family choice allowing MMRV; about 15% choose MMRV at the first visit. He stressed evidence and consensus that combination vaccines improve series completion and on-time vaccination. He cited recent CDC data showing kindergarten coverage below the 95% threshold needed for measles herd immunity. He cautioned that policies that reduce clarity or consistency around MMRV could further erode public confidence. Addressing antigen content, he explained that only the varicella antigen is higher in MMRV (the MMR antigens remain unchanged), which was

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necessary to demonstrate a non-inferior immune response compared with separate MMR plus varicella, likely due to local antigen interference in the combination product.

Dr. Kulldorff offered a correction, noting that the initial identification of an excess risk of febrile seizures with MMRV compared with MMR was made at CDC using the Vaccine Safety Datalink's rapid cycle analysis. He said the signal was detected after approximately 25,000 doses and highlighted the strong work of the CDC and the VSD in monitoring vaccine safety.

Dr. Hibbeln cautioned that the small risk of febrile seizures—likely without long-term consequence—must be weighed against the danger of vaccination coverage falling below 90%, which could lead to devastating outcomes such as fetal loss, neonatal death, and congenital rubella syndrome. He stressed avoiding actions that might drive nonvaccinating through fear or oversimplified "for or against" views of vaccines. He emphasized that any major change to long-standing guidance should have a powerful, clearly articulated rationale.

Proposed recommendations and discussion

Dr. Martin Kulldorff (ACIP Chair)

Dr. Martin Kulldorff, Chair of the ACIP, presented the proposed recommendations from the MMRV Vaccine Work Group.

Proposed Recommendation:

> The pediatric vaccine schedule should be updated to reflect the following change:
> -For measles, mumps, rubella and varicella vaccines given before age 4 years, the combined MMRV vaccine is not recommended.
> -Children in this age group should receive separate measles, mumps, and rubella vaccine and varicella vaccine (MMR+V).

Discussion

Dr. Stein asked how the proposed recommendation differs from current guidance, noting that the 2009 recommendation appears to call for two separate shots for the first dose.

Dr. Kulldorff outlined two differences. First, the proposal states that both options are acceptable, with a preference for MMR plus varicella for doses administered between 12 and 47 months of age. Second, for children who receive a "second" dose before age 4 (for example, after an early outbreak dose at 7 months followed by a dose at 12–15 months), that dose would be treated as a pre-4-year dose so that the preference would be separate MMR plus varicella rather than MMRV.

Dr. Levi stated that if adherence were guaranteed to be the same, separate MMR plus varicella doses would be preferable, given the added adverse events with MMRV and the lower antigen exposure with separate vaccines. He questioned whether separating the first-dose vaccines meaningfully reduces adherence, suggesting that safer profiles likely increase trust and adherence. In the absence of strong evidence either way, he favored the option that appears safer.

Dr. Pebsworth sought confirmation that at the first visit (12–15 months), approximately 85% of vaccinations are administered as separate MMR plus varicella and about 15% as MMRV.

Dr. Kulldorff confirmed that at the first visit (12–15 months), about 85% of vaccinations are administered as separate MMR plus varicella, and roughly 15% as MMRV. He commended

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pediatricians and nurses for prioritizing the option associated with fewer febrile seizures and shared a brief personal example illustrating providers' awareness of the rationale.

Dr. Meissner shared two points. First, an MMR dose given before 12 months is intended for infants traveling to measles-endemic areas and does not count toward the routine two-dose series; those children still need doses at 12–15 months and 4–6 years. He also clarified that MMRV is licensed only for ages 12 months through 12 years. Second, he cautioned against removing parental choice for the first dose, noting that while about 85% currently receive separate MMR and varicella, some parents prefer a single visit with MMRV, and that option should remain available.

Dr. Goldman inquired whether a fully vetted Evidence to Recommendations (EtR) presentation would be provided, addressing harms, benefits, acceptability, and feasibility, with input from practicing clinicians and liaisons. He argued the proposed recommendation could confuse the public, does not reflect real-world clinician experience with vaccine hesitancy, and might enable insurers and the Vaccines for Children program to decline coverage. He added that the change would remove parental choice for informed decision-making with their physicians. He urged the committee not to change recommendations and, if proceeding, to use the established EtR process with transparent data to support debate and discussion.

Dr. Hopkins agreed with Dr. Goldman.

Dr. Middleman endorsed Dr. Goldman's comments and emphasized the need to present all available evidence in a single, coherent, and scientifically vetted format, so that providers and patients can understand the full scope of information. She emphasized the importance of focusing on what the evidence reveals rather than beliefs unsupported by evidence.

Dr. Kulldorff thanked Dr. Srinivasan and Dr. Su for their excellent and informative presentations.

Dr. Levi requested clarification on what information had not been discussed or considered, noting that prior comments had implied missing data. He asked whether anyone is disputing the evidence of increased febrile seizures after MMRV, and what additional data they believe should be reviewed.

Dr. Goldman argued that the discussion was not thoroughly vetted and relied too narrowly on selected data points without incorporating real-world clinical experience. He noted that liaison members have been removed from work groups, reducing subject matter expertise and the patient voice. He emphasized that a complete assessment should address implementation, acceptability, feasibility, equity, and the balance of harms and benefits, and urged inclusion of physicians' practical experience with patients.

Dr. Middleman echoed Dr. Goldman's comments and requested that all available evidence be presented together, encompassing the full extent of scientific literature rather than only the few studies discussed.

Dr. Levi responded that he trusts the CDC staff to have presented all relevant data and noted that several colleagues are pediatricians with experience in patient care. He invited anyone who believes information is missing to specify it so the committee can consider it.

Dr. Hopkins appreciated the CDC data, describing it as thorough and informative, but noted that equity considerations and the practical implications for patients and practicing physicians had not been adequately addressed. He stated that without a full Evidence to Recommendations (EtR) review of these elements, the committee lacks a complete basis for decision-making.

Dr. Goldman agreed with Dr. Hopkins.

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Dr. Jshlay emphasized practical considerations at the 12-month visit, noting that children may receive multiple vaccines and some parents prefer fewer injections. She estimated that up to 7 vaccines can be given at a single visit and underscored the need for informed consent and alignment with parental preferences when scheduling and selecting vaccines.

Dr. Stein noted that the Vaccine Information Statement indicates an increased risk of fever and seizures after the combined MMRV shot compared with separate MMR and varicella shots. She asked how this risk is communicated to parents in practice and whether clinic time pressures, such as busy patient flow, ever limit the ability to provide clear informed consent. She invited input from medical professionals on how these discussions are handled.

Dr. Milhoan suggested asking parents directly about the adequacy of risk and benefit discussions rather than relying solely on clinicians' perspectives. He noted that in busy practices, informed consent is often incomplete across various medicines and vaccines, with rare but serious risks not always being thoroughly reviewed. He said that many parents felt they were given little information and concluded that current practices may not fully meet the standard for informed consent.

VFC Resolution Update: MMRV Vaccine
Jeanne Santoli (CDC/NCIRD)

Jeanne Santoli (CDC/NCIRD) presented the VFC resolution update with all revisions from the previously approved resolution shown in red. The purpose of the update is to provide revised guidance on the use of the combined measles, mumps, rubella, and varicella (MMRV) vaccine. The resolution includes three components: MMR, varicella, and the combined MMRV. No changes were made to the MMR or varicella components; eligibility, recommended schedules, dosage intervals, contraindications, and precautions remain the same. The changes apply only to the combined MMRV component and clarify eligible groups, recommended schedule, dosage, and contraindications to align with the proposed recommendations under discussion today by the ACIP.

Discussion

Dr. Kulldorff noted that, as is standard procedure, two votes will be conducted. The first will address the recommendation, followed by a separate vote on the VFC resolution. He added that this approach is consistent with the process used during the June meeting.

Dr. Griffin echoed comments from Dr. Milhoan, noting from her personal experience as a mother that vaccine information statements were not always consistently explained when her children received immunizations, with the expectation that parents would read the handout independently. She added that many of her patients and non-physician acquaintances had reported similar experiences, although she acknowledged that this was anecdotal. Dr. Griffin emphasized the value of having additional data for committee review and clarified her earlier comments regarding randomized controlled trials, acknowledging the ethical limitations of such studies. She concluded by stressing the importance of considering a broader range of studies and raw data, as well as individual experiences that collectively inform the balance of vaccine benefits and risks.

Dr. Jshlay shared that at the Public Health Institute of Denver Health, her large-scale immunization program provides the VFC and VIS forms before vaccination and reviews them with patients to ensure informed decision-making. She emphasized that providing the VIS before vaccination is a requirement and noted that local public health agencies across the country follow this same practice. She added that, although she could not comment on anecdotal reports, her clinic strives to uphold this standard.

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Dr. Middleman emphasized the importance of grounding public health recommendations in a comprehensive body of data rather than anecdotal evidence. She noted that while physicians focus on individual patients, public health decisions must consider the health of the entire population. She highlighted the breadth of studies that inform the evidence-to-recommendation process and stressed the need to evaluate all elements of public health, including disease impact, risks and benefits, feasibility, acceptability, cost-benefit ratio, and equity. Dr. Middleman questioned the urgency of deciding at this meeting and urged the committee to follow a methodical evidence-to-recommendation process to ensure scientific rigor and maintain public confidence.

Dr. Kulldorff apologized for sharing an anecdote about his twins' vaccinations but noted that the committee had engaged in a strong, science-based discussion. He commended the CDC colleagues for their presentations and highlighted the quality of the debate on various aspects of the vaccines.

Dr. Pebsworth acknowledged that at the 12–14-month visit, many vaccines are administered and noted that approximately 85% of pediatricians and parents currently choose MMR plus varicella separately. She then raised a technical question regarding the language of the posted vote, which states "recommends." She sought clarification on whether this language would prohibit the use of the FDA-licensed MMRV vaccine for certain patients, emphasizing the importance of preserving provider discretion to administer licensed products.

Dr. Kulldorff clarified that the committee's role is to make recommendations, while the FDA determines which vaccines can or cannot be used. He noted that committee votes may have consequences for insurance coverage, including through CMS, but emphasized that the authority to approve vaccine use rests with the FDA.

Dr. Srinivasan suggested that it would be helpful for a VFC representative to comment on how ACIP recommendations affect the Vaccines for Children program, given that the program funds many pediatric vaccines.

Dr. Santoli explained that if a vaccine is designated as "not recommended," it will not be covered under the VFC program for children. She noted that while there are ways to address individual-based decisions that allow for coverage, the current resolution under consideration would mean that VFC would not cover the vaccine even if a parent and physician chose it.

Dr. Johnson added that a "not recommended" designation could also affect coverage under Medicaid and the Children's Health Insurance Program, as well as individual and group insurance markets. She noted that this could impact overall coverage and potentially result in out-of-pocket costs, such as co-pays.

Dr. Kulldorff clarified that the coverage discussion pertains specifically to the MMRV vaccine. He emphasized that coverage for the MMR and varicella vaccines will remain unchanged, with both continuing to be fully covered.

Dr. Johnson confirmed.

Dr. Hibbeln requested clarification that under the proposed change, administration of the MMRV vaccine before four years of age would be considered "not recommended," and therefore would not be covered for payment.

Dr. Santoli clarified that, under the Vaccines for Children program, the MMRV vaccine would not be covered for children under the age of four.

Note: Text enclosed in [brackets] was added following the meeting, per the presenter's request.

Dr. Hibbeln expressed concern that under the proposed change, parents would lose the option to choose the MMRV vaccine for their child unless they were willing to pay out of pocket. He noted that if parents preferred a single vaccination rather than multiple shots, this option would effectively be taken away despite their understanding of the risks and benefits.

Dr. Santoli confirmed that VFC would not cover the vaccine for those children.

Vote: MMRV Vaccines Vote

Dr. Martin Kulldorff (ACIP Chair) read the following proposed ACIP voting language for MMRV vaccines into the record:

> The pediatric vaccine schedule should be updated to reflect the following change:
> -For measles, mumps, rubella and varicella vaccines given before age 4 years, the combined MMRV vaccine is not recommended.
> -Children in this age group should receive separate measles, mumps, and rubella vaccine and varicella vaccine (MMR+V).

Motion/Vote: MMRV Vaccines

Dr. Levi motioned to approve the recommended voting language, stating,
"The pediatric vaccine schedule should be updated to reflect the following change:
-For measles, mumps, rubella and varicella vaccines given before age 4 years, the combined MMRV vaccine is not recommended.
-Children in this age group should receive separate measles, mumps, and rubella vaccine and varicella vaccine (MMR+V)."
Dr. Pagano seconded the motion. No COIs were declared. The motion carried with 8 votes in favor, 3 votes opposed, and 1 abstention. The disposition of the vote was as follows:

8 Favored: Pagano, Milhoan, Stein, Griffin, Pollak, Pebsworth, Levi, Kulldorff
3 Opposed: Blackburn, Hibbeln, Meissner
1 Abstained: Malone

Discussion

Dr. Santoli requested clarification on the wording used during the vote discussion, noting that she had heard the term "compensate" and wanted to ensure it was understood correctly. She explained that a yes vote would align the VFC resolution with the recommendation vote that had already passed, meaning the combination vaccine would not be covered in VFC for children under four years of age. A 'no' vote would maintain the current VFC coverage as it stands today, which includes the combination vaccine for children aged 12 months through 12 years. She acknowledged that timing issues had prevented the full written materials from being available before the meeting, as the resolution had to be made late the previous evening to align with the committee's proposed language.

A CMS representative confirmed that the same coverage decision would apply to Medicaid, CHIP, and the individual and small group markets, clarifying that the combined vaccine for children under four years would not be covered if the resolution were to pass.

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Dr. Meissner expressed confusion, asking what would happen if the committee voted no, and emphasized the need for clarity.

Dr. Santoli reiterated that a no vote would maintain VFC coverage unchanged, meaning the combination vaccine would remain covered; however, CMS and VFC could ultimately have different coverage policies, potentially creating confusion.

Dr. Malone commented that it was difficult for the committee to vote without a written text of the resolution, even though the presentation was clear, and suggested that complete written information be provided in the future.

Dr. Pagano sought clarification on whether a recommendation automatically leads to reimbursement.

Dr. Levi stated that his understanding was that there are two parallel decisions: the recommendation and the resolution. If no new approval is granted, the previous decision remains in effect.

Dr. Pagano noted that this process seemed convoluted, as the committee was being asked to vote no to maintain coverage.

Dr. Milhoan requested clarification on the relationship between the VFC and CMS programs. Dr. Santoli explained that VFC covers Medicaid, uninsured children, American Indian and Alaska Native children, and underinsured children served in federally qualified health centers, while CHIP is administered separately under CMS.

A CMS representative confirmed that CHIP and the individual markets are not directly affected by this vote but rather by the broader ACIP recommendation.

While there was a VFC vote on the initial day of the meeting, with the results of 1 in favor, 8 opposed, and 3 abstained, the committee decided to reconsider the vote due to not fully understanding the implications. Dialogue to follow:

Dr. Kulldorff noted that most members were still new to ACIP and might not yet grasp specific technical issues. He explained that after the meeting, a member had raised concerns about the second vote taken on the VFC resolution regarding the MMRV vaccine and whether the committee had fully understood the implications. He stated that VFC votes are typically aligned to ensure equal coverage and access for all children, and that some consideration had been given to resolving the conflicting votes.

Dr. Pebsworth moved to reconsider the VFC resolution on MMRV that had been voted on the previous day.

Dr. Griffin seconded the motion.

Dr. Kulldorff explained that the committee would first vote on whether to reconsider the matter. If that vote passed, the resolution itself would then be voted on a second time. He asked members to state their names, declare any conflicts of interest, and indicate their votes. Results to follow:

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Vote: To Reconsider the original MMRV Vaccines- VFC Vote

Motion/Vote: MMRV Vaccines

Dr. Pebsworth motioned to reconsider the VFC resolution vote voted on September 18, 2025. Dr. Griffin seconded the motion. No COIs were declared. The motion carried with 10 votes in favor, 0 votes opposed, and 2 abstentions. The disposition of the vote was as follows:

10 Favored: Levi, Pebsworth, Hibbeln, Pollak, Griffin, Stein, Blackburn, Milhoan, Pagano, Kulldorff
0 Opposed:
2 Abstained: Malone, Meissner

Discussion

Dr. Goldman, representing the American College of Physicians, expressed concern about the vote taken the previous day because the committee had two conflicting votes on the same resolution, with the second primarily affecting children from lower socioeconomic backgrounds. He questioned whether the outcome of the first vote implied that children from lower socioeconomic groups should only receive what the committee had described as a harmful vaccine, or whether the second vote revealed that there was no evidence of harm from MMRV and that the risk was not a concern. He argued that the second vote should be considered valid for the entire population, as it indicated that there was insufficient data to support claims of harm.

Dr. Levi stated that the chair had already explained there was an error in the interpretation of the votes and suggested that the committee focus its time on scientific debate rather than pursuing discussion without merit.

Dr. Hibbeln stated that the committee had acknowledged the wording of the second vote was confusing and imprecise. He remarked that, considering the extensive work by CDC and the committee, the confusion was mainly due to wording and expressed appreciation for the more precise phrasing now provided.

Dr. Kulldorff emphasized that the vote's outcome ensures every child, including those in the Vaccines for Children program, will have access to vaccination against measles, mumps, rubella (also known as German measles), and varicella (chickenpox). He stated that this guarantees all children will be able to receive protection against these four critical diseases.

Vote: MMRV Vaccines- VFC Vote

Dr. Martin Kulldorff (ACIP Chair) read the following proposed ACIP voting language for MMRV vaccines into the record:

Approve the updated Vaccines for Children (VFC) resolution for prevention of measles, mumps, rubella and varicella.

Motion/Vote: MMRV Vaccines

Note: Text enclosed in [brackets] was added following the meeting, per the presenter's request.

Dr. Levi motioned to approve the recommended voting language to approve the updated Vaccines for Children (VFC) resolution for prevention of measles, mumps, rubella and varicella. Dr. Pebsworth seconded the motion. No COIs were declared. The motion carried with 9 votes in favor, 0 votes opposed, and 3 abstentions. The disposition of the vote was as follows:

9 Favored: Levi, Pebsworth, Hibbeln, Pollak, Griffin, Stein, Milhoan, Pagano, Kulldorff

0 Opposed:

3 Abstained: Blackburn, Malone, Meissner

HEPATITIS B VACCINES

Introduction

Dr. Martin Kulldorff (ACIP Chair)

ACIP Chair Dr. Martin Kulldorff opened the session by introducing the Hepatitis B Vaccine. He explained that the focus of the discussion today was very specific: to evaluate only the birth dose of the hepatitis B vaccine given within 24 hours of birth, and only for infants whose mothers have tested negative for hepatitis B. He clarified that no changes are being considered for infants born to mothers who test positive or whose status is unknown.

Hepatitis B Birth Dose Vaccination

Dr. Adam Langer (CDC/NCHHSTP)

Dr. Adam Langer (CDC/NCHHSTP) presented on Hepatitis B birth dose vaccination. Hepatitis B virus (HBV) infection causes hepatitis B, which affected an estimated 254 million people worldwide in 2022. While some infections clear naturally, many progress to chronic hepatitis B, an incurable condition that can lead to severe liver disease, liver cancer, and death.

HBV can be transmitted from mother to child (perinatal transmission) as well as through household or community exposure. [hepatitis B is easily transmitted through relatively casual contact; sexual contact or sharing of needles is not required to transmit the virus to others.] Without intervention, up to 85% of infants born to HBV-infected mothers will become infected. Risk of developing chronic infection is highest in children: about 90% of infants perinatally infected develop chronic hepatitis B, and roughly 25% infected in childhood die prematurely from related complications. [Likelihood of chronic infection increases inversely with age, so the youngest children (i.e., newborns and infants) are at greatest risk.]

In the U.S., an estimated 2.4 million people are living with hepatitis B, about half unaware of their infection. Roughly 70% of those with chronic hepatitis B were born in countries with intermediate to high prevalence, often infected at birth or early childhood. [Chronic hepatitis B is incurable and can ultimately be fatal, so immunization against hepatitis B is lifesaving, and the earlier in life the vaccination series is started, the more lives that will be saved and severe chronic illness that will be prevented.]

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Vaccination programs have reduced hepatitis B among U.S. children, but most reported cases now occur among unvaccinated adults. In 2023, about 14,400 acute cases were estimated, with the highest rates in adults aged 40–59 years.

Chronic hepatitis B carries significant healthcare costs. Analysis of claims data from 2004 to 2015 showed annual per-patient costs (adjusted to 2015 dollars) ranging from approximately $94,000 for less severe disease to roughly $325,000 for those requiring a liver transplant. Overall, more than $1 billion is spent annually on hepatitis B-related hospitalizations in the U.S.

Two products prevent perinatal hepatitis B virus (HBV) infection: the hepatitis B vaccine, which provides long-term protection and is used for both pre- and post-exposure prophylaxis, and hepatitis B immune globulin (HBIG), which offers temporary protection in specific post-exposure settings.

When used together, vaccination and HBIG prevent about 94% of mother-to-child transmissions. The hepatitis B vaccine is the cornerstone of prevention, with effectiveness increasing the sooner the birth dose is given after delivery.

The hepatitis B vaccine, available in the U.S. for more than 40 years, was the first vaccine to prevent infection with a cancer-causing virus. Two single-antigen recombinant vaccines are FDA-approved for use from birth: Recombivax HB (1986) and Engerix-B (1989). [These vaccines were tested using placebo-controlled randomized trials prior to licensure in the United States, so there is no need to do additional placebo-controlled studies now.] Extensive research and reviews by the Institute of Medicine and WHO confirm the vaccine's safety and effectiveness. [The vaccine has been routinely given to all newborns in the United States since 1991, and very few serious adverse effects of the vaccine have been identified over the 34 years that this vaccine has been in routine use. The worst reported adverse effect, anaphylaxis, is literally a one in a million occurrence, and this extremely rare reaction can be addressed with immediate treatment and causes no long-term injury to the vaccinated person.]

Full hepatitis B protection requires a multi-dose series, typically three doses. Protective antibody responses are seen in 25% of infants after the first dose, 63% after the second dose, and 98% after the full three-dose series. Immunity can last for decades; one Alaska-based study showed that more than 90% of individuals retained protection over 30 years after vaccination. [The sooner the vaccination series is started, the sooner that the child is protected.]

Since 1988, universal screening for hepatitis B surface antigen (HBsAg) has been recommended for pregnant women, with additional testing for at-risk women later in pregnancy or at delivery. Vaccination at birth has been recommended since 1984 for infants of women testing positive, with the timing specified as within 12 hours of birth starting in 1988. HBIG administration has also been recommended within 12 hours for infants of HBsAg-positive women since 1984, and since 2018 for infants under 2,000 grams born to women with unknown results.

In 1991, the U.S. adopted universal infant hepatitis B vaccination. Guidance on the timing of the birth dose has evolved from "before hospital discharge but no later than 2 months" (1991), to "administered in the birth hospital" (2005), to "within 24 hours of birth" (2018).

The universal hepatitis B birth dose provides a critical safety net for infants who may have unrecognized HBV exposure during pregnancy or early childhood, which can lead to severe outcomes. Gaps in post-exposure prophylaxis occur due to lack of prenatal care, missed

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screening, or administrative errors. One reported case involved a mother with a positive test result that was miscommunicated, resulting in her infant not receiving prophylaxis and later dying from fulminant hepatitis. Between 1999 and 2002, more than 500 similar transmission events were documented when prophylaxis was not administered.

In the U.S., 12–16% of pregnant women receive inadequate or no prenatal care, and a similar percentage are never tested for hepatitis B. The national perinatal hepatitis B prevention program identifies less than half of infants born to HBsAg-positive mothers annually, underscoring the importance of universal birth dose vaccination.

The birth dose also protects against household or community transmission. HBV can survive for over seven days on surfaces, and even microscopic amounts of blood or body fluid are sufficient to transmit the infection. Unvaccinated infants are at risk if they live with or are cared for by individuals with chronic HBV, many of whom are unaware of their infection. Studies before widespread use of the birth dose showed 7–11% of U.S.-born children of immigrant mothers with no HBV evidence tested positive, pointing to community exposure. [Even for infants born to mothers known to be HBsAg-negative, the birth dose and subsequent doses provide crucial protection against household and community (e.g., daycare) exposures that could occur as soon as the infant leaves the hospital.]

Initiating the hepatitis B series on the first day of life offers early protection and benefits infants of both positive and negative mothers. It poses no increased risk of adverse events compared to later vaccination.

Over three decades of data-driven, evidence-based hepatitis B vaccination recommendations for newborns and infants have led to significant reductions in U.S. acute hepatitis B cases. Following the 1991 recommendation for universal infant vaccination (within 12 hours for infants of mothers with unknown status), the number of reported acute cases fell by 69%, from 18,003 in 1991 to 5,494 in 2005. Following the 2005 guidance to administer the first dose before hospital discharge, later updated in 2018 to within 24 hours of life, cases dropped an additional 60% to 2,214 in 2023. However, after adjusting for underreporting, the estimated actual number of 2023 cases was 14,400.

Rescinding the universal birth dose recommendation poses risks, including more perinatal HBV transmission, increased lifetime risk of severe liver disease, added administrative complexity, gaps in care, reduced vaccine series completion, and higher lifetime healthcare costs. Harms would fall disproportionately on uninsured or low-engagement patients. The only potential benefit is a reduction in already rare adverse events; serious events, such as anaphylaxis, occur at a rate of 1.1 per 1 million doses.

CDC was asked to address four specific questions related to the hepatitis B birth dose. The first two questions, reviewed in this session, concern hepatitis B vaccination recommendations in developed countries: specifically, the recommended age of the first dose for infants born to test-positive mothers and for all other infants, and the prevalence of hepatitis B infection among pregnant women. The remaining two questions will be addressed later by colleagues from the Immunization Safety Office.

Countries differ in their approaches to the birth dose. Some recommend a universal birth dose for all infants regardless of maternal status, others recommend it only for infants of HBV-positive mothers, some provide a universal birth dose in limited regions, and some have no recommendation at all. Currently, 43 countries do not have a birth dose policy; however, with

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Gavi support beginning in 2024, many of these countries are either introducing the birth dose or have expressed plans to do so within the next three to five years.

Among the 38 countries reviewed by ACIP, 36, including the U.S., recommend a birth dose within 24 hours along with HBIG for infants born to HBV-positive mothers. The only exceptions are Ireland and Denmark, though both generally provide the vaccine within 24 hours. For infants born to test-negative mothers, eight countries provide a universal birth dose within 24 hours. Of the 38 countries, 26% limit the birth dose to infants of HBV-positive mothers but still recommend routine infant vaccination later. Canada's policies differ by province. Only four countries, Denmark, Finland, Iceland, and New Zealand, limit the birth dose to infants of HBV-positive mothers and do not offer universal infant vaccination.

The most recent prevalence data from 2023 or the past 10 years for hepatitis B among pregnant women were available in 20 of the 38 countries. Nine reported prevalence below 0.5% and all used selective birth dose policies. Eight countries reported prevalence between 0.5% and 0.9%, while three reported prevalence greater than 2%. No U.S. prevalence data have been available in the past 10 years. Only six of the 38 countries maintain national registries to track HBV prevalence in pregnant women, while the other 32, including the U.S., do not collect this data regularly.

Screening data were available in 19 of the 37 comparator countries. Several countries met the 2030 global target of screening 90% or more of pregnant women. In the U.S., an estimated 14% of pregnant women are not screened, placing the U.S. below the target. The U.S. is one of five countries not meeting the goal and one of only three without universal healthcare coverage. Unlike the U.S., most countries provide universal health coverage, ensuring access to prenatal care and vaccination, which supports higher screening rates and timely prophylaxis. This difference highlights the importance of the universal birth dose in the U.S. as a safety net for infants born to mothers with unknown HBV status. Notably, no country has reverted from universal to selective birth dose, and several are moving toward universal adoption.
The second question requested a systematic review of randomized trials on administering the hepatitis B vaccine within 24 hours of birth. The updated review screened 1,390 studies in addition to 833 from the existing review. Seventeen studies met the inclusion criteria, including seven from the earlier review and 10 from the update.

The risk of bias assessment revealed a high overall risk, primarily due to unclear methods of randomization and limited reporting on whether investigators were blinded to the outcomes, which could impact the results. The 17 studies were grouped by intervention type, including efficacy, timing of vaccination, product or formulation differences, dose and schedule, and HBIG co-intervention. Outcomes of interest included protection, efficacy, and safety.

Efficacy trials demonstrated high levels of protection among infants born to HBV-positive mothers. Birth dose vaccination alone reduced transmission by up to 94% and combining the vaccine with HBIG reduced transmission by up to 99%. Adverse events were few and generally mild, such as low-grade fever.

A timing study among infants of HBV-negative mothers compared vaccination at birth, 2 months, or 6 months, with a control group starting at 18 months. All timing groups showed high levels of protection (91%) with no significant safety differences.

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Several product and formulation trials comparing different hepatitis B vaccines found them to be non-inferior. Across studies, high levels of seroprotection and equivalent efficacy in preventing perinatal transmission were observed, with few reported adverse events.

Dose and schedule trials showed strong seroprotection in both HBV-positive and HBV-negative infants. One study reported 96% seroprotection in the intervention arm compared to 0% seroprotection in the comparator arm with no birth dose. Efficacy was consistently high across groups, and safety profiles were similar, with very few local or systemic adverse events.

The updated systematic review did not identify any new placebo-controlled trials assessing efficacy, which is unsurprising since the vaccine's efficacy was established in the 1980s, and withholding it would be considered unethical. There was limited reporting for pre-term, low birthweight, and extremely low birthweight infants, and no morbidity or mortality outcomes were reported. The studies were heterogeneous, and many were conducted before the CONSORT statement was widely adopted, resulting in weaker reporting standards. The risk of bias was primarily associated with randomization and outcome measurement; however, even studies with a high risk of bias can provide helpful information if the findings are consistent and the effects are significant.

Dr. Langer concluded that the body of evidence from both the existing and updated systematic reviews supports the birth dose as safe, effective, and capable of inducing strong seroprotection in infants born to mothers who are both test-positive and test-negative. CDC interprets these findings as continued support for the ACIP's universal birth dose recommendation, first made in 1991 and later strengthened in 2005 and 2018 as part of the national strategy for hepatitis B elimination.

Discussion

Dr. Griffin asked how many of the 17 studies included in the review had declared a conflict of interest.

Dr. Nyendak, an SME who oversaw the rapid systematic review, stated that, to her knowledge, there were no reported conflicts of interest but noted they would confirm and provide that information later.

Dr. Griffin noted that the ACIP group does not have open access to journals, and purchasing individual studies can cost $45 to $60 each, which becomes a significant barrier when reviewing hundreds of studies. In reviewing the 17 studies included in the systematic review, she found that eight declared conflicts of interest. Among the studies focused on adverse events, five of the eight had declared conflicts, while three others had unclear declarations. Several involved pharmaceutical funding, where companies both funded the study and provided the vaccine. She expressed concern about this issue and then referenced CDC data, stating that there were 912 hepatitis B-related deaths in 1991, the year the vaccine was approved, compared to 1,740 deaths in 2021. She asserted that percentage rates indicate an increasing death rate despite the adoption of the vaccine and asked what accounts for this change.

Dr. Nyendak clarified that after conferring with the systematic review team in real time, the team was aware of three studies that reported conflicts of interest and provided this as a correction to the record.

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Dr. Wester from the Division of Viral Hepatitis stated that the team would investigate the question further regarding hepatitis B death rates. She noted that, for surveillance purposes, reportable death rates come through the National Vital Statistics System and that reporting practices have evolved significantly over the decades referenced.

Dr. Levi reviewed the data by age group and noted that vaccination of infants born to HBV-positive mothers clearly reduced cases in children aged 0–19. However, he observed that after the 2005 recommendation for universal birth dose, further reductions mainly appeared in older age groups rather than in young children. He questioned whether the data demonstrate an added benefit of universal vaccination at birth for infants of test-negative mothers living in typical environments. Dr. Levi emphasized that the vaccine is critical for infants born to HBV-positive mothers and other high-risk populations but expressed uncertainty about the evidence supporting universal administration to all newborns.

Dr. Langer responded to Dr. Levi, identifying two questions: why declines are more visible in older age groups than in younger ones, and whether there are data on community and household exposures. He explained that the observed declines in older groups reflect a birth cohort effect, where individuals vaccinated as infants in the early 1990s have since aged into older cohorts. As time passes, those who benefited from early vaccination policies move into older age categories, which explains the shifts seen in the data.

Dr. Levi observed that since universal birth dose vaccination began prior to hospital discharge in 2005, infants born after that year would not yet have aged into the older cohorts where declines are being measured. He suggested that any measurable impact of the universal policy may not be evident until these cohorts are older. He noted that current data may not yet show a meaningful effect.
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Dr. Stein asked about the incidence of hepatitis B in children born to mothers confirmed as hepatitis B negative, noting this would help understand the risk. She also pointed out that only two of the reviewed clinical trials specifically stratified children born to negative mothers, and both were rated as high risk of bias. She asked how reliable the data are on hepatitis B incidence in this group.

An SME referred to slide 30, noting that in dose and schedule trials involving infants of hepatitis B surface antigen–negative mothers, efficacy was equivalent between intervention and comparator groups. The randomized efficacy literature has focused more on infants of surface antigen–positive mothers, where outcomes such as seroprotection, efficacy, and safety are more measurable and show larger effect sizes. Infections among infants of negative mothers typically result from missed or late maternal infection or early horizontal exposure from a household member or caregiver. This underscores the rationale for a universal birth dose as a safety net. Data have shown a 7–11% prevalence of infection among U.S.-born children of immigrant mothers with no evidence of maternal infection, reflecting community or household transmission as the only plausible explanation. The universal birth dose policy was adopted after risk-based strategies failed to prevent perinatal and early childhood transmission, with only 26% of acute hepatitis B cases linked to a reported risk factor, [and the universal birth dose policy has been demonstrated to be highly successful in reducing incidence of new hepatitis B infections in the United States.]

Dr. Kulldorff commented that although U.S. data on hepatitis B prevalence among pregnant women were not available, estimates based on women aged 20–40 suggest a prevalence of about 4–5% overall, with less than 0.1% among U.S.-born women. He noted that roughly 80%

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of infections are among immigrants and 20% among U.S.-born women, emphasizing that U.S. rates are very low compared to Western European countries, where only Portugal has a universal birth dose policy. He also reviewed adverse event data, noting five localized and ten systemic events among 178 vaccinated infants compared to three localized and four systemic events among unvaccinated infants. Although overlap between localized and systemic events was unclear, combining them produced a borderline statistically significant result ($p = 0.054$) with a relative risk slightly above two. Although the sample size was small, the data suggest somewhat higher adverse events for infants vaccinated at birth, which should be considered in deliberations.

Dr. Levi inquired about the duration of the clinical trials for safety monitoring and the surveillance time window for these results.

Dr. Kulldorff responded that he believed it was short-term.

Dr. Levi then asked whether the short-term safety monitoring period in the trials was only a few days, such as up to five, and clarified that if so, the data may suggest higher adverse events in the first days after vaccination but provide no information beyond that period.

An SME directed participants to slides 44 and 45, which show sample sizes and follow-up periods in months. Most safety data were collected after the first dose, with monitoring beginning at 24 hours. The follow-up periods were shown for study and ranged from five to 24 months.

Dr. Levi asked whether data from the longer follow-up periods could be used to compare adverse events overall.

SME responded that the studies reported safety outcomes for as long as each study continued.

Dr. Milhoan asked what specific signals were being tracked during follow-up, noting that if the period extended to 24 months, it would be important to know whether the criteria included hospitalizations, fevers, hepatitis, or other potential adverse reactions, especially since children would have received additional vaccines during that time.

SME explained that slide 41 of the extra slides shows the time points used in the studies. Seroprotection was reported at the first time point after the last dose in the series. Efficacy was measured at the latest available time point with the ongoing intervention, and safety was assessed at birth at the closest time point immediately after the birth dose, as requested.

Dr. Milhoan asked if it was for seroprotection rather than side effects.

SME clarified that it referred to the follow-up period.

Dr. Levi requested clarification on whether there were any follow-up reports of side effects beyond the first few days after birth.

SME responded that follow-up varied across studies and said they would provide clarification later.

Dr. Wester responded to questions about the prevalence of hepatitis B infection in the U.S. She explained that there is no disease surveillance registry to answer this directly, but NHANES data

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from 2013–2018 estimated national prevalence at 0.3%. She noted this may underrepresent populations with the highest burden. Stratification revealed a similar prevalence among males and females, as well as among reproductive-age adults (25–49 years). By country of birth, prevalence was 0.1% for U.S.-born individuals and 1.2% for non-U.S.-born individuals. A modeling study estimated that in 2015, approximately 0.5% of U.S. births were to women who were HBsAg-positive, with 40% of these women being U.S.-born and 60% non-U.S.-born. She also noted that evolving recommendations over the past three decades have had a generational impact. Finally, she clarified that the 1991 infant vaccination recommendation was intended for administration before hospital discharge. However, it allowed vaccination up to two months of age, with a preference for vaccination before discharge.

Dr. Malone asked if there were data on the number needed to treat to prevent a case of hepatitis B in a child born to an HBsAg-negative mother in the U.S. population.

Dr. Wester replied that such data are not available. She noted, however, that if delaying the first dose for infants of test-negative mothers were considered, it would be important to have modeling data to estimate potential harms from unrecognized exposures during pregnancy or early childhood.

Dr. Malone added that to assess the risk-benefit reasonably, more granular data on the number needed to treat for infants of mothers with negative test results are required, as well as a clear risk analysis of potential adverse events and their incidence rates for the vaccines.

Dr. Wester clarified that there is no data on new cases associated with delaying the birth dose recommendation to one month of age.

Dr. Kulldorff asked whether the FDA has any information on this and suggested it may be fair to say no.

Dr. Hoeg noted that the original clinical trial data from the 1980s, which appear on the product label, only included short-term follow-up of four to five days. She stated that this makes it difficult to directly compare the safety risks of giving the vaccine at birth versus later in early childhood. She asked how many of the studies presented by the CDC applied specifically to neonates and echoed earlier questions about follow-up and long-term safety data. She emphasized the need for more robust long-term data, particularly for infants of hepatitis B-negative mothers, where the risk of infection is low, to weigh risks and benefits thoroughly.

Dr. Griffin addressed Dr. Stein's earlier question about safety, noting that the CDC confirmed as early as 2020 that no cases of hepatitis B transmission had been documented in school settings, including elementary, middle, or high schools. She then referred to slide six, asking about its source and what year it was from.

Dr. Langer responded that multiple reports are stating the vaccine was safe, published in 1994, 2002–2004, 2012, and 2013.

Dr. Griffin followed up, noting that in 2012, the Institute of Medicine reviewed hepatitis B vaccine safety studies and concluded that evidence was inadequate to rule out the possibility that vaccination could lead to more than two dozen neurologic and autoimmune disorders. She asked how this statement could be reconciled with describing the vaccine as safe and effective.

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Dr. Wester added that, while the 2012 Institute of Medicine report stated there was insufficient evidence to accept or reject a causal relationship, an extensive body of literature has emerged over the past four decades. She noted that colleagues in the Immunization Safety Office would provide additional data and are better positioned to respond in detail.

Dr. Hibbeln stated that the question before the committee is whether the first dose of the hepatitis B vaccine should be delayed until one month of age for infants of hepatitis B-negative mothers. He said he was unclear if any safety or hazard data had been presented comparing vaccination before versus after one month. He asked why one month was chosen as the time point, and whether data exist showing a greater risk of adverse effects before or after that age.

Dr. Kulldorff noted that the current schedule recommends the second dose at one to two months of age, so delaying the first dose until one month would coincide with or come after the second dose. He suggested that the CDC is best suited to address the broader question of safety.

Dr. Hibbeln reiterated that the committee is being asked to vote on whether the first dose should be delayed until at least one month of age for infants of negative mothers. He wondered if data show that vaccination before one month carries a greater risk of adverse effects than after one month.

Dr. Malone added by asking whether there is data on a gradient of adverse events by age post-birth, rather than only at the one-month time point, and whether risk decreases over time. Dr. Hibbeln agreed, emphasizing that if the committee is to vote on delaying the dose to one month, data are needed comparing adverse effects before and after that time.

Dr. Malone asked whether one month represents a distinct point of higher or lower risk, or if risk changes more gradually over time, and whether data is available to clarify this.

Dr. Kulldorff suggested the committee proceed to the safety presentation to address these questions.

Dr. Pebsworth raised concern about data showing that 12–16% of women do not receive prenatal care or hepatitis B screening. She questioned whether infants are being born in the U.S. without the mother's hepatitis B status known, noting that a rapid test (stat titer) should be able to provide results within one to two hours, which has important implications for infant care. Dr. Kulldorff responded that while in principle maternal status should always be known, the standard test typically takes one to three days, so results may not be available before delivery.

Dr. Pebsworth noted reports that a stat titer can provide results in one to two hours and asked if this was accurate.

Dr. Griffin, speaking as an obstetrician-gynecologist, confirmed that the screening test can indeed be completed in under one hour, with results often available the same day. She added that in the U.S., 98–99% of women deliver in hospitals with laboratory capacity, and most receive prenatal care. While approximately 7% of women lacked prenatal care in 2023 (according to the March of Dimes), hospitals routinely test for hepatitis B surface antigen at delivery if prior results are unavailable, with results typically available within hours.

Dr. Levi asked whether informed consent discussions with mothers include the opportunity to test at delivery, assuming such talks take place as part of the decision to vaccinate the infant.

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Dr. Griffin added that women typically remain in the hospital for at least 24 hours postpartum, allowing time for confirmatory testing and administration of infant vaccinations and HBIG, if needed. She reflected that this raises an important question: are we vaccinating all newborns on day one to lower hepatitis B prevalence in high-risk populations, essentially asking babies to solve an adult problem?

Dr. Langer explained that while a rapid hepatitis B test can sometimes be completed within 30 minutes to an hour, this assumes an ideal situation. Factors such as births outside hospitals, laboratory backlogs, or the need for confirmatory testing can cause delays in results. He noted that vaccination within 12 hours can avoid these risks and ensure timely protection. He added that there are no data showing harm from vaccinating at birth compared to one month, but there are potential harms to delaying the dose, while the vaccination series would still be needed regardless.

Dr. Kulldorff clarified that initial rapid testing can identify if a mother is negative within a short time, while positive results require longer confirmatory testing.

Dr. Griffin agreed, noting that the purpose of screening is to quickly identify those at risk, which allows for counseling and informed consent. She confirmed that in practice, results are available within a few hours, certainly within the first day, while the patient is still in the hospital.

Dr. Kulldorff added that for the committee's decision, it is only necessary to know if the mother is negative. If the initial test is positive, the mother can be treated as positive without waiting for confirmation.

Dr. Griffin agreed.

Dr. Pollak noted that data suggest children not vaccinated in the perinatal period are much less likely to return for vaccination later, with a hazard ratio of three. He emphasized that this disproportionately affects single mothers, women of low socioeconomic status, persons of color, and high-risk groups such as Alaskans and First Nations. He requested data from the CDC on follow-up and vaccination completion among infants who were not vaccinated at birth, such as those weighing under 2,000 grams or those with contraindications.

Dr. Langer responded that there is an association between receiving the birth dose and completing the vaccine series on time. Infants who do not receive the birth dose are less likely to be vaccinated later.

Dr. Pagano asked whether this association is confounded by parental choice, noting that some parents may refuse the birth dose and also decline later doses.

Dr. Langer agreed that the association does not imply causation. Parents who accept the birth dose are more likely to complete the series, but the underlying factor may be parental willingness rather than the timing of the first dose.

Dr. Levi noted that Canada's provinces have a wide range of hepatitis B vaccination policies, with first doses given as early as two months or as late as 11–12 years. He asked whether outcomes differ by province and if delaying vaccination for infants of mothers with negative test results shows any impact on incidence.

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Dr. Meissner emphasized that targeting select groups for vaccination has historically been less effective than broad recommendations. He noted the difficulty of identifying and vaccinating high-risk groups such as IV drug users, sex workers, and people experiencing homelessness. He added that hepatitis B vaccination at birth, followed by the recommended series, likely provides lifelong protection, as even if antibodies wane, cellular immunity produces an anamnestic response upon exposure. He argued that no data suggest that vaccination at two or three months is safer than at birth, calling the vaccine extremely safe, with severe allergic reactions occurring in approximately one in a million doses. He questioned what would be gained by delaying the birth dose.

Dr. Hibbeln asked for clarification that hepatitis B can be transmitted to infants from sources other than the mother, noting that the virus survives on surfaces and can be spread by many people.

Dr. Levi responded that he was not aware of any documented data showing children becoming infected through such mechanisms, although he acknowledged that he could have missed relevant studies.

Dr. Langer pointed out that during his presentation, he discussed a study of U.S.-born children of immigrant mothers who tested negative at birth found that 7–11% later tested positive for hepatitis B surface antigen, proving infections occurred postnatally. These children were too young for sexual or injection drug exposures, and their mothers were confirmed negative, so transmission had to occur through casual or household contact. He added that the virus can survive on indoor surfaces for at least seven days, supporting the likelihood of community or household transmission.

Dr. Stein observed that the percentages cited for infections from non-maternal sources represent attributable risk rather than raw incidence counts. She emphasized that while still important, these numbers are not the same as direct incidence data.

Dr. Hibbeln responded that his concern was not about exact numbers but about the framing of the committee's vote, which divides infants only by maternal hepatitis B status. He argued that infections can occur from other household or community sources, and therefore, relying solely on maternal status is insufficient. He stated that the most prudent approach would be to vaccinate as many children as possible to protect them broadly.

Dr. Griffin noted that informed consent discussions and social history intake are part of medical practice, where providers assess risk factors with patients.

Dr. Hibbeln countered that if roughly half of infected people are unaware of their status, informed consent discussions cannot reliably identify risk.

Dr. Griffin replied that physicians should still ask these questions and document the responses in electronic medical records, which could eventually be analyzed using advanced tools.

Dr. Hibbeln responded that patients often cannot answer questions about their household infection status if no one in the household has been tested.

Dr. Griffin reiterated that risk assessment must start somewhere.

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Dr. Hibbeln concluded that if the goal is lifelong universal protection from a vaccine with very few side effects, then limiting the recommendation based on maternal status alone is flawed, since infection can occur from many sources throughout life.

Dr. Meissner emphasized that medicine is not precise, and the risk for hepatitis B cannot be reliably determined through questioning alone, similar to HIV. He added that maternal testing is not perfect, with potential errors in transcription, assay performance, and distinguishing between hepatitis B surface antigen and surface antibody. He concluded that no system will ever identify all hepatitis B surface antigen–positive mothers at delivery with 100% accuracy.

The ACIP chair, Dr. Kulldorff, requested a review of the 2004 study by Garly and colleagues titled *Hepatitis B vaccination associated with higher female than male mortality in Guinea-Bissau: an observational study*. The review included an assessment of non-specific effects of vaccination and findings from a rapid systematic review on mortality following hepatitis B vaccination.

Non-specific effects are defined as vaccine effects beyond protection against the target pathogen, possibly due to changes in the immune system. These differ from adverse, cross-protective, or indirect downstream effects. Clinical manifestations may include all-cause mortality, increased susceptibility to unrelated infections, or an increased risk of allergic and autoimmune diseases. Live attenuated and non-live vaccines may differ in these effects.

Garly and colleagues noted that while some studies have examined non-specific effects of vaccines on all-cause mortality, few have assessed hepatitis B vaccination specifically. Their study aimed to determine whether the hepatitis B vaccine was associated with sex-specific differences in mortality. The study was conducted within a trial of a two-dose standard measles vaccine in the Bandim Health Project surveillance system in Guinea-Bissau. Birth cohorts from March 1994 through February 2000 were included. Children born from March 1996 through February 1997 were eligible to receive a hepatitis B vaccine at 7.5, 9, and 10.5 months of age. The product used was a human plasma-derived vaccine, which is not licensed in the U.S. [This raises questions about the applicability or relevance of the Garly et al. study to current U.S. hepatitis B immunization recommendations.]

A Review of the Safety of Hepatitis B Birth Dose Vaccination

Dr. John Su (CDC/NCEZID)

Dr. John Su (CDC/NCEZID) reviewed the safety of hepatitis B birth dose vaccination. The ACIP chair requested safety data on hepatitis B administration within 24 hours of birth from the CDC's Vaccine Safety Datalink (VSD) and the FDA's Biologics Effectiveness and Safety System. The request included mild and serious adverse events, all-cause morbidity and mortality, short- and long-term safety, outcomes of predetermined concern, and data-mining results, with findings reported both combined and stratified by sex.

To address this, the CDC conducted a rapid systematic review of safety data on hepatitis B vaccination within 24 hours of birth. The key question was the safety of the vaccine when administered in the first 30 days of life. To capture a broad range of studies, the review included all vaccines administered within 30 days, not just 24 hours. The search was performed on July 31, 2025, using PICO(ST) criteria, and databases searched included Medline, EMBASE, CINAHL, and Cochrane.

Inclusion criteria were newborn infants receiving hepatitis B vaccine at 30 days or less, randomized controlled trials, observational studies, case series with 10 or more patients, and

surveillance data. Outcomes included safety, adverse events, serious adverse events, and side effects. Exclusion criteria included non-English articles, animal studies, populations not receiving the vaccine within 30 days or less, case series with fewer than 10 patients, clinical trial protocols, conference abstracts or posters, proceedings, or journal titles beginning with a number.

The search identified 1,916 studies; after removing duplicates, 1,907 remained. Title and abstract screening excluded 1,678, and full-text review excluded another 158. Of the 71 studies left, 20 either focused on the birth dose or reported results stratified by birth dose.

Among these, five defined birth dose as administration within 24 hours of birth, including one VSD study. Four, including another VSD study, used terms such as “at birth,” “birth dose,” or “within 120 hours.” One study reported that 85% of infants received hepatitis B on the day of birth, with none vaccinated beyond 8 days. The remaining 11 studies allowed vaccination at any time in the first month of life; although included in the systematic review provided to ACIP, they were not discussed at the meeting.

Studies evaluated local reactions. One randomized trial found 7.7% of infants experienced pain with movement or pressure within 5 days of vaccination. Three studies reported pain or soreness within 4 days for fewer than 10% of infants, with few severe cases. For injection site redness, one trial reported none within 5 days, while three studies reported 8–20% within 4 days, with no severe cases. For swelling, one trial reported a 7.7% rate within 5 days, while three studies reported 0–4% within 4 days, with no severe cases. One trial that evaluated local reactions as a combined outcome found 2.8% of infants experienced a reaction within the first week.

Studies also evaluated systemic reactions. Four studies on fever after hepatitis B vaccination within 24 hours of birth reported rates ranging from 0 to 5.6% during birth hospitalization up to 21 days after birth. Among three studies where vaccination occurred within 0–5 days of birth, fever within 4 days of vaccination was reported for 0–5.9% of newborns. Few cases were severe.

For anorexia or decreased appetite, one randomized trial of vaccination within 24 hours of birth reported no cases within 5 days of vaccination. In three studies where vaccination occurred within 5 days of birth, anorexia, feeding issues, or decreased appetite within 4 days of vaccination were reported in 2.6–16.5% of newborns, with few severe cases.

For diarrhea or vomiting, one randomized trial of vaccination within 24 hours of birth reported no cases within 5 days of vaccination. Two additional studies where vaccination occurred within 5 days of birth found diarrhea or vomiting within 3 days of vaccination in 8.1–11.7% and 4.4–22.3% of infants, respectively, with no severe cases.

For irritability or fussiness, one randomized trial of vaccination within 24 hours of birth reported 11.5% of infants affected within 5 days of vaccination. Across three other studies where vaccination occurred within 5 days of birth, irritability, fussiness, or unusual crying within 4 days of vaccination was reported in 1.5–22.1% of infants. Few cases were severe.

No studies specifically evaluated sleep disturbance after vaccination within 24 hours of birth. However, three studies where vaccination occurred within 5 days of birth reported drowsiness or increased sleep within 4 days of vaccination in 5.1–32.4% of infants, and restlessness or reduced sleep within 3 days of vaccination in 16.9–31.1% of infants. Few cases were severe.

A cohort study of vaccination within 24 hours of birth found no differences in care for allergic reactions between vaccinated and unvaccinated newborns within 21 days of life. No additional studies evaluated allergic reactions in infants vaccinated within 5 days of birth.

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One study evaluated infections after hepatitis B vaccination within 24 hours of birth. In this cohort study, vaccinated newborns were less likely to be evaluated for possible sepsis and less likely to have a positive blood or cerebrospinal fluid culture. No studies assessed infections among newborns vaccinated within 5 days of birth.

Two studies examined other adverse events. In one cohort, hepatitis B vaccination within 24 hours of birth did not increase the risk of seizures or other neurologic disorders. In another cohort of preterm infants identified through Australia's surveillance system, hepatitis B vaccination appeared to have a slight protective effect against bronchopulmonary dysplasia. In an additional cohort where vaccination was administered within 5 days of birth, one serious adverse event was reported: a cough that required hospitalization 37 days after vaccination, which the investigators deemed unrelated.

One study evaluated all-cause mortality after hepatitis B vaccination within 24 hours of birth. In a cohort of preterm infants in Australia, there were no differences in mortality within 3 months of life between vaccinated and unvaccinated infants. Two studies assessed mortality after hepatitis B vaccination within 8 days of birth. In one randomized trial, no deaths occurred during a 7-month follow-up period among infants who received the hepatitis B vaccine within 4 days of birth. In a large US cohort study including more than 350,000 live births between 1993 and 1998, 1,363 neonatal deaths within 29 days were identified. Of these, 72 (5%) occurred in infants who received the hepatitis B vaccine at birth. No significant differences were observed between vaccinated and unvaccinated newborns in rates of expected or unexpected deaths, including deaths due to sudden infant death syndrome.

Limitations of this rapid systematic review include the small number of studies on hepatitis B vaccination within 24 hours, inconsistent reporting of timing, and heterogeneous methods that prevented meta-analysis. Most studies have focused only on short-term outcomes, such as reactogenicity or mortality within 30 days, while long-term outcomes have not been captured.

Dr. Su concluded that the review found no increased risk for allergic reactions, mortality, sudden infant death syndrome, seizures, or other neurologic disease. Compared to infants who did not receive the birth dose, those who did had lower risks of invasive diagnostic procedures, positive cultures, and bronchopulmonary dysplasia. Results on short-term reactogenicity varied across studies.

Non-specific effects following hepatitis B vaccination
Dr. John Su (CDC/NCEZID)

Dr. John Su (CDC/NCEZID) shared data on non-specific effects following hepatitis B vaccination. The ACIP chair requested that the Immunization Safety Office present the 2004 study by Garly and colleagues, "Hepatitis B vaccination associated with higher female than male mortality in Guinea-Bissau: an observational study." In addition, Dr. Su presented the results of a rapid systematic review of non-specific effects (NSEs) of Hepatitis B vaccination, including data on mortality after hepatitis B vaccination. NSEs are effects beyond protection against the target pathogen, potentially mediated by immune system changes; they are distinct from adverse, cross-protective, or indirect effects, and may manifest as changes in all-cause mortality, unrelated infections, or risk of allergic and autoimmune diseases. Live-attenuated and non-live vaccines may differ in their NSEs.

The Garly 2004 study aimed to assess whether hepatitis B vaccination is associated with sex-specific differences in mortality. It was conducted within a two-dose standard measles vaccine trial embedded in the Bandim Health Project surveillance system in Guinea-Bissau. Birth cohorts from March 1994 through February 2000 were enrolled. Children born from March 1996

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to February 1997 were eligible for the hepatitis B vaccine at 7.5, 9, and 10.5 months of age. The hepatitis B product used was a human plasma–derived vaccine not licensed for use in the U.S.

Dr. Su summarized three mortality comparisons. First, across birth cohorts, mortality at 7.5–12 months was compared with mortality at 1.5–7.5 months; overall, the rate ratio was 0.97, but in the year when most children received the hepatitis B vaccine at 7.5 months, it was 1.62 (95% CI, 1.09–2.41). Second, among 5,441 children in the two-dose measles vaccine trial, the mortality rate ratio at 7.5–12 months was 1.81 (95% CI, 1.19–2.75) for hepatitis B-vaccinated children compared to unvaccinated children. Third, among measles-vaccinated children, the female-to-male mortality rate ratio was 1.66 (95% CI 0.80–3.45) through 12 months of age for those who also received hepatitis B vaccine; through 24 months of age, the rate ratio was 2.20 (95% CI 1.07–4.54) with both vaccines versus 0.96 (95% CI 0.70–1.32) with measles vaccine only. The study authors (Garly, et al.) concluded these analyses suggest changes in mortality patterns after hepatitis B vaccine introduction in a high-mortality setting, with a stronger effect among females, raising the possibility of sex-differential non-specific effects.

These analyses were not planned when the trial was designed, and the study was not randomized, so unbiased comparisons over the same time period could not be ensured. Hepatitis B vaccine was administered at 7.5, 9, and 10–10.5 months in this study; therefore, the effects may differ when given at birth or alongside other vaccines, such as BCG. A higher female-to-male mortality ratio could also reflect reduced male mortality.

A rapid systematic review was conducted to [address the question, “What are the non-specific effects of hepatitis B-containing vaccines administered in childhood?”] The review included studies published through August 20, 2025, among infants and children up to six years of age who received either a monovalent hepatitis B vaccine or a combined vaccine, compared with any or no comparator. Outcomes included non-specific effects; studies in any setting and of any duration of follow up were included for review.

Inclusion criteria allowed for clinical trials, observational studies, surveillance reports, and systematic reviews. Eligible populations included infants and children younger than seven years of age who had received a hepatitis B vaccine, either alone or in combination. Included studies evaluated outcomes related to non-specific effects. Exclusion criteria ruled out case reports and case series, narrative reviews, animal studies, children older than seven years, adults, vaccines other than hepatitis B, and studies assessing outcomes outside of non-specific effects.

A total of 2,068 studies were identified. After keyword screening, 237 remained; however, 221 were excluded during the title and abstract review. Sixteen full texts were reviewed, and eight were excluded, resulting in eight studies included in the final review.

Of the eight included studies, four evaluated the hepatitis B vaccine as part of a pentavalent vaccine and four evaluated the monovalent vaccine. Seven were cohort studies and one was a nested case series. Six studies were conducted in low- and middle-income countries and two in high-income countries. Four studies evaluated mortality, five assessed sex-differential mortality, and one examined another non-specific effect.

Among the three studies that evaluated mortality, two cohort studies in high-income countries found no association between hepatitis B vaccination and all-cause mortality. A cohort study conducted in a low- to middle-income country found an increased risk of all-cause mortality following vaccination.

Evidence regarding sex-specific mortality was inconsistent. One study observed both no difference and an increase in the female-to-male mortality ratio. Another study suggested that there is no difference in mortality by sex.

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One cohort study in a high-income country evaluated cancer-related and cardiovascular-related mortality and found no effect of hepatitis B vaccination on these outcomes.

Overall, there are few studies available to inform the non-specific effects of hepatitis B vaccination in children. Studies in high-income countries found no association with all-cause mortality, while one study in a low- to middle-income country suggested an increased risk. Evidence regarding sex-specific mortality was inconsistent.

Dr. Su concluded that non-specific effects may vary in settings with different background mortality rates and infectious diseases burden. These effects may not be generalizable across immunization programs and might also vary depending on the specific vaccine product used. For example, Heppacine is not licensed for use in the United States, where the hepatitis B vaccine is administered earlier and often in combination with other routine vaccines. The biological, molecular, and immunologic mechanisms underlying non-specific effects are not fully understood. In particular, the timing between vaccination and the onset of any non-specific effect, as well as the duration of such effects, remains uncertain. The duration of a vaccine's non-specific effect may also be complicated by subsequent vaccinations received.

Discussion

Rick Haupt (Merck), head of the ID Vaccines Medical and Scientific Affairs group, shared a manufacturer statement. He referred to Dr. Langer's presentation, which highlighted the rationale and importance of routine newborn vaccination as a crucial public health strategy to prevent chronic viral hepatitis and its severe long-term consequences. He noted that the risk of developing chronic hepatitis B infection is strongly age-dependent, with up to 90% of infants infected at birth progressing to chronic infection, which can lead to chronic liver disease and liver cancer. Transmission may occur from an infected mother or through close contact with an infected family member. He emphasized that the CDC has reported that one in two people is unaware of their infection status. He stated that Merck's Hep B vaccine, Mercivovax HB, was first approved in the United States in 1986 and has been a foundation of hepatitis B prevention, with more than 330 million doses distributed between 1990 and 2019. Universal infant and childhood vaccination for hepatitis B has resulted in a 99% decline in reported cases of acute hepatitis B among children, adolescents, and young adults under 19 years of age. He concluded that vaccines remain the best defense against many serious diseases, with strong scientific evidence supporting their use. He cautioned that reconsidering newborn hepatitis B vaccination on the established schedule would pose a serious risk to the health of children and the public and could lead to a resurgence of preventable infectious diseases.

Ayman Chit (Sanofi), head of the medical affairs department at Sanofi Vaccines in the United States, shared a manufacturer statement. He emphasized that the company's top priority is ensuring access to safe and effective vaccines. He stated that administration of hepatitis B dose early in life remains the most effective option for preventing hepatitis B infection in infants and children. He noted that scientific evidence strongly supports the safety of both hepatitis B vaccines and combination vaccines that include hepatitis B, and that these vaccines are continuously monitored by manufacturers, public health agencies, and regulators before and after approval. He cautioned that changes to the hepatitis B infant schedule could disrupt implementation and reduce the benefits provided by combination vaccines. Combination vaccines lessen the number of injections infants receive, improve provider workflow, and help limit administration errors. If recommendations change for one component, providers will need to stock both single-antigen and combination products, creating challenges with supply, storage, handling, administration, and documentation. He warned that delaying the hepatitis B birth dose puts infants at risk of infection and reduces families' options to use combination vaccines. He added that such a change would likely cause significant supply disruptions lasting a year or

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longer due to the production lead time, affecting not only combination vaccines but also single-antigen products such as Hib and polio. He concluded that maintaining current recommendations for hepatitis B vaccination is critical to ensure infants remain protected early in life, high-risk infants are not missed, and families continue to have access to widely available combination vaccines that protect against multiple vaccine-preventable diseases.

Dr. Griffin stated that regarding the first presentation, she wanted to know how many of the studies were based on thimerosal-containing vaccination.

Dr. Hause from the Immunization Safety Office stated that she did not have the number on hand but could provide it after a brief review.

Dr. Griffin stated that she asked because there has not been a hepatitis B vaccine containing thimerosal since 2001. She noted that she counted about five or six such studies and questioned the rationale for including them. She asked if any of the studies were designed to have safety as the primary endpoint, since many appeared to focus on immunogenicity.

Dr. Su stated that safety was part of the studies but deferred to colleagues for clarification on whether safety was the primary endpoint.

Dr. Hause stated that several studies evaluated safety as the primary endpoint and that several randomized controlled trials also included safety as a secondary endpoint.

Dr. Griffin asked how many studies were specifically designed with safety as the outcome.

Dr. Hause stated that three studies specifically examined safety as an outcome.

Dr. Griffin clarified that this meant three out of twenty studies and requested to go back to slide 23 from the first presentation.

Dr. Hause clarified that three out of nine studies were presented in the slides.

Dr. Griffin thanked her and requested that slide 23 be pulled up, noting it was a summary slide. She inquired about the commentary on bronchopulmonary dysplasia, pointing out that she had found one article, Morgan et al. (2025), and questioned whether that was the only study used in the summary.

Dr. Hause confirmed that it was.

Dr. Griffin expressed concern, stating that the authors of that study declared seven significant limitations. She highlighted the inability to control for confounding factors, including infections and respiratory support, and noted that clinician perception of newborn stability could also influence vaccination decisions. She emphasized that withholding vaccination in unwell infants could confound results and underestimate risks. She then asked if there were any other studies showing findings related to bronchopulmonary dysplasia.

Dr. Hause stated that the study in question was included because it met the criteria for systematic review. She noted that no other studies identified in the review met the criteria with bronchopulmonary dysplasia as the outcome.

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Dr. Pebsworth referred to slide 15 from the first presentation, which evaluated systemic reactions such as irritability, fussiness, or crying, noting rates of 20–22% among participants. She stated that these rates seemed very high, particularly since they may be early symptoms of neurologic problems requiring long-term follow-up, which is lacking in the available data. She commented on the Institute of Medicine (IOM) reports, clarifying that the IOM did not conclude that the hepatitis B vaccine was safe but instead reviewed multiple conditions and assessed the weight of epidemiologic evidence, mechanistic evidence, and causality conclusions. She noted that the IOM reviewed three reports on hepatitis B between 1994 and 2012 and concluded that the evidence was inadequate to accept or reject a causal relationship between the hepatitis B vaccine and conditions such as encephalitis and encephalopathy. Additionally, the IOM found that of 26 conditions reviewed, this same conclusion applied to at least 24 of them. She listed several of the conditions considered in the IOM report, including encephalitis, encephalopathy, seizures, acute disseminated encephalomyelitis, transverse myelitis, optic neuritis, neuromyelitis Optica, multiple sclerosis onset and relapse, Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, lupus, vasculitis, polyarteritis nodosa, psoriatic arthritis, and reactive arthritis, emphasizing that the IOM conclusions indicated uncertainty rather than confirmation of safety. She also referenced a 2024 systematic review on the safety of hepatitis B vaccines in preterm infants, noting that it found no publications on the timing of the birth dose and adverse events, and that reporting was limited to short-term outcomes, highlighting that research on the safety of hepatitis B vaccination in preterm infants within seven days of birth, especially regarding long-term morbidity, is lacking. She further referenced a 2016 mouse model study showing that neonatal hepatitis B vaccination impaired behavior and neurogenesis in early adulthood, with the conclusion that vaccination impaired hippocampal LTP and neurogenesis and that the possible mechanism involved alterations in the brain neuroimmune milieu from a systemic TH2 bias. She concluded that there are gaps in knowledge about the effects of hepatitis B vaccination on very young infants and stated that concluding the vaccine is safe may be premature.

Dr. Levi stated that the Garly paper was one of the most well-done examples of a natural randomized experiment. He recalled that children vaccinated between seven and a half months and 12 months showed almost 80% higher mortality compared to other cohorts. He asked why this result was not discussed and whether it was because the focus was on earlier age groups.

Dr. Su asked if Dr. Levi was referring to the Garly paper and clarified that he was reviewing his slides. [This finding was presented on slide nine. In comparison two, among children enrolled in the measles vaccine trial, compared with HBV-unvaccinated children, the mortality rate ratio for children 7.5-12 months of age from the HBV-vaccinated cohort was 1.81 (95% CI 1.19, 2.75).]

Dr. Kulldorff stated that while Dr. Su was reviewing, the discussion could move to Dr. Milhoan.

Dr. Milhoan stated that the neonatal period is a very sacred time for intervention and that medical decisions at this stage must be approached with caution, as any changes in the baby's condition lead to invasive evaluations and treatments. He explained that risks are higher for procedures such as anesthesia and surgery in newborns, particularly premature infants. He emphasized that while public health prioritizes populations, it does not always prioritize individual patients, and decisions for the most vulnerable must be made with utmost caution. He questioned whether seroconversion rates had been evaluated starting at two months rather than at birth, pointing out that while seroconversion occurs at a rate of 26% at birth, higher levels are achieved after subsequent doses, with approximately 95% after the third dose. He suggested that beginning vaccination later might reduce the number of doses required and decrease risk,

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since every injection carries some risk. He asked whether T-cell immunity, which may be more robust early in life, had been considered as part of the vaccine response.

Dr. Levi added that seroconversion rates were 25% after the first dose, 63% after the second dose, and 95% after the third dose.

Dr. Milhoan stated that if vaccination began at two months and continued at six months, the seroconversion rate should be examined to see whether earlier vaccination unnecessarily adds doses. He clarified that he was not advocating against vaccination but instead suggesting that risks could be reduced if the schedule were reevaluated. He also referred to slide 23, which summarized death outcomes, stating that rather than showing a positive effect of hepatitis B vaccination, the data reflected selection bias: healthier children were more likely to be vaccinated early, leading to more favorable outcomes unrelated to the vaccine. He noted that this reflected selection rather than a true protective effect.

Dr. Kulldorff added that this phenomenon is called “healthy vaccination.”

Dr. Milhoan continued by noting that while outcomes reported included allergic reactions and all-cause mortality, other important outcomes were missing. He asked whether data were available on whether infants required advanced care or were coded.

Dr. Su stated that he did not have that information and referred to the investigators of the paper.

Dr. Blackburn asked how the language was decided to recommend vaccination at one month rather than two months, noting that most other countries recommend delaying for hepatitis B-negative mothers. She stated that while she could see justification for this approach, she was concerned when reviewing safety data about the risks of fever and poor feeding. She explained that any fever in a newborn under 28 days is considered a medical emergency and typically prompts a full sepsis workup, spinal tap, hospitalization, and empiric IV antibiotics. She added that, as a parent with firsthand experience, early feeding is essential to successful breastfeeding, and a decreased appetite in the early days of life can have a significant impact. She emphasized that these risks should be taken into consideration when weighing the benefits and harms.

Dr. Kulldorff responded that the decision was related to the fact that the second dose in the U.S. is recommended between one and two months of age, and he noted that he had been personally involved in discussions about the recommendation with CDC staff.

Dr. Malone stated that while concerns about irritability, fever, and poor feeding may or may not be indicators of neurological problems, it is important not to base votes or recommendations on speculation. He emphasized that decisions should be based on data reflecting concrete risks or benefits, rather than hypothetical clinical outcomes for which there is no evidence. He referenced the IOM findings, noting that although neurological outcomes had been considered, there was no evidence to make a causal link either for or against such conditions. He concluded that the committee should not extend beyond the data when making determinations.

Dr. Meissner stated that there is no association or lack of association between the hepatitis B vaccine and bronchopulmonary dysplasia (BPD). He explained that BPD occurs in preterm babies who are typically more than 10 weeks early, weigh less than two pounds, and are often mechanically ventilated. He emphasized that the condition results from barotrauma or trauma associated with mechanical ventilation, making it biologically implausible for the hepatitis B

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vaccine to have any relationship with BPD, and he advised not placing too much concern there. He then referred to the Garly study and asked for clarification, noting that Dr. Su had given excellent presentations, and inquiring whether the vaccine in that study was a human plasma–derived hepatitis B vaccine.

Dr. Su stated that the Garly paper involved a plasma-derived hepatitis B vaccine.

Dr. Meissner explained that the original hepatitis B vaccine was produced from the plasma of people with chronic hepatitis B, which was then inactivated by heat or chemical treatment to prevent infection before being concentrated. He emphasized that this vaccine was very different from the current vaccine, which is made using cloned hepatitis B surface antigen in yeast, resulting in a pure and well-defined product. He stated that the vaccine used in the Garly study was not the same as the modern vaccine and therefore should not be emphasized in current discussions. He further noted that changing the recommendation for neonatal administration of the hepatitis B vaccine would increase the risk of harm without evidence of benefit, as fewer children would complete the full hepatitis B vaccine series if initiation were delayed. He noted that beginning vaccination in the hospital ensures that at least the first dose is administered. He stressed that there is no evidence to suggest that the vaccine becomes less safe over time, that it is extremely safe and pure, and that changing the recommendation could create unjustified public doubts. He concluded that there is no evidence of harm from administering the neonatal vaccine, either from presentations or from his review of the literature and expressed concern about changing the recommendation.

Dr. Malone stated that he agreed with Dr. Meissner that the BPD signal was artifactual. He noted that the reported improvement in risk of BPD in the paper likely reflects healthy vaccine bias or reporting bias. He concurred that the Garly study involved the historic plasma-derived vaccine, which was associated with adverse events not relevant to the modern product. He noted that the question of changing recommendations also raised moral and ethical considerations. He added that what he had not heard was clear data on the risks to premature infants, and he asked for clarification on whether there are differences in safety, effectiveness, immunogenicity, or seroconversion between premature infants and healthy newborns.

Dr. Su responded that he could speak about the safety aspects, noting that the data were limited to the studies that met the inclusion criteria. He stated that a few of those studies addressed adverse events in premature infants, but deferred to other experts in the room for further knowledge on that topic.

Dr. Hause stated that only one study met the criteria for the systematic review that looked at premature infants, which was the Morgan study with the outcome of bronchopulmonary dysplasia. She added that only one study specifically listed the use of a thimerosal-containing hepatitis B vaccine.

Dr. Malone stated that, based on the discussion, there appeared to be insufficient data to assess safety, immunogenicity, and seroconversion in premature infants, and he asked for confirmation.

Dr. Langer responded that under the current recommendation, newborns weighing less than 2,000 grams who are born to hepatitis B-negative mothers should not be vaccinated at birth. He clarified that the recommendation is to wait for one month.

Dr. Milhoan asked whether the one month referred to gestational age or corrected age.

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Dr. Langer stated that he would defer to colleagues on that detail.

Dr. Meissner stated that the recommendation is to wait until one month of age or until discharge from the neonatal unit to home.

Dr. Kulldorff confirmed that this was correct.

Dr. Stein stated that her question concerned the extensive data provided in the summary document, which included many detailed study summaries. She asked for clarification on what is meant by “low confidence.”

Dr. Hause explained that each study was reviewed for risk of bias and graded using standardized tools for systematic review. She stated that results varied by study, particularly in relation to study design, and that details could be provided to the committee after the meeting.

Dr. Stein added that several studies had shown potential long-term risks, but that bias might influence these findings, and she had not reviewed them in detail.

Dr. Hause stated that there are studies examining long-term outcomes in the larger systematic review. However, they were not included in the presentation because they did not assess hepatitis B doses given within the first 24 hours of life, which was the specific request of ACIP. She noted that those studies could be provided to the committee separately.

Dr. Middleman asked two questions. First, she asked what problem exists in the current schedule that prompted the discussion, noting that the hepatitis B immunization schedule has been highly successful, with a favorable benefit-to-risk ratio. She emphasized that while there are always risks and benefits to weigh, risk-based approaches to vaccination have historically not been effective across multiple vaccines. She expressed uncertainty about what specific issue had led to reopening the discussion. Second, she commented on the exclusion of liaison members from working groups, noting that liaison members bring extensive knowledge and represent patients. She emphasized that their perspectives on issues such as adjuvants or neonatal vaccination thresholds add value to vaccine recommendations. She asked how liaison members might be included again to contribute on behalf of their patients and their expertise.

Dr. Kulldorff responded to the second question, explaining that the exclusion of liaison members from working groups was a CDC-wide Federal Advisory Committee Act (FACA) policy, which was outside the control of ACIP. He stated that in the past, ACIP had not been following this requirement, and the change was necessary to align with FACA rules. He agreed that liaison member input is valuable, but clarified that outside experts, including those affiliated with organizations represented by liaison members, are included in working groups. He explained that these experts serve as individuals rather than representatives of their organizations. He concluded that while outside expertise is incorporated, ACIP must comply with FACA policy regarding liaison members. Regarding the first question, he invited Dr. Levi to respond.

Dr. Levi shared two personal experiences. He stated that he had received the hepatitis B vaccine as an adult before traveling to high-risk areas, and that all six of his children received the vaccine on the first day of life without prior discussion or informed consent. He suggested that this illustrates how often informed consent may not occur for this vaccine. He expressed concern about the frequent claim that “there is no evidence of harm,” emphasizing that the relevant question is whether there is evidence of no harm, particularly for a vaccine

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administered on the first day of life to healthy infants. He argued that the risk of not vaccinating on the first day of life is likely negligible during the first several months or even years. He questioned why there have been no large, long-term randomized clinical trials (RCTs) to resolve the debate about safety, stating that the lack of such trials reflects broader problems with the medical system and vaccine research. He reiterated his belief that the hepatitis B vaccine is life-saving and essential for high-risk infants and adults. Still, he stated that arguing from weak evidence undermines trust and is not a scientific approach. He described the absence of long-term RCTs as the "elephant in the room."

Dr. Fryhofer, a general internal medicine physician in full-time practice and the American Medical Association (AMA) liaison. She disclosed that she had received the hepatitis B vaccine as a medical student after rotating through a hepatitis ward, where she saw severely ill patients. She stated she was thankful the vaccine exists. She explained that the hepatitis B virus primarily affects the liver and can cause chronic infection, cirrhosis, liver cancer, and death. She noted that the virus can be transmitted in utero and through bloodborne routes, and that when transmission occurs in utero, 90% of infants remain chronically infected. She highlighted that administering the hepatitis B vaccine at birth has nearly eliminated perinatal hepatitis B, with only 13 cases reported in 2022. She emphasized that the birth dose is safe and effective and stated that the AMA strongly urges ACIP to maintain the recommendation for newborn vaccination.

Dr. Munoz, a pediatric infectious diseases physician specializing in transplant infectious diseases at an institution that performs the largest number of pediatric liver transplants in the country, and a clinician-investigator with many years of vaccine research experience, asked why the hepatitis B vaccine recommendation is under review and whether there is a specific reason for considering a change. She emphasized that the data presented show significant declines in hepatitis B incidence and long-term consequences due to vaccination, both in children and adults, and that this progress is directly attributable to vaccination. She noted that the vaccine strategy is safe, effective, and widely implemented globally, with U.S. data suggesting that hepatitis B could be eliminated through continued vaccination. She emphasized that risk-based strategies are imperfect due to potential false-negative tests, inadequate prenatal care, limited access, and gaps in understanding vaccine benefits. She warned that changing the recommendation could reintroduce vertical transmission or leave adolescents unprotected, resulting in severe disease. She concluded that the vaccine is very safe, that those at greatest risk would be most affected by changes. She urged the committee to maintain the current recommendation to protect both individuals and the broader public, especially the most vulnerable.

Dr. Paulsen, a liaison with the Pediatric Infectious Disease Society, stated that he agreed with the concerns raised by ACIP members regarding the protection of children in the newborn period, which he described as a sensitive time. He noted that the hepatitis B birth dose ultimately comes down to weighing risks and benefits. He emphasized that CDC presentations consistently showed the risks to be low and that the data specifically focused on the infant birth dose. He highlighted that fever in infants often prompts a sepsis workup, including a lumbar puncture, but that CDC data showed the risk of requiring such a workup was lower in infants who received the hepatitis B vaccine within 24 hours. He concluded that the benefit is avoiding a lifelong, chronic, vaccine-preventable infection. While in an ideal world, all maternal infections would be known and properly managed, public policy must be based on what protects the population broadly. He urged ACIP to continue preventing infection in children rather than treating hepatitis B as an adult problem.

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Dr. Buchanan, representing the National Association of Pediatric Nurse Practitioners, stated that she wanted to echo and reiterate the safety of the vaccine. She shared her personal experience caring for many children and administering the hepatitis B vaccine in clinics, emphasizing that under her care, no child had been harmed by the vaccine. She added that while members were sharing personal accounts, she also wanted to raise the broader question many were asking: why the vaccine's safety is being reconsidered now, given its well-established record of safety over several decades.

Dr. Hayes, representing the American College of Nurse Midwives, stated that in most facilities, when a woman in labor signs the consent form, it includes consent for the hepatitis B vaccine dose. She explained that in her experience, the process functions as a universal consent, with the option for refusal, meaning parents can decline the hepatitis B vaccine if they choose.

Dr. Jshlay, a family physician who provides prenatal care, stated that hepatitis B screening is often done early in pregnancy, but that risk can change over time. She noted that the growing uninsured population, including those losing commercial or Medicaid coverage, increases the likelihood of patients presenting without prenatal care at delivery, making it difficult to obtain timely test results. She added that many patients do not disclose risk information due to embarrassment or stigma. She emphasized that if vaccination approaches differ based on risk, mothers may be stigmatized; universal vaccination avoids this by ensuring all families are treated equally, which supports equity in care.

Dr. Hopkins stated that his greatest concerns related to equity and lack of knowledge. He noted that about 50% of adults in the population, including those presenting for delivery, do not know their hepatitis B status, and congenital hepatitis B infections continue to occur. He stated that removing the birth dose would increase population risk and that equity must remain central in the evidence-to-recommendation framework. He added that while additional long-term data may be needed, as Dr. Levi suggested, it would not make sense to remove a successful intervention while waiting for such data. He concluded that decisions should be made with care and based on the full body of evidence, rather than being rushed.

Dr. Malone stated that the central question repeatedly raised, particularly by liaison representatives, is why the issue of deferring the hepatitis B birth dose to one month is being considered now, given that no clear safety signal has been detected. He suggested that the timing appears to be less tied to scientific evidence and more to public trust, noting that a significant portion of the U.S. population has concerns about vaccine policy, mandates, and the administration of the hepatitis B vaccine at birth without meaningful informed consent. He observed that the birth setting is often stressful and overwhelming, making it difficult for parents to process information and provide truly informed consent, and that some parents feel the vaccine is administered unilaterally by medical professionals. He linked these concerns to broader declines in public trust in vaccines and public health following the COVID-19 pandemic. He referenced Sweden as an example where, despite the absence of vaccine mandates and a hepatitis B birth dose, vaccine uptake is high and infectious disease outcomes are strong, attributing this to greater public trust in Swedish public health. He concluded that the issue before ACIP is not driven by a safety signal but by public discomfort and mistrust, and that while data presented may provide reassurance, many concerns will likely persist. He clarified that he had no direct communication with CDC or HHS leadership on this issue and was offering his perspective based on public opinion trends.

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Proposed recommendations and discussion

Dr. Martin Kulldorff (ACIP Chair)

Proposed Recommendation #1:

All pregnant women should be tested for hepatitis B infection.

Proposed Recommendation #2:

The pediatric vaccine schedule should be updated to reflect the following change:

If a mother tests HBsAG-negative:

-The first dose of the Hepatitis B vaccine is not given until the child is at least one month old.

-Infants may receive a dose of Hepatitis B vaccine before one month, according to individual based decision-making.*

*Also referred to as shared clinical decision-making.

Dr. Kulldorff clarified that if parents choose to have the first dose administered on day one or at any time before one month, even if the mother tests negative, the dose will be covered by CMS, Medicare, Medicaid, and other health insurance providers.

VFC Resolution Update: Hepatitis B Vaccines

Jeanne Santoli (CDC/NCIRD)

Jeanne Santoli (CDC/NCIRD) presented on the resolution with all revisions from the previously approved resolution shown in red. The purpose of the update is to update the Recommended Vaccination Schedule and Intervals section to align with the proposed recommendations regarding the hepatitis B birth dose under discussion today by ACIP. She reviewed the changes to the infant vaccination table, clarifying that for infants weighing at least 2,000 grams and born to mothers who are hepatitis B surface antigen–negative, the timing of the first dose was revised to 1-2 months and the second dose was adjusted to 3-4 months for infants receiving single antigen vaccine. For infants weighing less than 2,000 grams and born to hepatitis B surface antigen–negative mothers, the timing was the same. She explained a revised footnote stating that only the single-antigen hepatitis B vaccine can be given at less than or equal to six weeks of age, replacing prior language that referred to birth. She highlighted two new footnotes reflecting individual-based or shared clinical decision-making for both ≥2,000-gram and <2,000-gram infants with hepatitis B surface antigen–negative mothers, allowing for one dose to be administered before one month of age. She confirmed that there were no changes to children's vaccination schedule table, related table notes, interrupted schedules, minimum dosing intervals, revaccination guidance, recommended dosage, contraindications, or precautions. She closed by noting the standard clause that new guidance published within six months would be incorporated by reference, which was also unchanged.

Votes

Discussion

Dr. Hayes suggested revising the wording slightly to specify the antigen test rather than the antibody test, to provide clearer guidance for clinicians.
Dr. Kulldorff agreed that this was a good suggestion and stated that CDC colleagues could refine the exact language to ensure the proper test was clearly identified.

Vote: Hepatitis B Vaccine Vote #1

Dr. Martin Kulldorff (ACIP Chair) read the following proposed ACIP voting language for the vaccine into the record:

Note: Text enclosed in [brackets] was added following the meeting, per the presenter's request.

All pregnant women should be tested for hepatitis B infection.

Motion/Vote: Hepatitis B Vaccine

Dr. Levi motioned to approve the recommended voting language, stating, "All pregnant women should be tested for hepatitis B infection." Dr. Griffin seconded the motion. No COIs were declared. The motion carried with 12 votes in favor, 0 votes opposed, and 0 abstentions. The disposition of the vote was as follows:

12 Favored: Malone, Hibbeln, Pagano, Milhoan, Blackburn, Griffin, Stein, Pollak, Pebsworth, Levi, Meissner, Kulldorff
0 Opposed:
0 Abstained:

Dr. Pebsworth stated that after reviewing the CDC's presentation, specifically slide 18 on the global distribution of vaccination policies, she noted that in 26 countries, the first dose of the hepatitis B vaccine is given to infants born to hepatitis B surface antigen–negative mothers at two or three months of age. She explained that this included most of Europe, listing England, France, Spain, Germany, Ireland, Norway, Denmark, Sweden, and Iceland. She pointed out that the CDC had also reported variable rates of reactogenicity within the first week of life, with data showing systemic reactions among vaccinated infants. According to the data presented, up to 5% developed a fever, 32% were drowsy or sleeping, 3% had reactions categorized as severe, and irritability, fussiness, or crying was reported for 11% within the first 24 hours and 22% within the first five days. She emphasized that these were not trivial reactions and could affect up to one-third of births. She referenced the 2016 Yang study, which reported that hepatitis B vaccination impaired behavior and neurogenesis, and a 2013 study by Celich, published in the European Journal of Pediatrics, which found that 30% of infants developed significant elevations in C-reactive protein without clinical signs of sepsis and with negative blood cultures. She explained that this indicated a robust inflammatory response occurring during a critical window of neurodevelopment, including neurogenesis and synaptic development. She concluded that, given these findings and CDC data on systemic adverse reactions, the committee should exercise caution and consider adopting a more prudent vaccination policy, similar to that of most European countries, where low-risk newborns are not vaccinated on the first day of life and vaccination is typically delayed until two to three months.

Dr. Malone stated that there were differences between what was presented and what was published regarding the findings of the Institute of Medicine. He explained that, in his interpretation, the IOM report indicated that for the 22 most claimed serious harms, all but one could not be assessed because studies had not been conducted to determine whether the vaccine caused harm or not. He argued that interpreting this absence of data as evidence of safety was misleading. He emphasized that case reports and case series suggest potential harm, and that the IOM report did not conclude safety but rather acknowledged a lack of data. He stated that for interventions in pregnancy and newborns, the burden must be to demonstrate safety, not to assume safety until proven otherwise, and he disagreed with the interpretation that the absence of data implies the product is safe.

Dr. Hibbeln stated that he is a strong advocate for clinical decision-making but noted that the wording of the question was logically inconsistent. He explained that the language said the dose should not be given until one month, but also allowed for clinical decision-making, which

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contradicts the prohibition. He suggested modifying the wording to state that the first dose of hepatitis B is not given until the child is one month old, except in cases where clinical decision-making dictates otherwise, which would resolve the inconsistency.

Dr. Kulldorff asked whether changing the wording to “not recommended” would address the concern.

Dr. Hibbeln responded that the phrasing still created conflict, as it both prohibited and allowed administration. He reiterated that the language should specify that the vaccine is not administered until one month, except in cases where a clinical decision is made.

Dr. Pollak raised a point of order, noting that the committee was debating language without a motion on the floor. He reminded members of Robert’s Rules of Order, explaining that a motion must be made before discussion, after which debate can occur. Then a vote should be taken to either accept or reject the proposal.

Dr. Malone moved to indefinitely postpone the question, noting uncertainty around safety, effectiveness, and timing.

Dr. Pollak motioned to table, and Dr. Malone seconded.

Vote: To table the Hepatitis B Vaccine Vote #2

Motion/Vote: Hepatitis B Vaccine

Dr. Pollak motioned to table the second vote on the Hepatitis B Vaccine. Dr. Malone seconded the motion. No COIs were declared. The motion carried with 11 votes in favor, 1 vote opposed, and 0 abstentions. The disposition of the vote was as follows:

11 Favored: Levi, Pebsworth, Hibbeln, Pollak, Griffin, Stein, Blackburn, Milhoan, Pagano, Malone, Meissner
1 Opposed: Kulldorff
0 Abstained:

Discussion

Dr. Meissner, responding to Dr. Malone’s earlier comments, stated that it is challenging to prove the absence of harm and that such a goal is not practical. He emphasized that extensive experience has been accumulated from administering the vaccine within the first 12 to 24 hours of life, and that the concerns raised about irritability or restlessness are not objective measures for assessing safety. He noted that since the motion to table had passed, there would be no votes on the hepatitis B vaccine during this meeting.

Dr. Stein cautioned against making absolute statements such as declaring the vaccine entirely safe or entirely unsafe. She emphasized that the perception of safety often depends on the perspectives of parents and children. She advised that the committee carefully consider the broader literature and patient experiences before reaching a conclusion.

Dr. Meissner responded that no vaccine is 100% safe or 100% effective. He stressed that providers must weigh whether the benefits of protection outweigh possible side effects for each

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patient. He concluded that, overall, the benefits of the newborn hepatitis B vaccine clearly outweigh any potential adverse effects.

Dr. Munoz stated that she was pleased with the decision to table the vote. She emphasized that there have been 30 years of progress in preventing hepatitis B disease and related cancers, and that the concerns raised about safety were based only on case reports and anecdotes rather than substantial evidence. She urged the committee to use proper processes to address potential concerns, including requesting additional studies if needed. She argued that dismissing a successful program would be more harmful than beneficial, given the data presented. She also commented on the previous vote, noting that hepatitis B testing is already a routine standard of care in prenatal and obstetric practice, and she asked what the committee's plan would be regarding that motion.

Dr. Kulldorff responded that hepatitis B testing is currently conducted in about 86–87% of pregnant women, but the goal should be to move closer to 100%.

Dr. Hopkins stated that if the issue of hepatitis B birth dose is revisited, it should undergo a full review by a work group, including the complete evidence-to-recommendations framework, with particular attention to the domains of equity and practical implementation.

Dr. Goldman echoed Dr. Hopkins' comments and asked the chair to explain what process would be used in the future to review evidence. He emphasized the importance of transparency about whether the committee would continue to use the evidence-to-recommendations framework and the GRADE process that work groups have traditionally used to evaluate trial power, quality, bias, and conflicts of interest. He noted that recent discussions had not gone through the work group process and stated that the public should be aware of how future evidence will be vetted. He commended the committee for tabling the vote to allow further discussion but requested clarification on future methodology.

Dr. Kulldorff stated that he hoped the committee could return to the issue at a future meeting and acknowledged that he could not provide a detailed response at that time.

Dr. Middleman stated that the concerns raised were not limited to hepatitis B but reflected broader issues that had been discussed across the committee. She emphasized that no intervention is without risk, noting that even common treatments, such as Tylenol, amoxicillin, or chemotherapy drugs, carry some level of risk, as does everyday activity, such as walking across the street. She explained that the committee's scientific responsibility is to determine whether the benefits outweigh the risks. She urged members to avoid being distracted by isolated studies and to rely on systematic approaches such as the GRADE framework or the evidence-to-recommendations process to evaluate risks and benefits. She emphasized that the consistent use of these methods is crucial for all vaccine decisions and that some concerns arose from their absence in recent deliberations.

Dr. Levi stated that while he appreciated the emphasis on scientific methods, he was puzzled that many of those advocating for rigorous approaches spoke with great confidence despite the absence of gold-standard, long-term randomized clinical trials against a placebo. He noted that such trials do not exist for this intervention and argued that if the committee seeks to uphold scientific rigor, it should do so consistently. He cautioned that confident statements about vaccines being "safe and effective" were being made without the highest standard of evidence and encouraged members to show greater humility and acknowledge the limitations in the available data.

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Dr. Kulldorff reminded the committee that the motion had been tabled. He encouraged those still wishing to comment to bring their remarks forward if the issue is returned at a future meeting.

Dr. Goldman stated that, as Dr. Levi had mentioned, the committee needs gold-standard evidence to guide decisions. He agreed that this is the role of the work groups and emphasized that the public should be adequately informed about the processes used to vet and discuss future vaccines. He emphasized that the evidence-to-recommendations framework was established to establish a consistent standard for evaluating vaccines, but noted that it had not been applied in recent deliberations. He urged the committee to clearly communicate how vaccine decisions will be analyzed in the future so the public can maintain trust, faith, and confidence in the committee's work.

Dr. Kulldorff responded that Dr. Goldman had already raised this comment previously and that he had addressed it at that time.

PUBLIC COMMENT

The floor was opened for public comment on September 18, 2025. The comments made during the meeting are summarized in this document. Members of the public were also invited to submit written public comments to ACIP through the Federal eRulemaking Portal under Docket Number ID CDC-2025-0454. Visit regulations.gov for access to read the comments received.

Ms. Anu Hosangadi
Hepatitis B Foundation

Ms. Hosangadi spoke on behalf of the Hepatitis B Foundation, emphasizing the long-established safety and efficacy of the hepatitis B vaccine. She noted that since 1982, over a billion doses have been administered worldwide with no new or unexpected safety concerns identified through decades of surveillance and studies. She cited multiple CDC and Vaccine Safety Datalink reviews confirming the vaccine's strong safety record, including studies in newborns and infants showing no increase in adverse outcomes. She highlighted the vaccine's effectiveness in providing long-term protection, its safety among pregnant women and individuals with HIV, and the global data supporting continued universal birth-dose administration. Ms. Hosangadi concluded by affirming that maintaining the universal hepatitis B birth dose is a proven, safe, and lifesaving intervention.

Samantha Sears,
National Consumers League

Ms. Sears, representing the National Consumers League, underscored the importance of ACIP grounding its recommendations in medical science, particularly amid rising public distrust and declining vaccination rates. She urged the committee to preserve the integrity of the U.S. immunization system and to combat misinformation through clear, consistent communication. Ms. Sears expressed concern about potential changes to the childhood vaccine schedule, warning that altering established recommendations could create confusion, reduce access, and impose financial burdens on families. She stressed the need for alignment between ACIP, the American Medical Association, and the American Academy of Pediatrics to avoid contradictory messaging and safeguard children's health.

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Dr. Rita Isabel Lechuga, MD, MPH
NASTAD

Dr. Lechuga, director of the hepatitis team at NASTAD, discussed the public health benefits of universal infant hepatitis B vaccination. She traced the policy's origins to ACIP's 1991 recommendation, which led to a sharp decline in childhood hepatitis B cases by replacing failing selective vaccination strategies. She noted that universal vaccination has been both cost-effective and lifesaving, reducing perinatal transmission from tens of thousands of annual cases to fewer than 1,000 today. Dr. Lechuga described hepatitis B as one of the first "anti-cancer" vaccines due to its ability to prevent hepatitis D and liver cancer. She concluded by expressing hope that continued adherence to the universal birth-dose policy will lead the U.S. to eliminate perinatal hepatitis B transmission.

Michele Montandon
Private Citizen

Ms. Montandon, a family physician and former CDC global health leader, expressed deep concern about the growing spread of vaccine misinformation and its effects on public trust and health systems. Drawing from her international experience treating vaccine-preventable diseases, she condemned recent political interference in public health leadership and decision-making, including the removal of ACIP members and changes to vaccine guidance outside standard scientific channels. She cited the tragic consequences of misinformation, including a recent attack on CDC headquarters, and warned that confusion among physicians and families is already escalating. Ms. Montandon urged the restoration of science-based leadership at HHS and CDC, emphasizing that delays or disruptions to vaccination endanger public safety and erode confidence in the healthcare system.

Dr. Judy Stone, MD
Private Citizen

Dr. Stone, an infectious disease physician with over 40 years of experience, provided a powerful account of witnessing children die from vaccine-preventable diseases. She reminded the committee of the tremendous progress vaccines have achieved in reducing child mortality and disease incidence in the U.S. Dr. Stone warned that misinformation and vaccine hesitancy are reversing these gains, citing the resurgence of measles and other infections. She emphasized that measles is highly contagious and can cause severe complications, including hospitalization and death. Dr. Stone urged ACIP to protect access to vaccines, maintain school vaccination requirements, and uphold its duty to safeguard community health, stressing that society must not go back to the pre-vaccine era.

Mr. Scott Bertani
HealthHIV

Mr. Bertani, director of advocacy at HealthHIV, urged the committee to uphold ACIP's legacy as an independent, science-driven body. He highlighted the public health importance of the hepatitis B birth dose and combination vaccines such as MMRV, which protect infants and reduce the long-term disease burden. He noted that declining vaccine uptake threatens individuals with chronic illnesses and immunocompromised populations, including people living with HIV. Mr. Bertani outlined three recommendations: preserve the evidence-based ACIP process, maintain the full immunization schedule as published, and reinstate universal COVID-

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19 vaccination for all individuals aged six months and older. He concluded by stressing that weakening these frameworks risks confusion, stigma, and inequities in access to care.

Evan Sachs
Washington Heights–Inwood Mask Bloc

Mr. Sachs, founder of the Washington Heights–Inwood Mask Bloc, spoke as a mutual aid provider and journalist. He compared vaccination to traffic laws and seatbelt use, describing them as shared rules that protect both individuals and communities. He argued that public health requires collective responsibility, not personal preference, and that vaccines, while not perfect, are overwhelmingly effective and essential for community safety. Mr. Sachs also emphasized the importance of layered protections, including masking, given that no single intervention is 100 percent effective. He encouraged continued public health measures grounded in science and social responsibility.

Ms. Melissa Kadri
Private Citizen

Ms. Kadri, a Master of Public Health student, offered an emotional testimony describing the loss of her uncle to COVID-19 and the subsequent death of her aunt from grief. She spoke about the devastating impact on her family and the broader implications of restricted vaccine access. Ms. Kadri emphasized the importance of maintaining herd immunity and cautioned that delaying or limiting childhood vaccinations contradicts scientific evidence and endangers lives. Using her family's story as an example, she implored the committee not to alter vaccine schedules in ways that could lead to preventable deaths and suffering, urging members to remember the human cost of their decisions.

Due to time constraints, Dr. Kulldorff announced that the discussions and votes on the MMRV and Hepatitis B vaccines would continue on September 19, 2025. Summaries of those discussions and votes are included in the sections above. The meeting was then recessed until September 19, 2025, at 8:30 a.m. EST.

FRIDAY: SEPTEMBER 19, 2025

WELCOME AND ROLL CALL

Call to Order/Roll Call

Dr. Martin Kulldorff, Chair of the ACIP, convened the meeting on September 19, 2025. Dr. Mina Zadeh, ACIP Executive Secretary from the CDC, welcomed the committee, followed by a roll call of members, ex officio members, and liaison representatives, each of whom announced their presence.

AGENCY UPDATES

The Centers for Disease Control and Prevention (CDC)

Dr. Brandi Limbago, representing CDC's National Center for Immunization and Respiratory Diseases (NCIRD), provided updates on response and preparedness activities. As of

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September 16, 2025, CDC confirmed 1,491 measles cases across 42 jurisdictions, the highest since 1992. Of these, 86 cases were linked to 38 outbreaks, compared with 69% of cases and 16 outbreaks in 2024. Most measles introductions originated from U.S. travelers returning from countries with active measles transmission, leading to outbreaks in under-vaccinated communities. Despite these increases, the overall risk to the general population remains low due to high vaccine coverage and population immunity.

She also reported on preparations for the 2025–2026 respiratory virus season, focusing on influenza, COVID-19, and RSV. Current data show low flu and RSV activity but increasing COVID-19 activity nationwide, with elevated emergency department visits and hospitalizations, particularly among children under 5, youth 5–17, and adults 65 and older. CDC is taking a coordinated approach to address these viruses by aligning programs, data systems, outreach, and communications. Additionally, the agency continues to monitor other respiratory pathogens, including Mycoplasma, Group A Streptococcus, and Pertussis.

Dr. Chris Braden provided an update on a significant outbreak response led by the National Center for Emerging and Zoonotic Infectious Diseases. On September 1, CDC received reports from local sources of suspected viral hemorrhagic fever in the Kasai Province of the Democratic Republic of Congo, which was later confirmed as Ebola virus Zaire. The index case was a pregnant woman admitted to Bulap General Hospital on August 20 with high fever, bloody diarrhea, hemorrhaging, vomiting, and weakness; she died on August 25 from multi-organ failure. Two healthcare providers who treated her also became ill and died.

Genomic sequencing at the DRC's National Public Health Laboratory indicated that the virus is genetically distinct from viruses in previous Ebola outbreaks, suggesting a new spillover event from wildlife. The DRC government promptly confirmed the outbreak and collaborated with CDC to initiate an emergency response. CDC has maintained a partnership with DRC for over 20 years, operating a country office since 2002 with about 30 staff members supporting laboratory capacity, workforce training, and public health infrastructure.

As of September 15, there were 37 confirmed cases and 19 deaths, with additional suspected cases under investigation. Approximately 944 contacts have been identified, and vaccination of healthcare workers and contacts began on September 13, with 369 vaccinations completed by September 15. All confirmed cases remain confined to Kasai Province, specifically the Bulabia health zone. The actual extent of the outbreak may be greater than currently known, though no related cases have been reported outside the DRC or in the United States, and the overall risk to the U.S. public remains low.

CDC issued a Health Alert Network advisory for U.S. public health departments and clinicians outlining case identification, testing, and biosafety recommendations. CDC headquarters is coordinating with its DRC country office, which has deployed additional staff to Kasai Province and Kinshasa to assist with response efforts. Technical support focuses on laboratory testing, surveillance, case investigation, contact tracing, and infection prevention and control measures.

Food and Drug Administration (FDA)

Dr. Tracy Beth Hoeg from the Food and Drug Administration (FDA) provided updates on recent regulatory actions and announcements. The four currently approved COVID-19 vaccines, MNEX Spike, Spikevax, Coity, and Newacovid, are indicated for adults aged 65 years and older, as well as for individuals at increased risk for severe COVID-19. Newacovid is authorized for individuals aged 12 years and older, while Spikevax is authorized for those aged six months and

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older. The previous Emergency Use Authorizations (EUAs) for Novavax, Pfizer, and Moderna have been revoked.

For the approved vaccine formulations, there are three ongoing post-marketing commitments, including studies on the persistence of the spike protein and associated symptoms, and randomized, saline placebo-controlled trials to evaluate safety and efficacy. Dr. Hoeg emphasized the importance of these trials, noting that real-world evidence can sometimes be misleading, citing a recent example involving the hepatitis B vaccine and apparent protection against bronchopulmonary dysplasia, which was likely due to healthy vaccine bias.
She also announced that randomized controlled trials will now be required to assess the safety of administering multiple vaccines concurrently. In addition, the live attenuated ICK vaccine for chikungunya virus has been temporarily suspended due to safety concerns.

Centers for Medicare and Medicaid Services (CMS), Health Resources and Services Administration (HRSA), Indian Health Service (IHS), and National Institutes of Health (NIH) did not report updates.

COVID-19 VACCINES

Dr. Retsef Levi (ACIP Work Group Chair) introduced the COVID-19 Work Group's immediate goals, which focused on discussing recently authorized vaccine products and determining which populations and subgroups should receive recommendations. Members discussed three possible options, which were to recommend, not recommend, or make an individual-based decision, and planned to define each later in the day. The work group emphasized the need to clearly communicate all risks and uncertainties to patients, noting that the current Vaccine Information Statement (VIS) does not accurately reflect the full scope of these concerns and should be updated for greater clarity and consistency. Members agreed that ACIP and its work groups should be able to consider any relevant data or information that supports vaccine policy decisions. Three focus clusters were established based on members' expertise to summarize available evidence, identify key issues and knowledge gaps, and develop potential policy options for review by ACIP. The work group reaffirmed its commitment to using all relevant published and unpublished data, including real-world experience, and to focusing on personalized risk-benefit analysis rather than general statements about safety or effectiveness. Members agreed to maintain respectful debate and transparency to ensure all perspectives and opinions are represented.

Dr. Arjun Srinivasan (CDC/NCIRD) shared updates on COVID-19 epidemiology. He explained that the data presented and discussed in this section come from the COVID-19–Associated Hospitalization Surveillance Network (COVID-NET). COVID-NET is one of three RESP-NET platforms, along with RSV-NET and FluSurv-NET, that collect data using similar methods and catchment areas on laboratory-confirmed COVID-19, RSV, and influenza-associated hospitalizations. It is a collaborative effort between CDC and state and local health departments that share data through cooperative agreements.

COVID-NET is a collaborative, population-based surveillance system that collects data from more than 300 acute care hospitals in 185 counties across 13 states, representing about 10% of the U.S. population. It gathers two primary types of information: population-based hospitalization rates and detailed clinical data from a stratified sample of patients. These data include demographics, outcomes, underlying conditions, treatments, and discharge diagnoses.

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The system's primary purpose is to monitor laboratory-confirmed COVID-19–associated hospitalizations among children and adults and provide timely information to decision-makers and the public. Hospitalization rates are updated weekly to assess disease burden and trends, while clinical data help identify who is most at risk and evaluate illness severity. A COVID-NET case is counted when a resident of the catchment area tests positive for SARS-CoV-2 within 14 days before or during hospitalization. Similar definitions are used for RSV and influenza surveillance systems.

Dr. Srinivasan noted that there has been ongoing interest in distinguishing between hospitalizations due to COVID-19 and those for COVID-19 illness. During the early stages of the pandemic, when there was no immunity or vaccination and asymptomatic transmission was common, hospitals screened all patients upon admission. This practice often identified patients who tested positive for SARS-CoV-2 but were hospitalized for unrelated reasons, such as surgery or childbirth. To address this, COVID-NET implemented an algorithm to identify hospitalizations primarily due to COVID-19, based on chief complaint and history of present illness. Data using this approach, dating back to March 2020, are posted monthly on the public COVID-NET dashboard. Although routine universal screening of all hospital admissions has largely ended, COVID-NET continues to use this algorithm to maintain consistency in surveillance.

Several factors must be considered when defining hospitalizations due to COVID-19. A positive SARS-CoV-2 test can influence the decision to admit a patient with comorbidities or other underlying conditions. At the same time, the presence of comorbidities or other conditions can also affect the decision to accept a SARS-CoV-2–positive patient. Data obtained from medical records, such as test results, treatments, discharge diagnoses, and coding, may lead to misclassification of hospitalizations as COVID-19-related or unrelated. ICD-10-CM codes in the U.S. are designed for billing and administrative purposes, not surveillance, and may either overcount or undercount true cases. In some instances, a COVID-19 ICD code can be used only to indicate a positive test rather than hospitalization for COVID-19 illness.

COVID-NET uses a standardized process to determine whether hospitalizations are due to COVID-19. This process relies on information from the chief complaint and history of present illness recorded at admission. Hospitalizations are classified as non-COVID-19-related if the admission was for obstetric care, surgery, psychiatric reasons, trauma, or for newborns hospitalized at birth. For remaining cases, if the medical record documents fever, respiratory symptoms, a COVID-19–like illness, or suspicion for COVID-19, the hospitalization is classified as due to COVID-19. Cases that do not clearly fit these criteria are reviewed by two COVID-NET physicians, with a third review if needed. Suppose a patient's medical record indicates that a positive SARS-CoV-2 test was incidental or that the hospitalization occurred for an unrelated reason, such as a localized infection or a surgical procedure. In that case, the case is classified as not related to COVID-19.

Using this algorithm, 87% of hospitalizations among SARS-CoV-2–positive patients in COVID-NET were determined to be due to COVID-19. Rates have increased over time, likely because universal screening of asymptomatic patients is no longer standard. Among children, 89% of hospitalizations were due to COVID-19, and the percentage increased with age in adults. Adults aged 65 years and older accounted for 70% of COVID-19–associated hospitalizations, with 91% of those admissions determined to be primarily due to COVID-19.

COVID-NET balances the need for detailed clinical data with the workload of chart abstraction. Data collection can be limited by timing and access, since ICD-10 codes are assigned after

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discharge and may only be available in billing systems. To address this, surveillance officers also review discharge summaries to capture conditions that developed during hospitalization. Combining discharge summaries with ICD-10 codes provides a more complete picture of each case and reduces bias that can occur when relying solely on billing data for public health surveillance.

COVID-NET examined classifying hospitalizations as being due to COVID-19using two different approaches: ICD-10-CM discharge diagnoses and the network's reason-for-admission algorithm. Data from the 2023–2024 season were used since ICD-10-CM codes are not yet available for the 2024–2025 season. During this period, COVID-NET identified more than 66,000 hospitalizations among patients of all ages, of which 7,279 were sampled for medical record abstraction. Using ICD-10-CM codes and discharge diagnoses, 81% of sampled hospitalizations had a COVID-19 discharge code listed in one of the first nine coding positions, 52% had a sepsis or respiratory-related diagnosis, and 88% had either a COVID-19 ICD-10 code or a respiratory diagnosis. 12% of cases had neither a COVID-19 ICD-10-CM code nor sepsis or respiratory-related discharge diagnosis.

Applying the reason-for-admission algorithm to the same sample, 85% of hospitalizations were classified as due to COVID-19. Of these, 91% also had either a COVID-19 ICD-10 code or a sepsis or respiratory-related diagnosis. Among the remaining 15% classified as hospitalizations with COVID-19, 64% had a COVID-19 ICD-10 diagnosis code.

Dr. Srinivasan summarized that the two classification methods show strong agreement. Overall, 88% of hospitalizations had a COVID-19 ICD-10 code or a respiratory-related diagnosis, and 85% were identified as COVID-19 as the likely primary reason for admission. 92% of hospitalizations identified through the reason-for-admission approach also had a COVID-19 ICD-10 code or a sepsis or respiratory diagnosis. The reason-for-admission approach is more conservative than relying solely on discharge diagnoses and can be completed more quickly. These findings support the notion that COVID-NET's methods provide a balanced approach to timeliness, accuracy, and population representation.

COVID-19–associated hospitalization rates per 100,000 population were determined by age group and reflect the cumulative risk of hospitalization for the 12 months from October 2024 through September 2025. The rates were based on the surveillance standard, which includes hospitalized residents in the COVID-NET catchment area who tested positive for SARS-CoV-2. Hospitalization rates were highest among adults aged 65 to 74 years and 75 years and older, as well as among infants younger than 6 months. Because no vaccine products are approved for infants under 6 months of age, protection against hospitalization must come from maternal vaccination.

A significant proportion of adults hospitalized due to COVID-19 experienced severe in-hospital outcomes, including admission to the intensive care unit and in-hospital death. About 15% of adults hospitalized with COVID-19 were admitted to the ICU, and in-hospital death occurred more frequently among adults aged 50 years and older. Among all adults hospitalized due to COVID-19 who died in the hospital, 84% were aged 50 years and older. These data include only deaths that occurred during hospitalization, although additional COVID-19–associated deaths occur outside the hospital, including some within 30 days after discharge.

Different respiratory viruses affect age groups differently, with the greatest overall impact seen at the extremes of age. Cumulative data show that RSV causes the highest burden of respiratory disease in children under one year. COVID-19 has the greatest impact on older

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adults but also remains a significant cause of hospitalization among infants, with rates comparable to influenza during October 2024-2025, a high-severity influenza season that was the most severe since the 2010–2011 season. COVID-19–associated hospitalization rates among infants younger than 6 months have remained close to those among adults aged 65 to 74 years, but in recent weeks have risen more rapidly, reaching 223 per 100,000 compared to 194 per 100,000 among adults, a 14% higher rate among infants compared to adults aged 65 to 74.

Dr. Srinivasan shared an update to a peer-reviewed study published in 2021, which had informed a previous infographic summarizing the relative risk of hospitalization among individuals with chronic conditions compared to those without. Data sources for the updated analysis included three primary datasets: COVID-NET data on hospitalizations due to COVID-19 from October 2022 through September 2023; the Behavioral Risk Factor Surveillance System (BRFSS), the largest ongoing health survey system in the world that collected data annually from hundreds of thousands of community-dwelling U.S. adults; and population data from the U.S. Census provided by the National Center for Health Statistics.

The analysis methodology was complex. COVID-NET provided weighted counts of individuals hospitalized due to COVID-19 who had underlying conditions, limited to community-dwelling adults aged 18 years and older, for consistency with BRFSS data. Weighted counts of adults with and without chronic diseases of interest were calculated using BRFSS data and state population modeling. Adjusted rate ratios of hospitalization rates for adults with versus without chronic conditions were then calculated. Chronic conditions examined were limited to those included in the BRFSS survey and included coronary artery disease, history of stroke, diabetes mellitus, chronic kidney disease, COPD, asthma, obesity, severe obesity, and current smoker.

Findings showed that the prevalence of most chronic conditions among adults hospitalized due to COVID-19 was higher than in the general population. Among adults, most chronic conditions increased the risk of being hospitalized due to COVID-19. The risk for hospitalization conferred by several conditions, such as coronary artery disease, diabetes, and obesity, appeared to decline with age but this may have reflected challenges in adjusting for coexisting conditions or low prevalence of some diseases within specific age groups; for example, severe obesity was uncommon among adults aged 75 years and older, while COPD was uncommon among adults younger than 50 years.

The analysis also showed that the risk for hospitalization due to COVID-19 increased with both the number of chronic conditions and with age. Having multiple comorbid conditions and older age were the strongest risk factors for hospitalization due to COVID-19 identified among adults. Adults with three or more underlying conditions were nearly six times more likely to be hospitalized due to COVID-19 compared with those with no underlying conditions. Hospitalization rates were 18.5 times higher among adults aged 75 years and older compared with those aged 18 to 49 years, making age 75 and above the greatest identified risk factor for hospitalization.

The analysis had several strengths, including the use of data from a robust COVID-19 hospitalization surveillance system that enabled comparisons across state-level prevalence data and allowed examination of how specific conditions, multiple comorbidities, and age contributed to hospitalization risk. However, there were also limitations. The results remained preliminary and under review. The analysis was limited to community-dwelling adults and did not include children or individuals living in long-term care facilities, where risks may have differed. Some conditions tended to co-occur, such as diabetes and chronic kidney disease, and adjustments

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for these comorbidities could not always be made due to limited data, particularly in younger adults. In addition, differences in rate ratios by outcomes (e.g., ICU admission) or by race and ethnicity could not be assessed due to the sparse data.

Dr. Malone asked whether there was a significant overlap and diagnostic difficulty between COVID-19 and other influenza-like illnesses.

Dr. Srinivasan confirmed that the symptoms of COVID-19 overlapped almost entirely with those of other respiratory illnesses.

Dr. Malone noted that when he had previously asked a CDC representative about the specificity and sensitivity of the diagnostic tests used, he was told those measures were “academic.” He expressed concern that sensitivity and specificity are fundamental to data validity and stated that diagnostic testing for COVID-19 has had limitations in both areas, which were not reflected in the models.

The NCIRD SME explained that the tests used in COVID-NET were FDA-approved diagnostic tests performed in hospitals and medical clinics nationwide. The SME clarified that COVID-NET did not conduct testing directly and that all tests were performed at the treating provider's discretion.

Dr. Malone stated that this confirmed the tests had known limitations in sensitivity and specificity that could affect data interpretation.

The NCIRD SME acknowledged that all clinical tests have defined sensitivity and specificity values but emphasized that the tests used were FDA-approved and used to identify patients who tested positive for SARS-CoV-2.

Dr. Malone added that if the tests were only 80% specific, the underlying classification of COVID-19 cases would be similarly ambiguous.

Dr. Natalie Thornburg, NCIRD laboratory SME, clarified that all tests used in COVID-NET had received FDA authorization through the Center for Devices and Radiological Health and met rigorous FDA test performance requirements, with specificity generally well above 90% both sensitivity and specificity at a similar level.

Dr. Arjun Srinivasan (CDC/NCIRD) shared updates to 2024-2025 COVID-19 implementation considerations. One of the primary sources utilized by the Immunization Services Division to assess vaccination coverage, including COVID-19 and other immunizations, was the National Immunization Survey (NIS). The NIS is a random-digit-dial cellular telephone survey of U.S. adults aged 18 years and older across local jurisdictions and territories. For children, data were reported by a parent or guardian, and all responses were self-reported. The survey included approximately 15,000 adults per week, or about 60,000 adults per month, and the data were weighted to represent the non-institutionalized U.S. population.

COVID-19 vaccination coverage for the 2024–2025 season was reported for adults aged 18 to 49 years, 50 to 64 years, and 65 years and older. From September 2024 through April 2025, coverage for at least one dose reached 44% among adults aged 65 years and older, 25% among those aged 50 to 64 years, and 14% among those aged 18 to 49 years.

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When comparing coverage between the 2023–2024 and 2024–2025 seasons, there was little change among adults aged 18 to 49 years and 50 to 64 years. However, vaccination coverage increased among older adults. For those aged 65 to 74 years, coverage rose by nearly five percentage points, and among adults aged 75 years and older, coverage increased by about eight percentage points. These differences were statistically significant in both age groups ($p < 0.05$).

COVID-19 vaccination coverage estimates for the pediatric population showed that approximately 5.6% of children younger than 4 years were up to date with vaccination according to current recommendations for that age group. Among children aged 5 to 17 years, being up to date was defined as having received at least one vaccination since August; nearly 16% met this criterion. Overall, about 13% of children aged 6 months to 17 years were up to date with their COVID-19 vaccinations by the end of April 2025.

Vaccination coverage among immunocompromised adults aged 18 years and older who received their first COVID-19 vaccine dose in August or September 2024 was 8% fully vaccinated with two doses by the end of March 2025. When analyzed by age, 16.6% of adults aged 50 to 64 years were fully vaccinated compared to 2.4% among those aged 18 to 49 years and 0.8% among those aged 65 years and older.

In summary, COVID-19 vaccination coverage among older adults improved during the 2024–2025 season compared to the previous season, while coverage among adults aged 18 to 64 years remained similar. Approximately 13% of children aged 6 months to 17 years were up to date with their COVID-19 vaccinations by the end of April 2025.

COVID-19 vaccination data for adults aged 18 years and older showed the distribution of vaccination sites among individuals who reported receiving a COVID-19 vaccine in 2024–2025 since August 2024. Data was collected between April 1 and April 27, 2025, from 9,359 respondents. Approximately 67% of adults reported receiving their vaccine at a pharmacy or drugstore, while 29% received theirs in a medical setting, such as a doctor's office. About 4% received their vaccine in a non-medical location, such as a workplace.

Additional data on vaccination among healthcare personnel were collected through CDC's National Healthcare Safety Network (NHSN), the nation's most widely used system for tracking healthcare-associated infections. NHSN provides process measures such as vaccination status for healthcare personnel. CMS-certified skilled nursing facilities and hospitals report both COVID-19 and influenza vaccination data through this system. Data from NHSN showed that influenza vaccination rates among acute care hospital staff and long-term care staff have remained relatively consistent from 2022, when NHSN began collecting vaccination data for healthcare personnel, through the 2024–2025 respiratory virus season. In contrast, COVID-19 vaccination coverage has continued to decline across seasons in both acute care and long-term care settings.

Dr. Arjun Srinivasan (CDC/NCIRD) provided an update on COVID-19 vaccine effectiveness. He first explained the difference between data from randomized controlled trials and real-world evidence to clarify how vaccine performance is evaluated. Randomized controlled trials are used to demonstrate vaccine efficacy under ideal, controlled conditions and to determine whether vaccination prevents disease compared with a placebo or another vaccine. Observational studies provide real-world evidence of vaccine effectiveness (VE) and determine how well vaccines protect populations with existing immunity from prior infection, vaccination, or both. He noted that efficacy and effectiveness are population-level estimates; for example, if a

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vaccine is 80%, it means that 80% fewer vaccinated people will develop the disease compared to an unvaccinated population, not that the vaccine works only 80% of the time.

He described how VE can be measured using several study designs, including case-control, cohort, and test-negative designs. Case-control studies compare vaccinated and unvaccinated individuals within the same population, whereas cohort studies follow at-risk groups over time to determine who develops illness. The test-negative design combines features of both and is widely used by CDC and other countries to measure the VE of COVID-19 vaccines. In this approach, individuals seeking care for respiratory illnesses are included; those who test positive for SARS-CoV-2 are considered cases, and those who test negative serve as controls. This method reduces bias by ensuring that both groups sought care for similar symptoms, minimizing confounding factors such as age and geography.

Dr. Srinivasan emphasized that the test-negative design offers several strengths. It efficiently studies rare outcomes, such as infectious diseases, by reducing bias using controls from the same health facilities. This approach allows for faster, more cost-effective data collection, often yielding results within the same season. When conducted among hospitalized populations, it helps mitigate healthy vaccine bias because both cases and controls are hospitalized for respiratory illness. Additionally, when electronic health record data are used to include the entire eligible at-risk population as controls, the design supports larger sample sizes. It enables stratified analyses by factors such as age and time since vaccination.

Dr. Srinivasan shared VE results from three CDC study platforms that include both children and adults. The first platform, the VISION Network, is a multi-site system utilizing electronic health records from over 300 emergency departments and urgent care clinics, as well as more than 200 hospitals. VISION uses a test-negative design and includes individuals of all ages with COVID-19–like illness and a clinical test result within 10 days before to 72 hours after their healthcare encounter. Cases are defined as those with a positive nucleic acid amplification test (NAT) or antigen test for SARS-CoV-2 and no positive RSV or influenza results, while controls are those with a negative SARS-CoV-2 NAT test and no positive influenza or RSV test, depending on age. Vaccination status is documented through electronic health records and state or city registries.

The second VE platform enrolls only children and includes participation from 26 pediatric hospitals in 20 states. The analysis presented was designed to evaluate the effectiveness of COVID-19 vaccination in pregnant women for preventing COVID-19–related hospitalizations among infants younger than six months.

The third platform, the IVY Network, includes 26 hospitals across 20 U.S. states and, like VISION, uses a test-negative design. However, IVY incorporates active enrollment through patient interviews and nasal swabbing. Participants included in the analysis were adults aged 18 years and older hospitalized with COVID-19–like illness. Cases were defined as those testing positive for SARS-CoV-2 by NAT or antigen testing, while controls were negative for SARS-CoV-2, influenza, and RSV by RT-PCR. Vaccination history was verified through medical records, vaccine registries, and plausible self-reports, and specimens were collected for centralized testing and sequencing.

Dr. Srinivasan also noted that methods for measuring COVID-19 VE have evolved by season. When vaccines were first introduced, absolute VE was measured, comparing health outcomes between vaccinated and unvaccinated individuals. During the bivalent vaccine period, relative VE was assessed, comparing outcomes among people who received a bivalent dose versus

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those who received only the original monovalent vaccine. More recently, analyses have shifted toward seasonal VE, similar to annual influenza evaluations, comparing people who received the current season's COVID-19 vaccine to those who did not, regardless of prior vaccination history.

Dr. Srinivasan presented COVID-19 VE data for 2023 to 2024 across emergency department and urgent care encounters, including results through August 2024, when the 2024 to 2025 vaccines were released. The reference group consisted of individuals who had not received the 2023–2024 COVID-19 vaccine. For those aged five years and older, this group included both unvaccinated individuals and those who had received one or more doses of the original monovalent or bivalent vaccines. For children younger than five years, both vaccinated and reference groups were required to have completed an initial vaccine series, and the 2023–2024 dose could have been part of or in addition to that series.

VE was evaluated by age group (9 months to 4 years, 5 to 17 years, and adults 18 years and older) and by time since vaccination. VE among those who received a 2023–2024 dose 7 to 59 days earlier and 60 to 299 days earlier was compared. Due to limited data, there were not enough children vaccinated 60 to 299 days earlier with positive SARS-CoV-2 tests to further divide the estimates for that group. Overall, VE was observed to be as strong or stronger among children as among adults, consistent with previous seasons' findings, which showed generally comparable VE across age groups.

For the 2024–2025 season, the same analysis framework was used; however, lower numbers of COVID-19 cases and lower vaccination coverage among children reduced statistical power. As a result, VE could not be estimated by time since dose. Instead, overall, VE was calculated for 7 to 179 days after receipt of a 2024–2025 COVID-19 vaccine dose. Findings showed that, similar to the 2023–2024 season, VE remained the same or higher in children than in adults.

Dr. Srinivasan presented VE data on receipt of a 2023–2024 COVID-19 vaccine during pregnancy for protection against emergency department and urgent care visits by pregnancy status. Among women who were pregnant at the time of their COVID-like illness encounter, VE was similar to that observed among non-pregnant women of the same age group. The time since vaccination was comparable across both groups, and the confidence intervals for VE fully overlapped, indicating consistent protection between pregnant and non-pregnant women.

He also shared VE estimates for maternal COVID-19 vaccination in preventing COVID-19–associated hospitalizations among infants, using data from the Overcoming COVID-19 Network during the 2022–2023 season. Maternal VE for infants is essential because infants younger than six months are not eligible for COVID-19 vaccination and have higher rates of severe illness than older children and most adult age groups. Vaccination during pregnancy remains the only means of protecting infants from severe COVID-19. The analysis included mothers who received their last dose of a COVID-19 mRNA vaccine between the first day of pregnancy and 14 days before delivery, compared to mothers who had not received any COVID-19 vaccination before or during pregnancy. VE was highest among the youngest infants, estimated at 54% during the first two months of life and 35% during the first five months of life. This pattern was consistent with findings in older children and adults, showing that VE decreases with increasing time since vaccination.

Dr. Srinivasan presented VE estimates for COVID-19–associated hospitalization among adults aged 65 years and older without documented immunocompromising conditions, using data from the VISION and IVY networks. VE estimates were nearly identical across both networks,

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providing reassurance of the results' consistency. During the seven to 179 days after vaccination, VE was 44% in VISION and 46% in IVY. VE began at 46% in VISION and 42% in IVY, declining to 32% in VISION and 40% in IVY during the 120–179-day period following vaccination. Confidence intervals for this later period were wider due to the smaller number of cases and controls who had been vaccinated four to six months before their encounter.

Dr. Srinivasan presented VE estimates for COVID-19-associated critical illness in adults aged 65 years and older, based on data from the VISION and IVY networks. In VISION, critical illness was defined as admission to intensive care or in-hospital death, and VE estimates were evaluated based on the time since vaccination. The point estimates remained stable across time intervals, including 120 to 179 days after vaccination, indicating relatively durable protection. This was consistent with previous years, showing that VE against the most severe outcomes remained strong over time with little evidence of waning.

In IVY, VE was evaluated for three outcomes of increasing severity, including acute respiratory failure, ICU admission or death, and invasive mechanical ventilation or death, measured during the 7 to 179 days after vaccination. VE was highest at 70% for invasive mechanical ventilation or death, again showing strong protection against the most severe outcomes. Among adults aged 65 years and older with immunocompromising conditions, VISION and IVY both showed similar trends. However, IVY lacked sufficient statistical power to estimate VE by time since vaccination. In VISION, VE appeared to increase over time, a pattern previously observed among immunocompromised adults and likely related to the faster waning of infection-induced immunity in this group. This would make the reference group, consisting of unvaccinated individuals, less protected over time, thereby increasing the apparent VE. For the overall period, VE was 38% in VISION and 36% in IVY, similar to VE observed in non-immunocompromised adults, providing reassurance that the vaccine continued to offer protection in immunocompromised populations.

Dr. Srinivasan summarized that for each respective year, receipt of an in-season COVID-19 vaccine dose provided additional protection against COVID-19–associated emergency department and urgent care visits among children, with similar protection observed across age groups. Among adults, vaccination also provided additional protection against COVID-19–associated emergency department and urgent care visits, hospitalizations in adults aged 65 years and older with and without immunocompromising conditions, and critical illness in adults aged 65 years and older. Protection appeared to be higher and more durable against critical illness compared to less severe outcomes.

He noted that VE should be interpreted as the added benefit of the 2023–2024 or 2024–2025 COVID-19 vaccination in a population with high levels of infection-induced immunity, vaccine-induced immunity, or both. Prior SARS-CoV-2 infection contributes to protection against future disease, but that protection decreases over time. An increase in SARS-CoV-2 circulation in the United States during late summer 2024, just before the 2024–2025 vaccines were approved and authorized, may have resulted in higher population-level immunity against JN.1 lineage strains. This, in turn, could have led to lower measured VE than would be observed in a population with less recent infection.

Dr. John Su (CDC/NCEZID) presented on the detection and evaluation of vaccine safety signals. He defined an adverse event following immunization as any unexpected or harmful medical occurrence occurring after vaccination that is not necessarily caused by the vaccine. He also described a signal as information arising from one or more sources, suggesting a new,

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potentially causal association between an intervention and an event that is considered likely enough to warrant further verification.

Signal detection and evaluation begin with identifying potential signals, which may emerge from clinical observations, such as case reports, or from vaccine safety surveillance systems. Suppose further assessment of the initial information continues to suggest a possible association between a vaccine and an adverse event. In that case, the next step is to conduct a hypothesis-testing study to either verify or rule out the signal. If the evidence confirms a causal association between vaccination and the event, public health actions or additional studies may follow, including evaluations of biological mechanisms or strategies to prevent similar occurrences.

CDC uses four complementary systems that work together to detect and evaluate potential vaccine safety concerns. One of these systems is the Vaccine Safety Datalink (VSD), which he used as an example to illustrate how signal detection and evaluation occur. The VSD is a collaboration between CDC and several integrated healthcare organizations with a combined population of more than 15 million people. It conducts active surveillance using electronic medical record data to detect safety signals and can also evaluate them using more robust study designs. The VSD links vaccination records, healthcare encounters, and patient characteristics into a standard data model for epidemiologic analyses.

The VSD uses rapid cycle analysis (RCA) to monitor a limited number of prespecified adverse events of special interest. Potential cases are identified using ICD-10 codes from healthcare encounters. RCA is designed to detect statistical signals, which are test statistics that exceed a specific threshold. However, a statistical signal does not necessarily indicate a genuine vaccine safety issue and requires further evaluation. Since 2020, the VSD has performed RCA using a vaccinated concurrent comparator method, which compares the incidence of an adverse event during a risk interval (e.g., 1 to 21 days after vaccination) with that during a control interval (e.g., 43 to 63 days after vaccination). This approach inherently adjusts for factors such as calendar time, age, sex, race, and VSD site. Detection using the RCA method is rapid but may include residual bias. When a statistical signal is detected, the VSD conducts additional evaluation using the self-controlled case series method, which requires full follow-up time but is less prone to bias.

Dr. Su noted that the VSD monitors a list of prespecified adverse events of special interest for COVID-19 vaccines, which are also tracked by multiple U.S. federal vaccine safety systems. One of these monitored outcomes is non-hemorrhagic, or ischemic, stroke. The VSD has monitored the risk of ischemic stroke following each dose of the COVID-19 vaccine since 2020 as new vaccine formulations were authorized and recommended. A statistical signal for ischemic stroke was first detected during the 2022–2023 season and again for the 2023–2024 formulation. Over the course of the 2022–2023 season, as more people were vaccinated and post-vaccination follow-up time increased, the rate ratio estimate decreased from a statistically significant level early in the season to a final value of 1.26, which was no longer statistically significant by the end of the monitoring period.

In 2023, CDC and FDA collaborated to further evaluate and communicate the ischemic stroke signal to the ACIP and the public. VSD was the only vaccine safety system to detect a signal for ischemic stroke. Other analyses conducted in the U.S. and in other countries did not observe similar findings. At the time, the interpretation was that the evidence did not support the existence of a vaccine safety concern.

The VSD RCA statistical signal for ischemic stroke during 2022–2023 was explicitly detected among people aged 65 years and older who received the Pfizer vaccine. Further assessment also examined whether the same-day administration of the influenza vaccine influenced the

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findings. During the 2023–2024 season, VSD RCA surveillance again detected statistical signals for ischemic stroke, this time following both the Moderna and Pfizer vaccines, as well as among different age groups from the prior season. These signals were presented to ACIP in 2024.

To further evaluate these findings, VSD conducted self-controlled case-series analyses for both seasons. For the 2022–2023 Pfizer vaccine analysis, subgroup evaluations included individuals who received the COVID-19 vaccine with or without same-day influenza vaccination. Across age groups and both 21-day and 42-day risk intervals, no statistically significant increased risk for ischemic stroke was identified for either separate or same-day administration.

Similarly, the self-controlled case series analysis for the 2023–2024 season, which examined both Pfizer and Moderna vaccines, found no statistically significant increased risk for ischemic stroke following vaccination, regardless of whether the influenza vaccine was administered on the same day.

The FDA also performed a self-controlled case series analysis for the 2023–2024 season among Medicare beneficiaries aged 65 years and older who received a COVID-19 vaccine. The FDA analysis likewise found no evidence of increased risk for ischemic stroke following vaccination with any manufacturer's product.

Dr. Su summarized that the VSD rapid cycle analysis surveillance monitored a list of prespecified adverse events of special interest, including ischemic stroke. The VSD detected statistical signals for ischemic stroke following COVID-19 vaccination during the 2022–2023 and 2023–2024 seasons. However, subsequent signal evaluations using self-controlled case series analyses in the VSD and other data sources did not confirm an increased risk of ischemic stroke.

Dr. Charlotte Kuperwasser from Tufts University School of Medicine and Dr. Wafik El-Deiry from the Legorreta Cancer Center at Brown University presented on safety uncertainties related to mRNA COVID-19 vaccines within the work group. Dr. Kuperwasser explained that the work group reviewed several key areas of scientific uncertainty related to mRNA COVID-19 vaccines. The review focused on four main topics: immune changes, biodistribution, frame shifting, and impurities. For immune changes, literature on both specific and nonspecific immune effects was examined, with an emphasis on the cumulative short- and long-term effects of repeated boosting, an area of emerging research. For biodistribution, clinical and scientific information was reviewed from both published literature and FDA data. Frame shifting was monitored due to its potential to alter protein products and downstream immune responses. Finally, published and unpublished data regarding residual DNA in existing mRNA vaccine products were reviewed.

The work group noted evidence that COVID-19 vaccination, particularly after multiple doses, is associated with a range of immune changes. One of the most well-documented findings is IgG4 class switching, first reported by Irrgang and colleagues, who found that individuals receiving Pfizer's BNT162b2 mRNA vaccine developed anti-spike IgG4 antibodies and IgG4-switched memory B cells within six months of their second dose, with levels increasing further after a third dose. These changes were associated with reduced antibody function consistent with IgG4's role in promoting immune tolerance. Additional studies have reported the production of anti-idiotype antibodies and persistent alterations in IgG glycosylation patterns, which may affect antibody-immune cell interactions and influence inflammatory versus tolerant responses.

The work group also discussed findings of long-lasting shifts in cytokine profiles, with elevated inflammatory cytokines persisting for months, which could increase the risk of recurrent or prolonged infections in some individuals. In addition, research from Akiko Iwasaki's laboratory at

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Yale demonstrated cellular immune changes, including reductions in circulating memory and effector CD4 T cells and increases in TNF-alpha–positive CD8 T cells following vaccination.

Dr. Kuperwasser noted that these and other studies raise questions about the persistence of the immunological changes associated with mRNA vaccination, as well as their long-term clinical significance and consequences. Given the long-term changes in cytokine profiles and T-cell ratios observed in vaccinated individuals, further research is needed to determine how vaccination may influence innate and adaptive immunity over time.

For biodistribution studies, Pfizer did not use the actual spike mRNA in its preclinical studies. Instead, a luciferase reporter mRNA packaged into the same lipid nanoparticles was used to track its movement through the bodies of rodents. The studies found that while most of the mRNA remained at the injection site, notable levels were also detected in the liver. Although this approach may underestimate the low-level or short-term distribution to other tissues, it demonstrates that vaccine components do not remain confined to the injection site.

For Moderna, no dedicated biodistribution study was conducted using the COVID-19 mRNA itself. Instead, data were provided from a surrogate product, CMV mRNA-1647, which used the same lipid nanoparticle formulation. In rat studies, high levels of mRNA were found at the injection site, as well as in multiple organs, including draining lymph nodes, spleen, eye, and liver. Lower levels were detected in additional tissues, including the heart, lungs, testes, and brain. This study indicated that the mRNA could cross the blood–brain barrier.

Consistent with animal studies, vaccine mRNA and spike protein have been detected in humans across multiple tissues, including blood, lymph nodes, heart, and brain. These findings indicate that the mRNA does not remain localized at the injection site. Persistence has been documented to last well beyond the initial hours or days, persisting for weeks in some tissues and, in certain studies, remaining detectable for several months.

Dr. Kuperwasser summarized that neither Moderna nor Pfizer used their actual commercial mRNA vaccine products in their preclinical biodistribution studies. Instead, both relied on surrogate constructs packaged in the same or similar lipid nanoparticles. The results of those studies showed that the mRNA and lipid nanoparticles were not confined to the injection site. Systemic distribution was observed, with evidence that the mRNA can cross the blood–brain barrier.

Consistent with these findings, studies in humans have confirmed that vaccine mRNA can be detected in multiple tissues, including lymph nodes, the heart, the central nervous system, and blood. Persistence was also not limited to the short term; in some reports, mRNA has been detected for weeks to months, and in some instances for as long as 706 days post-vaccination. Dr. Kuperwasser concluded that the data indicate widespread biodistribution and that persistence is more prolonged than initially expected, raising important questions and concerns for ongoing research and safety monitoring.

Dr. El-Deiry explained that the work group examined several additional areas of concern related to mRNA COVID-19 vaccines. The first topic was ribosomal frame shifting, a mechanism used by viruses to express different open reading frames that can facilitate infection. He noted that nucleotide-modified mRNA containing pseudouridine can significantly increase frameshifting, by as much as twofold. Evidence suggests that these unintended off-target proteins may trigger immune responses in humans, including the production of antibodies. However, the immunogenic or toxic properties of these non-spike proteins remain unknown, and the potential

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health consequences of prolonged or persistent production of non-spike proteins have not been studied.

Dr. El-Deiry also highlighted reports of DNA impurities found in Pfizer and Moderna mRNA vaccine vials. The most recent findings were reported by Speicher et al., who analyzed 32 vials representing 16 unique vaccine lots and found evidence of fragmented plasmid DNA in both Pfizer and Moderna vials. All Pfizer vials contained the SV40 enhancer origin of replication, which was not detected in the Moderna vials.

He noted that differences exist between the Pfizer and Moderna mRNA vaccines, primarily involving the SV40 promoter-enhancer origin sequences and the detectable amounts of DNA fragments. He also pointed out that the FDA's limit of 10 nanograms was established for naked DNA, not for DNA encapsulated in lipid nanoparticles, which can carry DNA into cells and their nuclei.

Dr. El-Deiry summarized that both the Pfizer and Moderna mRNA vaccines have been found to contain DNA levels exceeding FDA limits. He noted that these limits do not account for lipid nanoparticles, which can carry DNA into cells and nuclei. Concerns were raised about the potential for disruption of DNA integration and gene activation associated with SV40 promoter–enhancer sequences.

He added that there have not been reliable population-based studies in the U.S. evaluating cancer outcomes following COVID-19 vaccination. However, cancers have been reported in mRNA-vaccinated individuals in temporal association with immunization. A total of 48 case reports have been documented, including 24 cases of primary cutaneous lymphoma. He also referenced a study involving 96 cases of pancreatic ductal adenocarcinoma that found worse outcomes among individuals with higher IgG4 levels, which, as noted by Dr. Kuperwasser, may increase with repeated vaccination. Additionally, a case-control study of 76 colorectal cancer cases reported a higher frequency of mismatch repair–deficient cancers among vaccinated individuals.

Dr. El-Deiry stated that there are significant gaps in knowledge regarding the extent of DNA contamination in current vaccine lots. The biodistribution of any contaminating plasmid DNA capable of persistently producing spike protein, genomic DNA, or integrating into tissues or tumors in vaccinated individuals remains poorly understood. The mechanisms involved, as well as the relationship between the prevalence of adverse outcomes and the extent of contamination, require further investigation.

He added that there is limited understanding of how multiple vaccinations may relate to spike protein persistence, and that more research is needed to clarify potential cancer-related mechanisms. While questions about causality remain, several plausible mechanisms have been proposed. He also noted that variations in host susceptibility to adverse outcomes are emerging for certain other vaccine-related events, which may be relevant to the areas of uncertainty currently under discussion.

Dr. El-Deiry summarized that COVID-19 vaccine safety concerns arise from the unexpected biological activities associated with mRNA gene therapy platforms, raising questions about potential pathogenic mechanisms and protections for human research subjects. He recommended developing proactive, modernized safety surveillance programs that incorporate blood- and tissue-based monitoring, large-scale epidemiologic studies, and AI-driven analyses using reliable, standardized datasets. He emphasized the need for expanded autopsy programs

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to help clarify causality in serious outcomes and for systematic evaluation of COVID-19 vaccine safety. He also called for FDA approval policies calibrated to reflect gene therapy–level risks, with DNA impurity limits that account for lipid nanoparticles, and stressed the importance of stronger pharmaceutical accountability and CDC guidelines that ensure transparent risk disclosure, effective mitigation strategies, and robust informed consent practices.

Dr. Bruce Carleton (University of British Columbia) began by providing his disclosures, noting that the presented work was funded through a grant to the Global Vaccine Data Network (GVDN) supported by CDC. He also acknowledged additional government funding sources in Canada, listed his prior consultancies, and mentioned his current work related to COVID-19 vaccination data genomics, funded by React19. He explained that the GVDN is a collaborative network of 32 countries that continues to expand. In addition to the genomics research being presented, he noted that the network is preparing to publish the largest study to date on myocarditis and pericarditis following COVID-19 vaccination, which will also include analyses of booster doses.

Dr. Carleton explained that although the grant supporting this research was canceled with 48 hours' notice in March, he was able to complete some preliminary work. The study included 50 patients aged 11 to 83 years, representing diverse self-reported ancestries. Genetic ancestry testing is planned to help assess the generalizability of findings. Participants had received either the Pfizer or Moderna COVID-19 vaccines. Most myocarditis cases occurred after the second dose, with some following the first or third doses. Among the 30 patients with available data on symptom onset, the median time to myocarditis symptoms after vaccination was 4 days, with an interquartile range of 3 to 26 days.

The study methods included whole-exome sequencing of 50 myocarditis cases using an exome-capture library preparation on the NovaSeq 6000 system, achieving an average depth of 100x. Sequencing reads were aligned to the GRCh38 human reference genome, and 49 of the 50 samples passed quality control, with one excluded due to insufficient DNA quality. The analysis focused on identifying genetic variants found in at least 50% of the 49 cases, with global allele frequencies of 15% or lower according to ClinVar, a database that provides gene and allele frequency information. This approach helped identify genes that appeared more frequently in the study population than would be expected based on global reference data.

Dr. Carleton shared results from a genetic analysis that examined 18 genes, specifically focusing on the protein-coding region, or exome, of DNA. This approach allowed the identification of rare and known variants of significance. Seven variants across four genes were identified, all of which have been previously linked to the development of myocarditis or cardiac inflammation. Four of these variants were in the *TTN* (titin) gene, as expected given its large size, and three were identified in other genes.

Of the 30 patients with available data on time to onset of myocarditis after COVID-19 vaccination, results showed that as the number of homozygous variants increased, the time between vaccination and symptom onset decreased. While the number of cases was small, Dr. Carleton noted this as an interesting trend.

Among the identified genes, one of particular interest was *LDL receptor-related protein 8 (LRP8)*, a variant associated with cardiovascular inflammation and immune response, particularly in coronary artery disease and myocardial infarction. Ten patients were homozygous for the risk allele, and 19 were heterozygous.

Dr. Carleton discussed findings on the angiotensin II type 1 receptor (AGTR1) gene, which has previously been associated with COVID-19 and cardiovascular disease. In this small patient population, specific *AGTR1* genotypes were linked in earlier studies to more than 90% left

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anterior descending artery stenosis, as well as increased susceptibility to myocardial infarction and essential hypertension. Among the 49 cases analyzed, four patients were homozygous and 24 were heterozygous for the identified variant.

He presented a graphic illustrating how these variants function within the renin–angiotensin system. For *AGTR1*, the variant enhances angiotensin II signaling, leading to hypertension, vasoconstriction, and cardiac hypertrophy. In the case of *LRP8*, the variant reduces *APOE* activity, leading to increased p38 MAPK pathway activation and contributing to cardiac inflammation.

Regarding the *VKORC1* gene, Dr. Carleton explained that it is highly expressed in the heart and is known to be associated with warfarin dosage and vitamin K signaling. The gene has also been linked to arterial vascular disease and vessel calcification. Among the analyzed cases, three patients were homozygous and 24 were heterozygous for the identified variant. He briefly explained that disruption of the vitamin K cycle caused by these risk haplotype variants can result in vessel damage that promotes vascular calcification and atherosclerosis.

Regarding the TTN (titin) gene, Dr. Carleton explained that it is one of the most common causes of dilated cardiomyopathy. Approximately 25% of familial and 18% of idiopathic cardiomyopathy cases are attributed to *TTN* variants. These variants have also been associated with acute myocarditis, showing a higher prevalence in affected cases than in controls, as reported in previous research. In this analysis, three patients were homozygous for all four identified variants, two were homozygous for three variants, and 21 were heterozygous. He noted that *TTN* variants contribute to sarcomere insufficiency, which can lead to dilated cardiomyopathy.

Before the grant was canceled in March, Dr. Carleton explained that the goal had been to collect 275 cases for each of the adverse events listed in the table on the left, along with vaccinated control participants who did not experience adverse events. The study aimed to conduct case-control genetic analyses, beginning with genome-wide studies and then expanding to exome sequencing. The next planned phase would have involved whole-genome sequencing to include broader gene coverage and achieve a more comprehensive analysis of the genome.

As a final point, Dr. Carleton noted that genomic studies have revolutionized drug therapy, stating that more than 500 FDA-approved drugs now include genetic information in their labeling. Applying similar genomic research to vaccine adverse events would serve two key purposes. First, it would help clarify the biological mechanisms underlying the pathophysiology of adverse events. Second, it could enable more personalized vaccine strategies for patients with identified genetic risk variants. For example, individuals at higher risk of myocarditis following mRNA vaccination could be considered for alternative vaccines, such as protein-based or non-adenoviral vector vaccines.

Dr. Arjun Srinivasan (CDC/NCIRD) presented an economic analysis of the COVID-19 vaccine. The objectives of this study were to estimate the annual population-level disease burden and healthcare utilization associated with COVID-19 illness and vaccination, including resource use (e.g., outpatient visits and hospitalizations), total cases, total costs, deaths, and quality-adjusted life years (QALYs) lost. The study also aimed to estimate events averted by COVID-19 vaccination and incremental cost-effectiveness across subgroups defined by age and risk status.

The intervention strategies in the analysis compared vaccination with an updated generic mRNA booster to vaccination with no updated booster, meaning vaccination with either the primary series alone or the primary series plus the current booster. The target population included all U.S. adults, stratified by age groups (18–49 years, 50–64 years, and 65 years and older) and by risk status (high risk for COVID-19 complications or not). Pediatric and adolescent groups were

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excluded due to insufficient data for this phase of the analysis. The time horizon was one year, with long-term costs and QALYs lost due to sequelae and deaths beyond one year included. The study was conducted from a societal perspective using 2024 as the costing year and a 3% discount rate.

Simulation modeling was used to project costs and health outcomes for each age group. The model simulated the probability that an individual would remain disease-free or experience COVID-19 illness. Those who became ill could experience a non-hospitalized episode or require hospitalization, with symptomatic individuals potentially incurring outpatient or emergency department visits. Hospitalized patients could progress to severe illness requiring ICU care or ventilation. All individuals who experienced COVID-19 illness were considered at risk for long COVID, while hospitalized patients had additional probabilities of long-term complications or death.

As simulated individuals moved through the model, they accumulated costs and losses in QALYs associated with each health state. The model also included vaccine-related adverse events such as systemic reactions, anaphylaxis, and severe conditions like myocarditis, each associated with specific costs and QALY losses depending on severity. Every probability, cost, and quality adjustment included a most likely estimate and a plausible range of parameter values. Identical cohorts were analyzed using two submodels: one in which all individuals received a dose of the COVID-19 vaccine and another in which they did not, to compare outcomes between vaccinated and unvaccinated groups.

Key inputs were used to inform the model, many of which were based on unpublished epidemiological data that best reflected the current evidence on COVID-19 illness and vaccination effectiveness. These inputs included categories such as infection rates, hospitalization trends, and long COVID outcomes.

Actual monthly hospitalization rates from COVID-NET data were incorporated to capture changes in hospitalization patterns across seasons, using data from the 2023–2024 season. The analysis used seasonally adjusted vaccine impact (SAVI) to integrate vaccine effectiveness with hospitalization data, accounting for vaccination timing and seasonal variations in illness rates.

Costs included direct medical expenses related to COVID-19 illness and vaccination, as well as productivity losses from both paid and unpaid work resulting from the illness. Time costs for vaccination were also factored in. Quality-of-life adjustments were applied to illness events and vaccine-related adverse events, represented as decrements in QALYs in the model.

The analysis was designed to project disaggregated health and economic outcomes stratified by intervention strategy, age group, and risk subgroup. Outcomes included cases, hospitalizations, deaths, costs, QALYs, adverse events, and the number needed to vaccinate. Incremental cost-effectiveness ratios (ICERs), expressed in dollars per QALY gained, were calculated by comparing an updated COVID-19 dose to no updated dose. This metric measured the additional investment in vaccination or cost savings associated with changes in health outcomes, accounting for offsets from averted illnesses. Uncertainty analyses, including probabilistic sensitivity analysis, univariate and multi-way sensitivity analyses, and scenario analyses, were performed to assess the robustness of the results to variations in input parameters.

Preliminary results from this phase of modeling were still under analysis. The results projected cases, long COVID cases, hospitalizations, ICU stays, and deaths, stratified by age and risk group, based on cohorts of 100,000 individuals. The data showed that the number of COVID-19 cases was relatively similar across age and risk groups. However, hospitalizations, ICU stays, and deaths varied substantially, with a much higher burden of severe illness observed among

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adults aged 65 years and older. Vaccination in this group averted a significant proportion of these severe outcomes, highlighting the greater benefit of vaccination among older adults and those at higher risk for complications.

The results showed ICERs for each age group from a societal perspective. Across all age groups, vaccination required an additional investment, reflected in the incremental costs, but yielded additional health benefits measured in QALYs. ICERs ranged from $498,000 per QALY gained for non–high-risk adults aged 18 to 49 years to $149,000 per QALY gained for non–high-risk adults aged 65 years and older. For high-risk adults, ICERs ranged from $ 44,000 to $ 375,000 per QALY gained, indicating greater cost-effectiveness among older and higher-risk populations.

Results from the probabilistic sensitivity analysis revealed that key input parameters were modeled as distributions, enabling the generation of quasi-confidence intervals for each outcome. The findings demonstrated substantial uncertainty in ICERs for most groups, except for high-risk adults aged 65 years and older. This uncertainty reflects the current state of evidence available for COVID-19, as it is a relatively new pathogen.

Additional results showed the number needed to vaccinate (NNV) to prevent one case, one hospitalization, or one death for each age and risk group. NNV values were lowest among high-risk and older adults, indicating a greater benefit from vaccination in these populations. When ICERs were expressed using alternative health benefit measures such as cost per hospitalization or cost per death averted, the results again showed lower costs for higher-risk and older age groups, reinforcing the cost-effectiveness of vaccination in these populations.

Uncertainty analyses showed that ICERs for the non–high-risk 65 and older age group were highly sensitive to changes in SAVI, probability of hospitalization, and vaccine dose cost. Similar patterns were observed across other age and risk groups; however, the results for high-risk adults aged 65 and older were the most stable when input parameters were varied.

When the probability of hospitalization was increased to its upper bound, ICERs became more favorable across all groups and were cost-saving for the high-risk group aged 65 and older. ICERs were less favorable when using the lower bound for hospitalization probability. Results were also highly sensitive to vaccination costs, particularly the vaccine dose itself. Lowering the cost per dose to $60 reduced ICERs to less than $198,000 per QALY for both high-risk and non–high–risk adults aged 50 and older, making vaccination cost-saving for the high-risk group aged 65 and older.

Few cost-effectiveness analyses include vaccine wastage as a separate cost component. When it is included, this typically occurs for new vaccines, where the price per dose has not yet been established. The conventional assumption is that any costs associated with wastage are already reflected in the price per dose if manufacturers allow returns, or in the administration fee if providers bear the cost of unused doses. Conducting scenario analyses on the price per dose can provide valuable insights when vaccine wastage is not fully accounted for under base assumptions.

This analysis included several limitations. Unpublished data were used to derive key model parameters, including VE, symptomatic illness, and the probabilities of hospitalization and critical illness. Data sources varied in representativeness and generalizability, potentially affecting the precision of estimates. VE values were based on data from a single prior season, and only a few COVID-19 seasons were available to inform estimates of seasonality. Evidence on long COVID remains limited, and the model did not account for reductions in transmission, which represents a conservative approach.

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In summary, vaccination was shown to avert substantial morbidity and mortality across all age and risk groups based on disaggregated outcome estimates. The impact varied considerably by age and risk status. Overall economic favorability declined compared to earlier seasons, reflecting a reduced burden of illness. ICERs for adults aged 65 years and older remained robust across plausible parameter ranges. In comparison, ICERs for adults aged 18 to 49 years and 50 to 64 years were more sensitive to input changes and were favorable only under certain conditions for high-risk adults aged 50 to 64 years.

Sanofi Manufacturer Update

Dr. Katie Sharf, Medical Director for Sanofi and a practicing infectious disease physician, shared that during the pandemic, she served on the front lines treating COVID-19 patients and provided clinical oversight for Oregon's state-run mass vaccination site, which administered more than half a million doses. She introduced Nuvaxovid COVID-19 Vaccine Adjuvanted, a recombinant protein-based COVID-19 vaccine built on a well-established technology platform and the only non–mRNA protein-based COVID-19 vaccine available in the U.S., offering an additional protection option. In May, the FDA fully licensed Nuvaxovid based on phase 3 clinical trial data demonstrating its safety and effectiveness in preventing COVID-19. The vaccine is indicated for adults aged 65 and older and individuals aged 12 through 64 who are at higher risk for severe illness. Other global regulatory agencies, including the European Medicines Agency, also approve it. Dr. Sharf stated that safety and effectiveness remain top priorities, with post-marketing data from over 5 million doses administered globally showing no new safety signals for the 2023–2024 or 2024–2025 formulations. Sanofi continues to monitor and report any safety findings and has begun commercializing the vaccine in the U.S., with shipments already underway to healthcare providers and retailers. She concluded by affirming Sanofi's commitment to expanding awareness and access to Nuvaxovid, ensuring that eligible individuals can obtain the nation's only protein-based, non–mRNA COVID-19 vaccine.

Moderna Manufacturer Update

Dr. Bishoy Rizkalla, representing Moderna Medical Affairs, stated that the COVID-19 pandemic posed an unprecedented global challenge. Moderna partnered with the U.S. government through Operation Warp Speed to deliver one of the first authorized vaccines and has since worked with health authorities worldwide to ensure timely access to updated vaccines as variants emerged. Real-world evaluations involving millions of U.S. recipients demonstrated that updated vaccination provided additional protection, particularly for adults aged 65 and older and individuals with risk factors for severe outcomes. These findings were confirmed during the past winter by CDC and governments in Canada, the UK, and across Europe. Dr. Rizkalla explained that Moderna monitors safety through clinical trials, post-authorization studies, and global pharmacovigilance, reviewing every safety signal that arises. Product labels in more than 90 countries reflect all verified signals. The FDA and other health authorities, including those in Canada, the UK, and Europe, have recently approved the updated 2025–2026 booster, concluding that the benefits outweigh the risks for individuals aged 65 and older, as well as for younger individuals with certain underlying health conditions or risk factors. He noted that one of the day's presentations included claims that were not aligned with the broader body of scientific evidence, some of which extended beyond the support of reference studies or contradicted published data. He clarified that claims of long-term persistence of vaccine-derived spike protein or mRNA are refuted by well-controlled biodistribution studies that meet global regulatory standards and have been reviewed by the FDA, showing no evidence of long-term persistence. He added that such studies cannot distinguish between spike proteins from viral infection and those from vaccination, and that one even reported higher spike levels in unvaccinated controls.

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Residual DNA was also mischaracterized, as it is a tightly regulated quality attribute that is tested by validated, FDA-approved assays. Each vaccine lot is tested by Moderna and independently reviewed by the FDA before release. Both animal studies and real-world monitoring of over one billion doses have shown no evidence of genotoxicity. Dr. Rizkalla emphasized Moderna's commitment to transparency and rigorous assessment of the totality of the evidence, pledging to continue publishing validated data and to collaborate with regulators to assess any potential safety signals. He concluded by underscoring the importance of preserving access to FDA-approved vaccines, affirming that Americans should retain the right to choose protection supported by the full weight of scientific evidence.

Pfizer Manufacturer Update

Dr. Paul Balmer, U.S. Vaccines Medical Affairs Lead at Pfizer, thanked the committee and acknowledged the statements from other manufacturers. He noted that COVID-19 has transitioned from a pandemic to an endemic disease but continues to hospitalize hundreds of thousands of Americans and cause thousands of deaths each year. Dr. Balmer emphasized that Pfizer and BioNTech remain deeply committed to producing safe and effective vaccines that protect lives in the U.S. and globally. The Pfizer-BioNTech COVID-19 vaccine has been reviewed by multiple regulatory authorities, including the FDA, and meets all safety and quality control standards. Pfizer's safety systems work in coordination with U.S. government monitoring programs, with all safety data reported through appropriate channels and supplemented by ongoing scientific studies approved by the FDA. He explained that Pfizer conducts real-world data studies involving millions of people and carefully reviews every reported adverse event, ensuring each is submitted to VAERS, which serves as an early warning system but cannot determine causation. FDA and CDC use additional enhanced safety systems, including COVID-19 pregnancy registries and V-safe real-time reporting, to evaluate causation and monitor for rare safety signals. Since the COVID-19 vaccine's approval in 2020, global regulatory assessments have consistently shown that the benefits of mRNA vaccination outweigh the risks. In the past year alone, vaccination prevented an estimated 68,000 to 100,000 hospitalizations, 13,000 to 18,000 ICU admissions, and 5,000 to 7,000 deaths in the U.S. Dr. Balmer concluded by reaffirming Pfizer and BioNTech's dedication to vaccine safety, quality, and effectiveness through continuous monitoring and research, noting that with more than 5 billion doses distributed worldwide and authorization in 83 countries, the vaccines remain among the most closely monitored medical products ever licensed.

Discussion

Dr. Meissner stated that, as Dr. Malone mentioned, there is nothing unique about COVID-19 as a respiratory viral infection and that it cannot be clinically distinguished from RSV or influenza. He noted the ongoing challenge of distinguishing between patients hospitalized with COVID-19 and those hospitalized because of it, and asked whether CDC physicians or hospital clinicians make those determinations. He noted that Massachusetts addressed this issue early in the pandemic, finding that only about one-third of patients hospitalized with COVID-19 were admitted primarily for the disease, while the rest were incidentally positive. He explained that Massachusetts used dexamethasone treatment as a surrogate marker to help differentiate between true COVID-19 illness and incidental infection. Dr. Meissner emphasized that this is a critical issue and asked for more information on how CDC classifies hospitalizations as COVID-19 illnesses. He then raised a second question regarding vaccination of pregnant women and

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hospitalizations among their infants, expressing skepticism about whether those infants were hospitalized because of COVID-19. He asked what symptoms or criteria distinguished those cases from infants who tested positive but were not admitted.

Dr. Srinivasan noted that CDC data indicated approximately 30% of patients had COVID-19 listed as their principal discharge diagnosis, which coincides with the Massachusetts data referenced by Dr. Meissner. He added that other studies have shown similar findings, with COVID-19 as the primary reason for hospitalization in about 30–50% of cases.

Dr. Meissner responded that SARS-CoV-2 can colonize the pharynx and yield a positive PCR result even in the absence of symptoms, underscoring the importance of distinguishing infection from disease. He said he appreciated CDC's willingness to continue discussing the issue.

Dr. Taylor addressed the topic of infant hospitalizations, explaining that infants hospitalized at the time of birth are excluded from the analysis, as are admissions for labor and delivery, injuries, or scheduled procedures. He explained that determining the primary reason for hospitalization is challenging and relies on the medical record since CDC staff are not the treating clinicians. The agency works with state and local health departments to make the best determinations possible with the available data. He acknowledged that ICD-10 codes and treatment indicators, such as steroid use, each offer incomplete perspectives and that different methods can produce different interpretations. He stated that CDC's approach focuses on identifying hospitalizations where COVID-19 had a meaningful impact on care or admission. Although the process is not perfect, he said the algorithm represents an evidence-based method refined over several years to balance accuracy with timeliness.

Dr. Meissner acknowledged the complexity of the task and commended the team for their efforts. He expressed concern that recommendations for vaccinating pregnant women are being made based on data he considers uncertain and suggested that this uncertainty should be more clearly communicated.

Dr. Patton explained that the COVID-NET system collects all hospitalizations among residents within specific surveillance catchment areas, capturing them at the population level for those counties. She described the detailed process used to determine which hospitalizations are due to COVID-19, noting that the data show significant impacts among children and infants. She stated that one in five infants under six months hospitalized with COVID-19 are admitted to the ICU, one in four children aged 0–17 is admitted to the ICU, and up to 40% of children hospitalized due to COVID-19 experience a severe outcome such as death, ICU admission, or mechanical ventilation. She reiterated that infants hospitalized at birth are excluded from COVID-NET data and clarified that testing decisions are made by hospitals, not by CDC. She emphasized that infants under six months have hospitalization rates comparable to adults aged 65–74, as confirmed by national surveillance and other systems.

Dr. Meissner responded that, according to CDC's own data, weekly hospitalization rates since February have been below 0.8 per 100,000, suggesting the burden is currently low. He argued that decisions about future vaccines should rely on recent data rather than cumulative data, given changes in the virus and population immunity. He pointed out that since October of the

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previous year, hospitalization rates for children under 18 have been less than one per thousand and currently less than 0.4 per 100,000.

Dr. Patton clarified that the figures referenced by Dr. Meissner represent weekly rates, whereas cumulative rates offer a broader annual perspective by dividing total hospitalizations by the population within the surveillance area. She explained that including older children, who are hospitalized at lower rates, can make overall rates appear smaller. She emphasized the importance of examining population-specific data to understand how COVID-19 affects different age groups. Infants under six months have the highest hospitalization rate among all children at 223 per 100,000, followed by infants aged 6–11 months. She concluded that this stratified approach allows the surveillance system to identify which groups are most affected by COVID-19 hospitalizations.

Dr. Meissner acknowledged Dr. Patton's earlier points and agreed they were valid but noted that current hospitalization rates for infants under six months of age appear relatively low and may be overstated. He stated that the virus has become less severe over time and that most individuals now have immunity from prior infection or vaccination, which should be taken into consideration when forming recommendations. He then asked at what point low vaccine uptake influences CDC guidance, questioning whether recommendations should be changed if fewer than 20% of people choose vaccination. He compared this to prohibition, suggesting that issuing recommendations the public is unlikely to follow could undermine CDC's credibility.

Dr. Patton clarified that the cumulative hospitalization rate refers to a single season rather than multiple years and represents data for the most recent year only.

Dr. Griffin noted that Dr. Meissner's comments are relevant to obstetrics and gynecology, particularly regarding vaccination during pregnancy. She said that unaddressed confounding factors, such as maternal comorbidities and vaccination timing, could influence outcomes. She proposed further investigation into conditions like preeclampsia, hypertension, diabetes, and obesity, which are increasingly common in women of childbearing age and may affect infant susceptibility. She then asked several questions related to vaccine safety and regulation, including which regulatory bodies approved Pfizer and Moderna's decision not to use the final product in biodistribution studies, whether the companies were aware of plasmid DNA or SV40 contamination, and if they attempted to replicate those findings or conduct population-level testing. She also asked Dr. Carleton why his study was canceled within 48 hours and requested comments from the CDC presenter regarding vaccine effectiveness data reported by CDC.

Dr. Carleton stated that he was unsure why the grant was canceled. He said that HHS indicated the period of performance ended on March 25 and explained that the grant had been a multi-year project involving international surveillance. He added that this information was provided to him by the principal investigators.

The Moderna representative stated that biodistribution studies were conducted to assess the persistence of the mRNA drug product, lipid nanoparticles, and spike protein. The studies were submitted to the FDA and demonstrated that the components primarily localized to the injection site and draining lymph node, with some detection in other tissues and organs that cleared rapidly, showing no detectable spike protein more than 14 days after injection.

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Dr. Griffin asked whether the final product used in vaccination was also used in these studies.

The Moderna representative responded that the studies used commercially representative material manufactured using the same process as the vaccine product, confirming that the mRNA used was identical to that contained in the administered vaccine.

A Pfizer representative stated that the company's biodistribution studies were conducted in consultation with the FDA and used a luciferase-based product manufactured in the same way as Pfizer's drug substance and lipid nanoparticle formulation.

Dr. Malone asked whether Pfizer had used a less sensitive detection method, noting that whole-body imaging with a VIN camera is less precise than tissue dissection followed by luminescence measurement with a luminometer. He also stated that data submitted to the FDA appeared to have been edited compared to submissions to other regulatory agencies and asked Pfizer to comment.

The Pfizer representative responded that the company had no further comment beyond confirming that all biodistribution studies were conducted in close collaboration with the FDA and were included in the data supporting its licensed product.

A Moderna representative added that the detection method used in the biodistribution study for the COVID-19 vaccine employed methods specific to the spike protein, rather than colorimetric techniques.

Dr. Griffin asked whether the companies measured DNA impurities in their vaccine products.

The Moderna representative explained that each lot is tested for detectable DNA using industry-standard methods designed to detect DNA, not RNA, noting that some alternative methods have limitations in distinguishing between the two.

The Pfizer representative added that Pfizer also measures residual DNA within its product and that its assay is validated to detect DNA, not RNA specifically.

Dr. Malone asked whether the thresholds used to determine lot release for DNA contamination were based on standards developed for naked DNA or whether they reflected the enhanced delivery efficiency of the lipid nanoparticle formulation.

A Pfizer representative responded that the thresholds for residual DNA testing were in line with the WHO's approved guidelines for DNA impurities in vaccine products.

Dr. Malone clarified his question, asking whether the FDA had explicitly established those thresholds for naked DNA.

The Pfizer representative reiterated that the company followed WHO guidelines for residual DNA within vaccine products.

Dr. Malone stated that this response did not directly answer his question.

A Moderna representative explained that the thresholds were explicitly developed for Moderna's product.

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Dr. Malone asked whether alternative lot-release thresholds had been established through integration studies using DNA fragments in the company's delivery formulation.

The Moderna representative stated that all safety data are based on control of these thresholds, which are specific to Moderna's product and form the basis for assessing the product's safety.

Dr. Griffin explained that this issue is especially relevant for obstetricians and gynecologists, as many patients ask whether the vaccine is present in breast milk. She referenced a study by Hanna et al., which found evidence of COVID-19 mRNA vaccines in human breast milk and noted that the authors had NIH grants. She also mentioned another recent study, published in the American Journal of Obstetrics and Gynecology, on the transplacental transmission of COVID-19 mRNA. The study analyzed placental, maternal, and cord blood following vaccination; however, she was unable to access the full article to review potential conflicts of interest. She continued by citing an in vitro study showing intracellular reverse transcription of the Pfizer-BioNTech COVID-19 mRNA vaccine in human liver cell lines. She explained that reverse transcription is the process of converting RNA back into DNA, which was previously thought not to occur with these vaccines. She said this raises potential concerns about genetic and epigenetic effects. She then referenced a rat study by Erdogan et al. that reported prenatal exposure to COVID-19 mRNA vaccines induced autism-like behaviors in male neonatal rats. She said these are the types of studies that prompt questions from parents, and that she was bringing them forward to encourage further discussion and responses from industry and regulatory experts.

A Pfizer representative, serving as the research and scientific lead for the COVID-19 vaccine franchise, stated that, from a biological standpoint, it is not plausible for RNA to reverse-transcribe into DNA or integrate into the human genome. He explained that this process requires specific molecules and enzymes that do not exist in humans and are typically found only in retroviruses.

A Moderna representative agreed with Pfizer's statement and added that the FDA's SEERs letter, issued in 2023, evaluated data from hundreds of millions of individuals and found no evidence or indication of genotoxicity related to mRNA COVID-19 vaccines.

Dr. Milhoan stated that as a pediatric cardiologist, he often hears from parents asking what he would do if it were his own child, particularly when vaccine recommendations are discussed. He noted that vaccine uptake among healthcare providers is currently around 10%, which he believes is significant and reflective of broader hesitancy among the general population. He thanked Dr. Meissner for addressing related concerns and acknowledged Dr. Carleton for raising the importance of individualizing care, even within vaccination strategies. He shared that he is seeing a marked increase in cases of dysautonomia, or dysfunction of the autonomic nervous system, among children. He said this disruption within the community warrants further attention. He added that hospitalization decisions for children are often subjective and situational, explaining that pediatricians sometimes admit children with RSV or COVID-19 primarily for observation rather than due to severe illness. He stated that factors such as parental exhaustion or a need for close monitoring can influence these decisions. He inquired

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whether the length of stay was captured in the hospitalization data or if admissions were categorized as positive or negative.

Dr. Taylor explained that length-of-stay data are collected for patients who meet the case definition and are hospitalized, but exclude cases classified as observation.

Dr. Milhoan clarified that, even when admissions are labeled as observation, children may remain for more than 24 hours, complicating classification. He said this nuance can affect how hospitalization data are interpreted and expressed appreciation for the work being done while noting that such subtleties may obscure the whole picture. He then inquired about vaccine hesitancy and data interpretation, stating that the discussion of vaccine effectiveness appeared to have overlooked whether vaccines prevent infection. He referenced the Cleveland Clinic study of more than 50,000 healthcare workers and asked whether those findings were considered. He also wondered whether vaccine effectiveness data were developed prospectively or retrospectively.

Dr. Srinivasan responded that case data are challenging to interpret because widespread at-home testing makes it impossible to capture the whole universe of cases, unlike earlier in the pandemic when testing occurred primarily in healthcare settings.

An SME representative, Ruth Link-Gelles, explained that previous data had shown vaccine effectiveness against SARS-CoV-2 infection through pharmacy-based testing. However, she noted that, with increased home testing and fewer people seeking testing in pharmacies or outpatient settings, those data are no longer sufficient to assess vaccine effectiveness against infection. She stated that people are now less likely to get formally tested for COVID-like symptoms, making it difficult to capture accurate infection data. Because of this, current analyses focus on emergency department and urgent care visits, as well as hospitalizations, to measure vaccine effectiveness against severe disease, the primary goal of respiratory virus vaccines. She added that when vaccine effectiveness against infection could still be measured, it was consistent with levels typically observed with other respiratory vaccines, such as influenza. Similarly, vaccine effectiveness against hospitalization and severe disease has remained comparable to that of the flu over time.

Dr. Milhoan responded that he raised this issue because early CDC communications stated that receiving the vaccine would prevent COVID-19 infection. At the time, studies often excluded vaccinated individuals from testing for COVID-like illnesses based on that assumption. He said it is now clear that injectable vaccines are limited in their ability to prevent respiratory infections because of a lack of mucosal IgA immunity. He also shared concerns from his background in pharmacology, stating he was surprised by what he perceives as a lack of pharmacologic rigor in evaluating dosing, timing, accumulation, and pharmacokinetics for the vaccine. He questioned how long a biologic that produces another biologic, such as the spike protein, remains active, citing a Yale study that showed the spike protein persisted in blood samples. He concluded by expressing confusion about why, given evidence of contamination, the vaccine has not been withdrawn in the same manner as other biologics or medications when contamination is identified.

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Dr. Hoeg stated that some information on vaccine composition is proprietary but confirmed that the data provided by Pfizer and Moderna to the FDA were within established regulatory limits. She emphasized that the FDA takes product safety and public health very seriously and expressed appreciation for independent researchers who brought these issues to light. She said the FDA is aware of the concerns and is not ignoring them, and that she could only share the information the agency has received from the sponsors regarding DNA levels in their products.

Dr. Milhoan asked whether there were any plans for an independent post-production evaluation by the FDA.

Dr. Hoeg responded that such discussions are ongoing and reiterated that the FDA takes the matter seriously and appreciates those who have raised the concern.

Dr. Pollak asked both CDC and vaccine manufacturers to address antibody production and immunity following COVID-19 vaccination and booster shots. He said many people assume vaccination automatically provides immunity, but experience with influenza vaccines shows that is not always the case. He noted that people often question vaccine effectiveness when they contract COVID-19 or the flu after being vaccinated, and that this uncertainty contributes to vaccine hesitancy. He asked about the percentage of individuals who fail to produce antibodies after vaccination, as this affects the risk-benefit ratio, and questioned the need for boosters if sufficient antibodies have already been generated. He inquired about the antibody titer level at which an individual is considered protected. He suggested that if adequate neutralizing antibodies are produced, boosters may not be necessary, even with emerging viral strains. Dr. Pollak also inquired whether immune response studies considered cytokine gene polymorphisms, which can influence individual inflammatory responses, and whether independent laboratories had confirmed results regarding IgG4 and anti-idiotype antibodies. He concluded by asking whether CDC has data defining antibody levels that indicate protection and whether those levels are used when determining booster recommendations.

An SME representative, Dr. Thornburg from CDC's Laboratory and NCIRD, explained that numerous studies, including those conducted by CDC and vaccine manufacturers, have examined antibody responses following vaccination and infection. She said that most people develop strong neutralizing antibodies that correlate with protection. Still, immunity against upper respiratory viruses is generally not sterilizing due to how the immune system interacts with mucosal surfaces and the continuous evolution of viruses. She noted that it is challenging to define a specific antibody level that guarantees protection, as antibody responses fluctuate over time and can vary with the emergence of new viral lineages. Therefore, while neutralizing antibodies are protective, their effectiveness fluctuates, meaning a test result today cannot reliably predict susceptibility even a week later.

Dr. Malone responded that there are no well-defined or standardized correlates of protection for COVID-19, either cellular or humoral, and that no formal analyses have been completed to establish them. He said that, without this validation, it is inaccurate to claim a correlation between antibody levels and protection.

Dr. Meissner agreed that identifying a correlate of protection is complex but stated that neutralizing or binding antibody levels have been shown to correlate with protection against

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symptomatic infection during the first few months after vaccination. He cited a study published in the *New England Journal of Medicine* as evidence.

Dr. Malone challenged him to identify the study, asserting that protection is more likely driven by cellular immune responses rather than antibodies.

Dr. Meissner agreed, adding that while antibody protection wanes over time, cellular immunity continues to protect against severe disease, such as hospitalization and death. He concluded that correlates of protection are multifaceted, involving multiple components of the immune system, and that any antibody-based correlation is temporary.

Dr. Malone stated that in clinical testing and pathology, defined correlates of protection require rigorous and validated methods. He said that the "soft endpoints" being discussed do not meet that standard and criticized the tendency of some regulatory agencies, including the FDA, to treat antibody titers in animal models as indicators of vaccine effectiveness. He said this practice is unscientific and misleading, emphasizing that an indicator of immune response is not the same as a proven correlate of protection. He explained that defining a true correlate of protection is extremely difficult, even for influenza, where existing correlates only apply to specific vaccine types. He expressed concern that public statements from health officials and media have misrepresented antibody levels as established measures of protection, which he said is inaccurate and contributes to confusion.

Dr. Meissner responded that the issue is indeed complex and agreed with Dr. Malone's distinction between mechanistic and non-mechanistic correlates of protection. He explained that mechanistic correlates are directly linked to the immune processes that inactivate the virus, while statistical associations with unrelated immune responses are not true correlates. He noted that the definition of correlates of protection depends on the endpoint being measured, whether it is severe disease, mild illness, asymptomatic infection, or complete prevention of infection. Each endpoint involves different immune components, including mucosal IgA, systemic IgG, and multiple T-cell subclasses. He said these factors make it challenging to define a single correlate of protection but added that some studies, such as one published in the *New England Journal of Medicine*, have identified antibody levels that correlate with protection shortly after vaccination.

Dr. Malone asked whether they agreed that antibody titers cannot serve as a surrogate for individual protection and that antibody presence does not necessarily indicate protection.

Dr. Meissner acknowledged that protection.

Dr. Pollak expressed his appreciation for the discussion between Dr. Malone and Dr. Meissner and suggested that any statement issued by the committee should acknowledge that the COVID-19 vaccine does not guarantee 100% protection. He said this clarification is necessary because many members of the public believe that vaccination automatically provides full immunity. He explained that when people realize vaccination may not provide complete immunity, they begin to weigh the benefits and risks differently, which can influence their willingness to get vaccinated. He emphasized that clear communication from the committee is essential to address this misunderstanding.

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Dr. Blackburn thanked the speakers and highlighted the key role of pharmacists in vaccine access. She noted that pharmacies have administered approximately 67% of COVID-19 vaccines to adults aged 18 and above. She stated that maintaining access to vaccines in pharmacy settings is essential for providing timely patient care. She also referred to the earlier discussion about low vaccine uptake among healthcare professionals, reported at around 10%. She asked whether any surveys had been conducted to understand the reasons behind the low uptake. Additionally, she inquired whether higher influenza vaccination rates might have been influenced by flu vaccine mandates in healthcare systems and how this compares to COVID-19 vaccination uptake.

Dr. Black, an SME representative from the Immunization Services Division, responded that the data shown from NHSN are based on facility-reported vaccination coverage submitted to CMS. She explained that these reports may miss undocumented vaccinations and that influenza coverage tends to appear higher because many facilities require flu vaccination and provide it on-site, which improves documentation. She added that survey data show higher coverage rates than facility reports, with about 40% of healthcare personnel overall reporting vaccination and closer to 50% among physicians. When asked about reasons for non-vaccination, most respondents stated that they did not feel at risk of contracting COVID-19 or were not concerned about it. She noted that vaccine demand tends to rise when new variants emerge or disease levels increase. She added that access and convenience, such as whether vaccines are available on site, significantly affect coverage.

Dr. Blackburn then raised concerns about the package insert information for the COVID-19 vaccines Comirnaty and Spikevax, noting that section 13.1 states that the vaccines have not been evaluated for potential carcinogenicity, genotoxicity, or impairment of male fertility. She explained that while this language is standard for many drugs, some medications explicitly state that studies have shown no evidence of tumorigenic or mutagenic effects. Given reports of rising cancer rates and the individual case reports presented earlier, she suggested that additional studies be conducted to assess these concerns more fully. She shared that her mother experienced a dermatologic immune reaction after a COVID booster in early 2022 and was later diagnosed with EGFR-positive lung cancer, as were four others in her small hometown of fewer than 13,000 residents. She questioned whether this could represent a potential cancer cluster and asked whether CDC epidemiologists are tracking such patterns or investigating possible links to vaccines, viruses, or environmental factors. She also expressed concern that the Mississippi Cancer Registry still relies on faxed reporting and does not track biomarkers, which limits surveillance capabilities, and emphasized the need for more robust studies to confirm or rule out potential risks.

Dr. Hoeg responded that while she initially thought the question was directed to CDC, she appreciated the concern and agreed that thorough epidemiological studies are essential to determine whether there is an increase in cancer rates potentially associated with COVID-19 vaccines or specific cancer types. She said these questions would be valuable for CDC to explore further. She noted that novel research methods could be applied to investigate potential carcinogenic risks but acknowledged that such studies are complex and challenging to conduct.

Note: Text enclosed in [brackets] was added following the meeting, per the presenter's request.

She reiterated that the FDA's primary responsibility is to protect public health and that the agency takes these questions seriously, appreciating the information being shared.

Dr. Kulldorff commended Pfizer for conducting a randomized, placebo-controlled clinical trial of the COVID-19 vaccine in pregnant women, stating that such studies are essential for understanding vaccine safety in this population. He noted that the trial included approximately 350 participants, split evenly between the vaccine and placebo groups. He stated that the data Pfizer shared appeared to show a fourfold higher rate of birth defects among vaccinated participants. He said his own calculation indicated a p-value of 0.05 and described this as concerning, even with the small sample size. He asked Pfizer to comment on the finding and to confirm whether vaccinations were administered between 22 and 32 weeks of pregnancy.

A Pfizer representative, who serves as the head of Vaccine Clinical Research and Development, clarified that the study was initially designed before vaccination during pregnancy was recommended and was stopped early once those recommendations changed. She said about 350 women were randomized 1:1 between vaccine and placebo and received the vaccine between 24 and 36 weeks of pregnancy. She stated that congenital abnormalities occurred in about 5% of the vaccine group and 3% of the placebo group, not a fourfold increase as suggested. She noted that the observed rates were consistent with the background rates of congenital anomalies in the general population and noted that most such anomalies occur in the first trimester, before vaccination, making causality unlikely.

Dr. Kulldorff said that according to the materials Pfizer provided, there were eight birth defects in the vaccinated group and two in the unvaccinated group, suggesting a four-fold difference. He asked whether those numbers were incorrect.

The Pfizer representative replied that the data could be viewed in different ways, as congenital anomalies may be reported either as serious adverse events or as adverse events of special interest. She stated that upon review of serious adverse events, the rates were approximately 5% versus 3%, and she referred Dr. Kulldorff to the tables published on Pfizer's website for full details.

Dr. Kulldorff asked again whether Pfizer disputed the numbers eight and two.

The representative stated that the data were presented transparently and publicly, reiterating that differences in reporting categories explain the variation.

Dr. Hayes, from the American College of Nurse-Midwives, interjected to note that major birth defects generally occur during the first trimester, before vaccination in this study.

Dr. Kulldorff replied that birth defects are typically identified after birth, which is why he sought clarification on the data.

Dr. Griffin asked for additional details, requesting that Pfizer specify which congenital anomalies were reported, noting that while significant structural development occurs before 24 weeks, certain anomalies can appear later in pregnancy. Dr. Griffin added that certain congenital anomalies can still develop after 24 weeks of pregnancy, such as microcephaly,

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ventriculomegaly, or kidney anomalies. She explained that this was why she had asked Pfizer to specify which anomalies were reported in the study.

Dr. Stein asked whether there was an explanation for the relatively high rate of hospitalization among infants younger than six months and if there were any data on underlying medical conditions or comorbidities in that group.

Dr. Taylor responded that CDC collects data on comorbidities across all age groups. He explained that for some groups, such as children aged 6 to 23 months, prematurity is present in about 20% of cases. Although those data were not included in the slides for this meeting, they have been presented to the committee previously. He said that overall, the patterns of underlying medical conditions are not substantially different in the under-six-month age group. Because many chronic conditions take time to develop, such comorbidities are generally less common among very young infants.

Dr. Patton stated that CDC reviews medical conditions across all patients and that among infants younger than six months hospitalized due to COVID, 71% had no underlying conditions.

Dr. Stein inquired about the effectiveness of vaccines in immunocompromised adults aged 65 and older and whether analyses are stratified by comorbidities, emphasizing the importance of identifying high-risk groups.

SME representative Ruth Link-Gelles explained that CDC collects data on both immunocompromising and non-immunocompromising conditions. Sensitivity analyses that stratify or control for non-immunocompromising underlying conditions consistently show no impact on vaccine effectiveness. In contrast, vaccine effectiveness often differs for people with immunocompromising conditions, so primary analyses stratify by immunocompromised status and may control for other conditions.

Dr. Malone asked whether older adults, who experience immunosenescence, respond to vaccination in the same way as younger cohorts.

The SME representative clarified that “underlying medical conditions” refers to diagnoses such as cancer or diabetes, not age. CDC also stratifies by age. Earlier in the pandemic, when coverage was higher, analyses using 10-year brackets above age 65 showed a decline in effectiveness beginning around age 75. This evidence contributed to the recent recommendation for an additional annual dose for adults aged 65 and above, who may have lower or more quickly waning protection.

Dr. Stein asked about the vaccine safety signal presentation, noting that it included a table of adverse events of special interest and questioning whether the list was complete. She also asked why the analysis focused on stroke and whether other conditions had been considered but not shown.

Dr. Su explained that multiple CDC vaccine safety monitoring systems serve different purposes. He said the VSD conducts detailed statistical analyses, and the example presented focused on stroke. Other systems, such as the Vaccine Adverse Event Reporting System (VAERS), serve as passive surveillance tools designed to detect unusual patterns or new potential safety signals

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rather than determine causality. He said the systems complement each other, each with strengths and limitations, and together they provide comprehensive safety monitoring.

Dr. Stein concluded by commending Dr. Srinivasan's vaccine effectiveness presentation, saying it clearly described the limits of the test-negative design. She said the analysis appropriately focused on individuals presenting with respiratory symptoms and emphasized that these findings represent vaccine effectiveness against severe outcomes, not infection. She agreed with earlier comments that results should be interpreted within that context.

Dr. Hayes, representing the American College of Nurse Midwives, thanked the presenters for their work and commended the quality of the data that have been monitored over the past five years. She also recognized Dr. Tom Shimabukuro for his contributions to the V-safe program, which has been instrumental in collecting data on COVID-19 vaccination during pregnancy. She expressed appreciation for his efforts and the broader team's continued commitment to monitoring vaccine safety in this population.

Dr. Fryhofer, a general internal medicine physician in Atlanta and adjunct associate professor of medicine at Emory University, introduced herself as an ACIP liaison who has served on multiple vaccine workgroups, including the COVID-19 Vaccine Work Group since its inception. She said the presentations on biodistribution and T-cell studies were highly technical, complex, and somewhat confusing. She expressed surprise that such preliminary research was presented to the full committee rather than in a workgroup setting. She emphasized that the findings underscored the need for continued research. She noted that on August 5, HHS canceled $500 million in contracts and 22 grants related to mRNA vaccine development, describing the decision as a major setback that leaves the country more vulnerable to future pandemics and threatens progress in mRNA-based cancer treatments. She said mRNA vaccines developed through Operation Warp Speed were essential to ending the COVID-19 pandemic and remain a critical tool for public health preparedness. She also shared a personal perspective, explaining that she has two grandchildren due in November and expressed concern about whether they will be protected through maternal vaccination and later eligible for their own COVID-19 vaccinations at six months of age. She urged the committee to make vaccines available to protect infants, noting that hospitalization rates are highest among children under two years old and that maternal vaccination can significantly reduce that risk. She expressed concern about what she described as an erosion of committee integrity and transparency in the development of vaccine recommendations. She said data are sometimes selectively used to support specific conclusions rather than reflecting the full body of evidence, undermining trust and introducing bias. She emphasized that in June, the AMA and 79 other medical societies reaffirmed their support for vaccines as the best protection during respiratory virus season, including COVID-19 vaccines. She concluded by saying that while the administration has stated it will continue to make vaccines available to everyone who wants them, recent federal policy decisions appear to contradict that goal.

Dr. Hopkins stated that severe COVID-19 illness continues to cause hospitalizations and deaths, with the greatest impact among adults aged 75 years and older but also causing significant illness in younger adults and children. He noted that while most adults hospitalized with severe disease have comorbidities, many hospitalized children do not. He said vaccines

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remain effective in preventing severe disease across all tested age groups and that vaccination provides additional protection beyond any immunity gained from prior infection. He emphasized that infants under six months of age have no protection unless their mothers were vaccinated during pregnancy and concluded by stressing that access to COVID-19 vaccines must be maintained for everyone who wishes to be vaccinated, adding that low uptake should not be used as a reason to limit access or protection against severe outcomes.

Dr. Paulsen acknowledged that vaccine trust remains low in some populations and emphasized that ACIP should continue to evaluate the science objectively, raising valid concerns when warranted but affirming vaccine safety when supported by evidence. He noted that no medical intervention is entirely risk-free, but vaccines provide significant benefits that outweigh potential risks. He cautioned against basing policy decisions on anecdotal or limited basic science findings and urged the committee to rely on robust data. Regarding Dr. Carleton's findings on myocarditis, he said the research was valuable and deserving of further study but did not outweigh the evidence that vaccines are safe and effective. He highlighted that young children, particularly those aged 6 to 23 months, face hospitalization risks similar to adults aged 50 to 64 and that over half of hospitalized children have no underlying conditions. Dr. Paulsen said that all members share the goal of protecting children and minimizing harm and urged the committee to base its recommendations on data rather than theoretical concerns. He concluded by requesting that the proposed voting language be made publicly available before the presentation to ensure transparency.

Dr. Munoz, representing the Infectious Diseases Society of America, thanked the committee and said she agreed with many of the points made by her liaison colleagues. She emphasized that the discussions raised important scientific questions and highlighted the need for continued funding to advance research. She described mRNA technology as a breakthrough that enabled control of the COVID-19 pandemic both in the United States and globally. She noted that mRNA vaccines have been administered to more people in a short time than almost any other vaccine, providing extensive safety data from clinical trials and effectiveness data from post-authorization studies. Dr. Munoz added that mRNA vaccines have been the primary vaccines used in pregnancy and that strong evidence supports their value in protecting infants who are too young to be vaccinated. She concluded by advocating for continued access and protection for the most vulnerable populations, including older adults, immunocompromised individuals, people with high-risk conditions, and especially children under two years old and infants under six months who rely on maternal antibodies. She urged continued funding, research, and long-term follow-up to support the safe development and application of this technology for future vaccines.

Dr. Buchanan thanked the committee for the discussion on COVID-19 vaccines and said she would like additional clarity on the specific question being addressed regarding vaccine recommendations. She expressed concern about access issues in Georgia, explaining that although earlier statements suggested there should be no barriers, many providers in the state are limiting vaccine availability for their patients. She shared an example of a colleague whose grandchild has not yet been born, but whose mother was denied the COVID-19 vaccine for her two older children by their pediatrician. Dr. Buchanan said this reflects a real and ongoing

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access problem and urged the committee to clarify guidance and ensure that COVID-19 vaccines remain available to all who wish to receive them.

Dr. Retsef Levi (ACIP WG Chair) presented the 2025–2026 COVID-19 vaccine discussion framing. He reported that while the working group did not reach complete consensus, most members shared concerns about how COVID-19 vaccine data are being assessed and communicated. Members felt that current evaluations of protection against severe outcomes such as hospitalization, ICU admission, death, and long COVID are based on low-quality data and uncertain analyses.

Dr. Levi stated that vaccine-related injuries are not adequately recognized by existing monitoring systems, leading affected individuals to receive inadequate care. He emphasized that this lack of recognition is both an ethical and public health issue that undermines trust in vaccination programs.

Dr. Levi noted that published research indicates ongoing safety uncertainties and potential biological adaptations related to mRNA vaccines that are not being thoroughly examined. He recommended more transparent communication of risks and uncertainties to both healthcare providers and patients to support informed consent. The group plans to develop recommendations to enhance diagnosis and support for individuals affected by vaccine injuries, as well as to strengthen safety surveillance systems.

He discussed concerns about the reliability of vaccine effectiveness assessments, stating that the “number needed to vaccinate” (NNV) has not been shared for recently authorized products despite FDA requests. Data from the United Kingdom show higher NNV estimates than those used in U.S. models, raising questions about the accuracy of benefit calculations. Dr. Levi said that with multiple booster cycles completed and less virulent variants circulating, vaccine efficacy should be reassessed using current data and communicated transparently to support informed decision-making.

Dr. Levi addressed methodological issues with current analyses, stating that the test-negative design is not appropriate for evaluating hospitalization or mortality. He said this approach can produce misleading results and may overestimate vaccine effectiveness. While not establishing specific efficacy levels, he called for more rigorous study designs and supported the FDA's plans to conduct new randomized controlled trials. He noted that existing mRNA trials did not show benefits for all-cause mortality or hospitalization and that protection appears short-lived, lasting only a few months. [Adenovirus COVID vaccines did reduce all-cause mortality in the clinical trials.] He added that repeated vaccination may increase vulnerability to other respiratory viruses, referencing evidence of increased RSV susceptibility in children.

He observed that recent data show lower COVID-19 incidence compared to prior years, with reduced severity despite stable vaccination rates. He suggested this may reflect viral evolution toward lower virulence but emphasized the need for continued monitoring.

Dr. Levi reviewed safety issues the group felt CDC has not fully acknowledged, including myocarditis, cardiovascular events, prolonged post-vaccine syndromes, and possible regulatory gaps. He referenced case reports of adolescent deaths following Pfizer vaccination, attributed by pathologists to fulminant myocarditis, noting disagreement with CDC conclusions. He questioned inconsistencies in how vaccine- and infection-related deaths are classified and called for a stronger safety culture and transparent communication.

He cited studies showing subclinical myocarditis in 2 to 3 percent of vaccinated individuals, with elevated troponin levels suggesting heart injury, including among females. He stated that long-term monitoring systems for myocarditis are lacking, which undermines public trust.

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Dr. Levi described post-vaccine syndrome (PVS) as a prolonged, complex condition with overlapping symptoms similar to long COVID. The true frequency is unknown, and current systems do not capture such cases because diagnostic codes are absent. He referenced new research by Professor Christine Stabell Benn indicating that existing safety monitoring is not designed to detect chronic vaccine-related conditions.

He also discussed discrepancies between public messaging and recent findings on mRNA persistence, noting evidence that vaccine components may remain in the body longer than stated on CDC's website. He said products that behave differently from their intended mechanism require closer safety review and transparent reporting.

Vaccination during pregnancy was a key area of debate. While some members supported recommendations for pregnant women, most expressed caution due to limited safety data. The group chose not to bring the issue to a vote and urged the FDA and CDC to reexamine available evidence before issuing further guidance.

Dr. Levi noted that the group felt there were not sufficient data to compare specific vaccine products but highlighted that adenovirus-based vaccines appeared to reduce all-cause mortality in early trials, while mRNA vaccines did not. Some studies, including VA data, suggested Moderna's vaccine provided higher protection with fewer adverse events. He encouraged FDA and CDC to evaluate a broader range of vaccine options to ensure the best balance of risk and benefit.

He emphasized that public trust in COVID-19 vaccines is at a critical low point. He cited surveys showing a decline in confidence in the "safe and effective" message and noted that only about 8% of healthcare workers reportedly agree with current vaccine recommendations. He said restoring trust requires transparency and accountability.

Dr. Levi addressed informed consent, stating that current practices do not ensure patients receive meaningful information. The Vaccine Information Statement does not adequately present risks, benefits, or uncertainties. The working group recommended that CDC create a more comprehensive, plain-language informed consent process for patients and providers that clearly describes known risks and data limitations. Dr. Levi said improving informed consent is essential to rebuilding trust and upholding ethical standards in public health communication.

He explained that this concern led to one of the group's formal recommendations: that CDC establish a more consistent and comprehensive informed consent process. He said this process should use clear, accessible language for both patients and healthcare providers, outlining known risks, data limitations, and areas of uncertainty. He added that strengthening informed consent is vital to rebuilding public trust and ensuring vaccine decisions are made transparently and ethically.

Recommended Updates to the Vaccine Information Statement:

1. Current assessments regarding the protection provided by COVID-19 vaccines and especially seasonal COVID-19 boosters against severe outcomes (e.g., death, hospitalization and long COVID) are of low quality. At best, the additional protection provided by a seasonal booster is moderate and of short duration.
2. There is evidence that repeated seasonal mRNA boosters cause acquired changes in the immune system and may be associated with increased vulnerability to future infections, including SARS-CoV-2 and other respiratory viruses. These risks, as well as potential risks of autoimmunity, chronic inflammation, immune tolerance and impaired immune surveillance including immune fatigue or suppression, are currently not well understood.

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3. There are documented deaths from symptomatic and subclinical myocarditis, pericarditis and potentially other cardiovascular conditions post COVID-19 vaccination, including of healthy children, with probable causal relationship to the mRNA vaccines. This risk is likely relatively small but currently not well understood.
4. Clinical reports demonstrate that in some cases COVID-19 vaccines can cause prolonged and debilitating post vaccine syndrome (PVS). The injuries associated with PVS involve diverse symptoms and conditions, many overlapping with long COVID injuries. Some of the observed symptoms and conditions may include insomnia, chronic pain and fatigue, dysautonomia (e.g., POTS), immune dysregulation and deficiency, autoimmune disorders, severe neuropathy and other neurodegenerative conditions, cardiovascular and neurovascular injuries, and severe clotting. The frequency of PVS and related risk factors are currently not well understood.
5. There is evidence that in some individuals vaccinated with mRNA COVID-19 vaccines, the resulting spike protein, the mRNA and the nano-lipids formulation components persist in different body organs, including lymph nodes and the heart, for a prolonged period of months and possibly years in some patients. Prolonged and persistent exposure to spike, mRNA and nano-lipids particles is associated with post-vaccine syndrome (PVS) injuries as well as potentially other side effects that are currently only partially understood.
6. The safety and the efficacy of COVID-19 vaccination during pregnancy have never been tested in appropriately powered randomized clinical trials. In one randomized trial there was observed numerical imbalance of higher number of babies with congenital malformation among those born to vaccinated women.

Dr. Levi clarified that the group is not asking CDC to adopt specific wording but is urging the agency to update the Vaccine Information Statement and other communication materials to reflect current knowledge and uncertainties better. He said the goal is for CDC to develop clear, balanced language that helps patients and healthcare providers have honest discussions about both the benefits and risks of vaccination. This approach, he explained, would allow for informed consent that accurately reflects what is known and not yet known, ensuring that vaccine guidance remains transparent and aligned with ethical public health communication.

He outlined the guiding principles the working group used when developing vaccination policy recommendations. The group agreed that vaccination should remain within the FDA-authorized population and that benefits, risks, and uncertainties must be clearly communicated as part of informed consent. Members debated whether vaccination guidance should be based on population-level recommendations or individual clinical decisions. The majority supported an individual-based approach, concluding that COVID-19 vaccines should be prescribed by a clinician rather than administered under standing orders. This approach would allow for personalized discussions between patients and healthcare providers about prior infections, immune response, comorbidities, and the balance of risks and benefits. He noted that this level of individual consideration is more appropriate now that the situation is no longer an emergency. While some concerns were raised about access, he said most high-risk individuals are already engaged with healthcare providers, making the prescription-based model reasonable. He added that a minority of members held differing views, which would be shared by Dr. Bernstein.

Dr. Henry Bernstein (Zucker School of Medicine) shared additional considerations from the work group regarding COVID-19 vaccination policy and practices. He emphasized that clear and

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consistent vaccine recommendations are critical for maintaining public confidence, increasing vaccination rates, and reducing disease incidence. When coverage declines due to loss of trust, outbreaks can reemerge, underscoring the importance of transparency and effective communication. He noted that vaccine development is a complex and lengthy process that often takes years and involves collaboration between public and private sectors. Operation Warp Speed was cited as an example of a successful partnership, with COVID-19 vaccines continuing to perform well in preventing severe illness and death.

Dr. Bernstein also highlighted that vaccine safety is rigorously evaluated at every stage, from development to post-implementation monitoring. He commended CDC's unprecedented safety surveillance efforts during the pandemic, describing them as vital for maintaining public trust. He specifically discussed the Vaccine Adverse Event Reporting System (VAERS), explaining that it serves as the nation's early warning system for potential vaccine safety issues. He clarified that while anyone can submit reports to VAERS, the system does not establish causation but serves as a valuable signal-detection tool that identifies patterns warranting further investigation.

Dr. Henry Bernstein explained that COVID-19 vaccine safety monitoring has been extensive, continuous, and remains ongoing. He noted that multiple systems are in place to evaluate safety, including a pregnancy registry that tracks maternal and infant outcomes over time. Rapid-cycle analyses are also conducted to monitor specific outcomes and quickly identify potential concerns warranting further investigation.

He emphasized that the COVID-19 vaccine continues to provide additional protection against COVID-19–related emergency room visits, urgent care visits, hospitalizations, and critical illness. Among children and adults alike, vaccinated individuals experience lower rates of these outcomes than unvaccinated individuals. He added that vaccine effectiveness should be viewed as an added layer of protection in a population where many people already have infection-induced or vaccine-induced immunity, or both.

Dr. Bernstein also highlighted ACIP's three guiding principles: science, safety, and access. Science remains central to ACIP's decisions, and the data continue to show that COVID-19 vaccines are both safe and effective. He emphasized that equitable and easy access to vaccines for everyone who wants them is essential to maintaining public health protection.

Dr. Henry Bernstein discussed ongoing challenges and data related to COVID-19 vaccination, emphasizing how shared clinical decision-making and the requirement for provider prescriptions create unnecessary barriers to vaccination. While healthcare providers routinely discuss the benefits and risks of vaccines with patients, shared clinical decision-making can lead to confusion, as it lacks a clear default in favor of vaccination and is often interpreted as optional. The added requirement for a prescription further complicates access and does not effectively target those at the highest risk of harm.

He noted that the U.S. has approximately 330 million people, including more than 18 million children under the age of five, who are more likely to be infection-naive or unvaccinated, highlighting a key population for ongoing protection efforts. COVID-19 vaccines have demonstrated safety in children ages six months to eleven years, with no confirmed cases of myocarditis in those under five. Rapid-cycle analyses have also shown no increased risk for 22 other prespecified health outcomes following vaccination.

Dr. Bernstein referenced CDC data showing that hospitalization rates for COVID-19 remain highest among infants and young children under two years old, particularly those under six months. Although their overall numbers are small, the population's large size means the impact remains significant. Infants under six months experience hospitalization rates comparable to adults aged 65 to 74, underscoring the importance of maternal vaccination.

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He explained that vaccination during pregnancy provides protective antibodies to newborns and young infants, similar to other vaccines such as RSV, influenza, and Tdap, all of which protect infants too young to be vaccinated. Ongoing monitoring shows no increased risks for maternal, pregnancy, or infant outcomes associated with COVID-19 vaccination during pregnancy, and the benefits continue to outweigh any potential risks. Dr. Bernstein also emphasized that older adults, notably those aged 65 and above, experience reduced immune responses with age and therefore benefit significantly from staying up to date with COVID-19 vaccination.

Key Messages for Consideration:

1. COVID-19 vaccination rates in the younger pediatric population are very low: the primary COVID-19 vaccination series is needed
2. Antepartum vaccination especially helps protect infection-naïve newborns and young infants under 6 months of age
3. Older people do not make as good an immune response as when younger ("Immunosenescence")
4. COVID-19 vaccination matters for pregnant women, pediatric patients especially < 2 years of age, people 65 years and older, those of any age with a weakened immune system or chronic medical conditions, and anyone who feels they want protection for themselves or their family.

Dr. Retsef Levi (ACIP WG Chair) presented the final proposed recommendations from the COVID-19 Vaccine Work Group.

Proposed Recommendations:

1. It is the sense of the committee that the CDC engages in an effort to promote more consistent and comprehensive informed consent processes, and as part of that considers adding language accessible to patients and medical providers to describe at least the six risks and uncertainties included in the WG chair presentation.
2. It is the sense of the committee that state and local jurisdictions should require a prescription for the administration of a COVID-19 vaccination.
3. It is the sense of the committee that in conversations with patients before COVID-19 vaccination, authorized healthcare providers discuss the risks and benefits of the vaccination for the individual patient. The discussion should consider known risk factors for severe outcomes from COVID-19, such as age, prior infections, immunosuppression, and certain comorbidities identified by the CDC, and include a discussion of the potential benefits and risks of vaccination and related uncertainties, especially those outlined in the vaccine information statement, as part of informed consent.
4. The pediatric and adult immunization schedules for administration of FDA-approved COVID-19 vaccines should be updated as follows:
    - Adults 65 and older: Vaccination based on individual-based decision-making*
    - Individuals 6 months to 64 years: Vaccination based on individual-based decision-making—with an emphasis that the risk-benefit of vaccination is most favorable for individuals who are at an increased risk for severe COVID-19 disease and lowest for individuals who are not at an increased risk, according to the CDC list of COVID-19 risk factors.
      **Also known as shared clinical decision making.*

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Discussion for COVID-19 Vaccines Vote #4

Dr. Hibbeln stated that, in his view, the committee's discussions clearly demonstrate that members are not opposed to vaccines. He emphasized that the robust scientific debate, mutual respect among members, and inclusion of external experts reflect a thoughtful, open-minded approach rather than any predetermined stance. He noted that understanding the risks and benefits of vaccines is essential to the committee's work, acknowledging the difficulty of quantifying these factors. Dr. Hibbeln concluded by affirming that the FDA, CDC, and the committee are collectively committed to evaluating and clearly communicating both the risks and benefits of vaccination to the public.

Dr. Meissner requested clarification on whether adults aged 65 and older would be eligible to receive the COVID-19 vaccine at a pharmacy under the proposed recommendation.

Dr. Kulldorff responded that the recommendation ensures coverage with zero cost-sharing under SHIP, ACA plans, and Medicare Part B for all individuals aged six months and older, including children up to age 18. He explained that this means there would be no insurance restrictions on receiving the vaccine.

Dr. Meissner then asked if a prescription would be required.

Dr. Kulldorff clarified that the prescription issue was addressed in a separate vote (Vote #2) and is outside the committee's authority, as state regulations determine prescriptions.

Vote: COVID-19 Vaccines Vote #4

Dr. Martin Kulldorff (ACIP Chair) read the following proposed ACIP voting language for the vaccine into the record:

The pediatric and adult immunization schedules for administration of FDA-approved COVID-19 vaccines should be updated as follows:

- Adults 65 and older: Vaccination based on individual-based decision-making*
- Individuals 6 months to 64 years: Vaccination based on individual-based decision-making—with an emphasis that the risk-benefit of vaccination is most favorable for individuals who are at an increased risk for severe COVID-19 disease and lowest for individuals who are not at an increased risk, according to the CDC list of COVID-19 risk factors.

**Also known as shared clinical decision making.*

Motion/Vote: COVID-19 Vaccines

Dr. Hibbeln motioned to approve the recommended voting language, stating, "The pediatric and adult immunization schedules for administration of FDA-approved COVID-19 vaccines should be updated as follows:

o Adults 65 and older: Vaccination based on individual-based decision-making*

o Individuals 6 months to 64 years: Vaccination based on individual-based decision-making—with an emphasis that the risk-benefit of vaccination is most favorable for individuals

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who are at an increased risk for severe COVID-19 disease and lowest for individuals who are not at an increased risk, according to the CDC list of COVID-19 risk factors.
*Also known as shared clinical decision making." Dr. Malone seconded the motion. No COIs were declared. The motion carried with 12 votes in favor, 0 votes opposed, and 0 abstentions. The disposition of the vote was as follows:

12 Favored: Meissner, Pollak, Malone, Pagano, Milhoan, Blackburn, Griffin, Stein, Hibbeln, Pebsworth, Levi, Kulldorff
0 Opposed:
0 Abstained:

Discussion for COVID-19 Vaccines Vote #1

Dr. Meissner asked whether the recommendation implied that informed consent must be obtained before COVID-19 vaccination.

Dr. Levi explained that the intent was to send a strong message urging CDC to improve its communication of risks and uncertainties to patients and healthcare providers, including through updates to the Vaccine Information Statement (VIS) and other communication materials. He clarified that the group was not prescribing exact language but strongly recommending that CDC ensure communications support informed consent.

Dr. Hibbeln added that the recommendation encourages CDC to enhance consistency and clarity in its communication but does not impose any formal requirements.

Dr. Malone agreed, noting that the regulation of medical practice and informed consent fall under state, not federal, authority. He stated that the intent was to encourage CDC to provide information that states can use to enhance their own informed consent processes.

Dr. Levi emphasized that the VIS is produced and updated by CDC, making it directly relevant to this recommendation.

Dr. Malone further explained that, historically, informed consent practices and the VIS have involved complex interactions between states and CDC. While the federal government cannot regulate these requirements, CDC can help improve communication and transparency.

Dr. Kulldorff noted that this type of recommendation is usually implemented by CDC without a formal vote, expressing confidence that CDC leadership has the capacity to act on the discussion.

Dr. Meissner then clarified that VIS documents are already legally required for all vaccines and asked if the proposed change would affect the content rather than the requirement itself.

Dr. Levi confirmed that the intent is to update the VIS content to reflect current risks and uncertainties better.

Dr. Middleman commented that vaccine recommendations are typically measurable and policy-focused, whereas this proposal is more clinical in nature. She asked for clarification on the

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phrase “it is the sense of the committee,” emphasizing that ASIP recommendations must remain evidence-based.

Dr. Levi responded that ACIP’s charter allows it to consider broader vaccination policy issues and that the current COVID-19 VIS does not reflect the latest risk information. He said the working group’s recommendations are based on a thorough review of the literature and available evidence, and that transparency about uncertainties is essential. He concluded that communicating known risks, limitations, and uncertainties, even when evidence is incomplete, is fundamental to maintaining public trust and aligns with ACIP’s mission.

Vote: COVID-19 Vaccines Vote #1

Dr. Martin Kulldorff (ACIP Chair) read the following proposed ACIP voting language for the vaccine into the record:

> It is the sense of the committee that the CDC engages in an effort to promote more consistent and comprehensive informed consent processes, and as part of that considers adding language accessible to patients and medical providers to describe at least the six risks and uncertainties included in the WG chair presentation.

Motion/Vote: COVID-19 Vaccines

Dr. Malone motioned to approve the recommended voting language, stating, “It is the sense of the committee that the CDC engages in an effort to promote more consistent and comprehensive informed consent processes, and as part of that considers adding language accessible to patients and medical providers to describe at least the six risks and uncertainties included in the WG chair presentation.” Dr. Stein seconded the motion. No COIs were declared. The motion carried with 11 votes in favor, 1 vote opposed, and 0 abstentions. The disposition of the vote was as follows:

11 Favored: Meissner, Pollak, Stein, Milhoan, Blackburn, Malone, Pagano, Griffin, Hibbeln, Pebsworth, Levi
1 Opposed: Kulldorff
0 Abstained:

Discussion for COVID-19 Vaccines Vote #2

Dr. Blackburn noted that pharmacists are not currently authorized providers under Medicare Part B and therefore cannot write prescriptions.

Dr. Kulldorff acknowledged that this is the case in some states, where pharmacists do not have the authority to prescribe medications.

Dr. Blackburn added that while pharmacists can often operate under collaborative practice agreements, requiring a prescription would still create a barrier to vaccine access.

Note: Text enclosed in [brackets] was added following the meeting, per the presenter’s request.

Dr. Kulldorff asked whether she was proposing an amendment to the vote or suggesting that the prescription requirement be removed.

Dr. Blackburn replied that she was suggesting an amendment, as requiring a prescription would not be practical.

Dr. Malone clarified that the prescription requirement is central to the vote and that, unless specific amendment language is proposed, the issue would proceed to a yes-or-no vote.

Dr. Stein said she fully supports informed consent and believes that discussing risks, benefits, and uncertainties is essential. However, she expressed strong concern about requiring a prescription, explaining that underinsured populations and those with limited access to healthcare would face barriers. She noted that these individuals often have the highest risk of comorbid conditions, underscoring the critical need for access.

Dr. Meissner agreed and stated that he is strongly opposed to requiring a prescription. He said that the Vaccine Information Statement already provides much of the information that would be discussed with a physician. Requiring a prescription, he argued, would create a major barrier to vaccine access. He added that individuals should be able to obtain the vaccine for themselves or their children without needing a prescription.

Dr. Hibbeln also expressed concern, noting that about 30 percent of Americans lack ready access to a primary care provider. He said that in Texas and other rural states, access is even more limited. This lack of access would prevent many people from having the required risk-benefit discussions with providers. He agreed with Dr. Blackburn, Dr. Stein, and Dr. Meissner that requiring a prescription would create a significant barrier to implementing the goals of informed consent and equitable vaccine access.

Dr. Levi explained that the vote is intended to give states flexibility to determine their own approaches. He acknowledged concerns about access but questioned whether the argument against prescriptions is consistent, noting that antibiotics and other prescription drugs are not available over the counter for similar reasons. He said the COVID-19 vaccine involves nuanced medical considerations that justify a clinical discussion before administration. He added that most individuals at higher risk already see healthcare providers regularly for other prescriptions, and that in practice, most states would likely find ways to allow pharmacies to participate. He concluded that the goal is to strengthen informed consent and ensure the process is meaningful.

Dr. Griffin said she is sensitive to access concerns but agreed with Dr. Levi that obtaining a prescription encourages informed discussions between patients and providers. She said the process would promote informed consent, similar to that for other medical treatments, such as prescriptions for chronic conditions. She added that access barriers should be addressed separately rather than by eliminating the informed consent step.

Dr. Meissner responded that he disagreed with the comparison between vaccines and antibiotics. He explained that antibiotics are used to treat illness and require timely medical judgment, whereas vaccines are preventive and given to healthy people. He said requiring

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prescriptions for vaccines would raise healthcare costs and create unnecessary barriers. He argued that if a person wants to receive the vaccine, a physician is unlikely to discourage them, so that a prescription would serve little purpose.

Dr. Malone stated that COVID-19 vaccines are already limited to individuals with underlying health conditions, meaning they are not being given to completely healthy populations. He emphasized that informed consent is essential because risk-benefit assessments must be tailored to each individual. He said decisions should be made collaboratively between patients and licensed healthcare providers, ensuring that choices are based on medical evaluation rather than marketing or public messaging.

Dr. Blackburn clarified that pharmacists are licensed healthcare professionals trained in immunology and certified to assess vaccine risks and benefits. She shared data showing that during the 2024–2025 season, 90 percent of COVID-19 vaccines were administered in pharmacies. She said requiring prescriptions would reduce access and create unnecessary barriers, particularly since pharmacists are already trained to provide patient-specific vaccine counseling.

Dr. Meissner reiterated that access is a major concern, noting that it can take him up to a year to see his internist. He said this kind of delay would make it extremely difficult for many people to obtain prescriptions. He emphasized that restricting access is not consistent with ACIP's role and asked for clarification on whether the requirement would apply to all individuals or only to those at high risk.

Dr. Malone clarified that he did not question pharmacists' qualifications and that prescriptive authority is determined by state law. He described the recommendation language as general and said it leaves flexibility for states and local jurisdictions to assess implementation.

Dr. Levi agreed that pharmacists should be part of the solution and said most states already allow pharmacists to provide vaccines under collaborative arrangements. He said the intent is to send a message that informed consent should involve a deliberate and documented discussion. He acknowledged that pharmacy-based vaccinations often lack such debate and said the recommendation aims to improve this process, not to eliminate pharmacy participation.

Dr. Blackburn added that at least 19 states currently require pharmacists' vaccine authority to be tied to ACIP recommendations, and recent confusion about guidance has already affected access. She cited examples of pharmacies like CVS and Walgreens reducing vaccine availability due to unclear policies.

Dr. Goode, representing the American Pharmacists Association, said that many states base pharmacists' vaccination authority directly on ACIP recommendations. If ACIP were to require prescriptions, pharmacists in those states might no longer be permitted to administer the vaccine. She emphasized that pharmacists are among the most accessible healthcare providers and are well-trained to assess the risks and benefits. She reiterated that 90 percent of COVID-19 vaccines have been given in pharmacies and warned that requiring prescriptions would reduce access, worsen health inequities, and limit patient choice.

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Dr. Middleman expressed deep concern about treating vaccines like prescriptions, explaining that vaccines are a primary prevention tool, not a treatment. She said requiring prescriptions would overwhelm physicians' offices and create confusion about how vaccine orders work, since vaccines are generally given under standing orders rather than individual prescriptions. She cautioned that adding new barriers to access undermines public health goals and efforts to build trust in vaccination.

Dr. Moehling, representing the Association for Prevention, Teaching, and Research, thanked the committee and echoed the concerns raised by other liaison representatives and Dr. Blackburn. She urged the committee to consider how requiring a prescription carefully would affect access, noting that pharmacists are currently the primary providers administering COVID-19 vaccines to most patients. She pointed out that the committee's previous votes, particularly Vote #4, support individual choice in vaccination decisions, and that Vote #1 emphasized the importance of a more informed consent process, which she fully supports. Dr. Moehling suggested that the committee hear from the CMS representative to clarify how a prescription requirement might limit pharmacists' ability to administer the vaccine and impact overall access to it.

Vote: COVID-19 Vaccines Vote #2

Dr. Martin Kulldorff (ACIP Chair) read the following proposed ACIP voting language for the vaccine into the record:

> It is the sense of the committee that state and local jurisdictions should require a prescription for the administration of a COVID-19 vaccination.

Motion/Vote: COVID-19 Vaccines

Dr. Hibbeln motioned to approve the recommended voting language, stating, "It is the sense of the committee that state and local jurisdictions should require a prescription for the administration of a COVID-19 vaccination." Dr. Malone seconded the motion. No COIs were declared. The motion carried with 6 votes in favor, 6 votes opposed, and 0 abstentions. The disposition of the vote was as follows:

6 Favored: Milhoan, Malone, Pagano, Griffin, Pebsworth, Levi,
6 Opposed: Meissner, Pollak, Stein, Blackburn, Hibbeln, Kulldorff
0 Abstained:

*Due to a tie (6–6) on the vote, the chair, Dr. Kulldorff, cast the deciding vote. His "no" vote broke the tie, causing the motion to require a prescription for COVID-19 vaccination to fail.

Vote: COVID-19 Vaccines Vote #3

Dr. Martin Kulldorff (ACIP Chair) read the following proposed ACIP voting language for the vaccine into the record:

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It is the sense of the committee that in conversations with patients before COVID-19 vaccination, authorized healthcare providers discuss the risks and benefits of the vaccination for the individual patient. The discussion should consider known risk factors for severe outcomes from COVID-19, such as age, prior infections, immunosuppression, and certain comorbidities identified by the CDC, and include a discussion of the potential benefits and risks of vaccination and related uncertainties, especially those outlined in the vaccine information statement, as part of informed consent.

Motion/Vote: COVID-19 Vaccines

Dr. Malone motioned to approve the recommended voting language, stating, "It is the sense of the committee that in conversations with patients before COVID-19 vaccination, authorized healthcare providers discuss the risks and benefits of the vaccination for the individual patient. The discussion should consider known risk factors for severe outcomes from COVID-19, such as age, prior infections, immunosuppression, and certain comorbidities identified by the CDC, and include a discussion of the potential benefits and risks of vaccination and related uncertainties, especially those outlined in the vaccine information statement, as part of informed consent." Dr. Milhoan seconded the motion. No COIs were declared. The motion carried with 12 votes in favor, 0 votes opposed, and 0 abstentions. The disposition of the vote was as follows:

12 Favored: Pollak, Pagano, Stein, Blackburn, Milhoan, Meissner, Griffin, Pebsworth, Levi, Hibbeln, Kulldorff, Malone
0 Opposed:
0 Abstained:

PUBLIC COMMENT

The floor was opened for public comment on September 19, 2025. The comments made during the meeting are summarized in this document. Members of the public were also invited to submit written public comments to ACIP through the Federal eRulemaking Portal under Docket Number ID CDC-2025-0454. Visit regulations.gov for access to read the comments received.

Robert Blancato
National Association of Nutrition and Aging Services Programs

Mr. Blancato spoke on behalf of the National Association of Nutrition and Aging Services Programs, emphasizing the importance of vaccine access for older adults. He highlighted that vaccination is the most effective and cost-efficient way to protect aging populations and reduce hospitalizations. He praised recent CDC guidance expanding RSV vaccine eligibility to adults aged 50 and older and encouraged similar action for COVID-19 vaccines, noting racial and ethnic disparities in hospitalization rates. He urged the ACIP to lower the age-based COVID-19 vaccination recommendation to include younger adults at higher risk. He cited a joint letter from

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the Alliance for Aging Research, signed by more than 75 organizations, calling for equitable, broad access to vaccines. Mr. Blancato concluded by recommending that the ACIP include experts in geriatric care to ensure that older adult perspectives are represented in vaccination policy decisions.

Miss Nissa Shaffi
Allergy and Asthma Network

Miss Shaffi, representing the Allergy and Asthma Network, underscored the importance of maintaining vaccine access and insurance coverage for individuals with asthma, allergies, and chronic respiratory conditions. She expressed concern about recent state-level efforts requiring prescriptions for COVID-19 vaccines, warning that such measures would create barriers, increase disease burden, and threaten herd immunity. Miss Shaffi noted that people with respiratory illnesses face a higher risk of infections such as influenza, COVID-19, and RSV, and that limiting vaccine access could have severe public health consequences. She emphasized that ACIP's recommendations drive insurance coverage under Medicare, Medicaid, and private plans. She urged the committee to preserve strong, evidence-based recommendations to ensure vaccines remain available and affordable for vulnerable populations.

Mr. Noah Louis-Ferdinand
Voices for Vaccines

Mr. Louis-Ferdinand, communications coordinator for Voices for Vaccines, expressed support for ACIP's careful review of the hepatitis B birth dose, affirming the strong evidence of safety and effectiveness. He highlighted that the timely administration of the birth dose prevents chronic infection and liver cancer and is critical because not all mothers are tested for hepatitis B before delivery. He also commented on COVID-19 vaccination, urging the committee to avoid decisions that would limit access for immunocompromised individuals. Mr. Louis-Ferdinand cautioned against spreading misinformation and called for high-quality, evidence-based communication from public health authorities. He noted that claims linking COVID-19 vaccines to cancer or DNA changes are unsupported and emphasized the importance of maintaining scientific rigor in all ACIP deliberations.

Mrs. Candace DeMatteis
Partnership to Fight Infectious Disease

Mrs. DeMatteis, vice president of policy and advocacy for the Partnership to Fight Infectious Disease, voiced concern over changes in ACIP membership and departures from its established evidence-to-recommendations process. She noted that the committee's credibility rests on transparent, science-based decision-making and warned that deviations could erode public trust. Mrs. DeMatteis criticized discussions driven by skepticism rather than new evidence, particularly regarding the hepatitis B birth dose. They cautioned that inconsistent recommendations could disrupt insurance coverage and vaccine access across states. She urged ACIP to recommit to its long-standing deliberative process, emphasizing that rigorous, evidence-based procedures are essential to preserving confidence and ensuring equitable vaccine access.

Dr. Daniel Crawford, DNP
National Association of Pediatric Nurse Practitioners

Dr. Crawford, representing the National Association of Pediatric Nurse Practitioners,

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emphasized that nurses play a vital role in vaccine delivery and public trust. He expressed concern that recent changes to ACIP and the removal of subject matter experts have undermined confidence in the committee's decisions. Dr. Crawford noted that hepatitis B vaccines have an outstanding safety record and prevent thousands of deaths each year. He criticized the committee's decision to remove the combined MMRV vaccine for children under four, stating it created confusion among parents and providers. He urged a return to data-driven deliberations and reaffirmed that vaccines remain among the most effective and safest tools for protecting children's health.

Mrs. Patricia Armstrong
Private Citizen

Mrs. Armstrong spoke as a private citizen, expressing concern about the spread of misinformation and the decline in public confidence in vaccines. She described how false claims about vaccine ingredients and side effects have fueled fear, contributing to the resurgence of diseases such as measles. She called for more substantial public education efforts, including clear, accessible materials, collaborations with media and influencers, and increased outreach to both conservative and liberal audiences. Mrs. Armstrong urged government and health institutions to communicate scientific facts in simple and engaging ways to combat misinformation and prevent further vaccine hesitancy.

Mr. Steven Furr, MD, FAAFP
American Academy of Family Physicians

Dr. Furr, representing the American Academy of Family Physicians, highlighted the essential role of family physicians in vaccine delivery and patient education. Drawing on his decades of experience, he reflected on the dramatic decline in severe infections, such as Haemophilus influenzae type B, following routine vaccination. He expressed concern that recent ACIP changes weaken the evidence-to-recommendation process and reduce transparency by excluding practicing clinicians. Dr. Furr emphasized that universal hepatitis B vaccination at birth remains critical to preventing transmission and that narrowing recommendations for MMRV and COVID-19 vaccines undermines patient autonomy. He urged ACIP to restore scientific integrity, transparency, and consistency to rebuild trust in public health recommendations.

Dr. Richard Dang, PharmD
University of Southern California

Dr. Dang, a pharmacist and associate professor at the University of Southern California, advocated for practical, evidence-based access to vaccines. He opposed requiring prescriptions for COVID-19 vaccines, noting that pharmacists administered most vaccines during the 2024–2025 season and that such requirements would create unnecessary barriers. He stressed that pharmacies are among the most accessible healthcare settings, serving 90 percent of Americans within five miles. Dr. Dang urged ACIP to base recommendations on sound evidence, preserve patient choice, and maintain consistency to avoid confusion. He reaffirmed that COVID-19 vaccines have been extensively monitored, are safe, and should remain available to everyone six months and older who wishes to be vaccinated.

Mr. Richard So, MPH/MPA
Hep B Free

Mr. So, executive director of Hep B Free, spoke about the real-world impact of hepatitis B and

the importance of maintaining universal infant vaccination. He described stories from affected families and the long-term success of the birth dose in preventing new infections. Mr. So cautioned that framing hepatitis B as a sexual or drug-related disease overlooks other transmission routes and the vulnerability of infants. He noted that when previous birth dose recommendations were suspended, vaccination rates declined, and trust was eroded for years afterward. He urged ACIP to preserve the proven policy of universal birth dose vaccination to protect children and prevent future outbreaks.

Ms. Wendy Lou
Private Citizen (Hepatitis B Patient Advocate)

Ms. Lou shared her personal story as a patient living with chronic hepatitis B, which she likely contracted at birth before the vaccine was available. She described the lifelong medical, financial, and emotional burden of chronic infection and the stigma associated with the disease. Ms. Lou emphasized that the hepatitis B birth dose prevents 90% of infections in newborns and that up to 25 percent of those with chronic infection die from related complications. She credited the vaccine for protecting her children and expressed relief that they are free from the disease. Ms. Lou urged ACIP not to weaken the birth dose recommendation, stating that it saves lives and prevents needless suffering across generations.

With no additional business to be addressed at the September 2025 ACIP meeting, the meeting was officially adjourned.

ACIP MEMBERSHIP ROSTER

CHAIR

KULLDORFF, Martin, PHD
Biostatistician, Epidemiologist
Formerly Harvard University Professor of Medicine
6/13/2025 – 6/30/2029

EXECUTIVE SECRETARY

ZADEH, Mina, PHD, MPH
Designated Federal Officer (DFO)
Supervisory Program Specialist
Office of the Director, Office of the Chief of Staff
Centers for Disease Control and Prevention

VOTING MEMBERS

BLACKBURN, Hillary, PharmD, M.B.A.
Director of Medication Access and Affordability
AscensionRx
Term: 9/11/2025-6/30/2029

GRIFFIN, Evelyn, M.D.
Obstetrician and Gynecologist
Baton Rouge General Hospital

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Term: 9/11/2025-6/30/2029

HIBBELN, Joseph R., MD, ABNP, CAPT USPHS (Ret.)
Psychiatrist, Neuroscientist
Formerly Chief of Section on Nutritional Neurosciences
National Institutes of Health
Term: 6/13/2025 – 6/30/2029

LEVI, Retsef, PHD
Professor of Operations Management
MIT Sloan School of Management
Leading expert in Healthcare Analytics
Term: 6/13/2025 – 6/30/2029

MALONE, Robert W., MD, MS
Vaccinologist, Scientist, Biochemist
Contributor to mRNA Vaccine Technology
Term: 6/13/2025 – 6/30/2029

MEISSNER, H. Cody, MD
Professor of Pediatrics
Dartmouth Geisel School of Medicine
Previously Chief of Division of Pediatric Infectious Disease
Tufts-New England Medical Center
Former CDC ACIP member
Former FDA's Vaccine & Related Biological Products Advisory Committee
Term: 6/13/2025 – 6/30/2029

MILHOAN, Kirk, M.D., Ph.D.
Medical Director
For Hearts and Souls Free Medical Clinic
Term: 9/11/2025-6/30/2029

PAGANO, James V., MD, FACEP
Emergency Medicine Physician with More than 40 Years Clinical Experience
Term: 6/13/2025 – 6/30/2029

PEBSWORTH, Vicky, PhD, RN
ACIP Consumer Representative
Focus Bioethics and Vaccine Safety
Research Director
National Vaccine Information Center
Former FDA Vaccines & Related
Biological Products Advisory Committee
Term: 6/13/2025 – 6/30/2029

POLLAK, Raymond, M.D., F.A.C.S., F.R.C.S.
Surgeon, transplant immunobiologist, and transplant specialist
Term: 9/11/2025-6/30/2029

STEIN, Catherine M., Ph.D.

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Professor, Department of Population and Quantitative Health
Case Western Reserve University
Term: 9/11/2025-6/30/2029

EX OFFICIO MEMBERS

Centers for Medicare and Medicaid Services (CMS)
JOHNSON, Andrew, CMS

Food and Drug Administration (FDA)
HOEG, Tracy Beth, MD, PHD
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Health Resources and Services Administration (HRSA)
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Indian Health Service (IHS)
CLARK, Matthew, MD, FAAP, FACP
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Office of Infectious Disease and HIV/AIDS Policy (OIDP)

National Institutes of Health (NIH)
KURILLA, Michael, MD-PhD
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LIAISON REPRESENTATIVES

American Academy of Family Physicians (AAFP)
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American College of Nurse Midwives (ACNM) (alternate)
MEHARRY, Pamela M., PHD, CNM
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American College of Obstetricians and Gynecologists (ACOG)
SWAMY, Geeta K., M.D.
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Vice Dean for Scientific Integrity
Haywood Brown, MD Distinguished Professor of Women's Health
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American College of Physicians (ACP)
GOLDMAN, Jason M. MD, FACP
Affiliate Assistant Professor of Clinical Biomedical Science
Florida Atlantic University

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Boca Raton, FL
Private Practice
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American Geriatrics Society (AGS)
SCHMADER, Kenneth, MD
Professor of Medicine-Geriatrics
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America's Health Insurance Plans (AHIP)
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Plan Performance Medical Director
Anthem Blue Cross and Blue Shield
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American Immunization Registry Association (AIRA)
COYLE, Rebecca, MSEd
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American Immunization Registry Association (AIRA) (alternate)
LONDO, Courtnay, MA
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American Medical Association (AMA)
FRYHOFER, Sandra Adamson, MD
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American Nurses Association (ANA)
RESNICK, Barbara, PhD, RN, CRNP, FAAN, FAANP
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American Osteopathic Association (AOA)
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American Pharmacists Association (APhA)
GOODE, Jean-Venable "Kelly" R., PharmD, BCPS, FAPhA, FCCP
Professor and Director, PGY1 Community-Based Pharmacy Residency Program
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Association of Immunization Managers (AIM)
HOWELL, Molly, MPH
Immunization Program Manager
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Association for Prevention Teaching and Research (APTR)
ZIMMERMAN, Richard, MD, MPH
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Association of State and Territorial Health Officials (ASTHO)
JUTHANI, Manisha, MD
Commissioner
Connecticut Department of Public Health
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Biotechnology Innovation Organization (BIO)
ARTHUR, Phyllis A., MBA
Senior Vice President, Infectious Diseases and Emerging Science Policy
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Council of State and Territorial Epidemiologists (CSTE)
HAHN, Christine, MD
State Epidemiologist
Division of Public Health
Idaho Department of Health and Welfare
Boise, ID

Canadian National Advisory Committee on Immunization (NACI)
TUNIS, Matthew, PhD
Executive Secretary, National Advisory Committee on Immunization (NACI)
Centre for Immunization Programs (CIP)
Public Health Agency of Canada, Government of Canada

Infectious Diseases Society of America (IDSA)
MUNOZ-RIVAS, Flor, MD, MSc
Chief and Medical Director
Transplant Infectious Diseases
Texas Children's Hospital
Houston TX

Infectious Diseases Society of America (IDSA) (alternate)
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International Society for Travel Medicine (ISTM)
BARNETT, Elizabeth D, MD
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National Association of County and City Health Officials (NACCHO)
SHLAY, Judith, MD, MSPH
Associate Director, Public Health Institute at Denver Health
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National Association of Pediatric Nurse Practitioners (NAPNAP)
BUCHANAN, Stacy Briana, DNP, RN, CPNP-PC
Assistant Professor-Clinical Track
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Emory University
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National Foundation for Infectious Diseases (NFID)
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Chief, Division of General Internal Medicine
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National Foundation for Infectious Diseases (NFID) (alternate)
DALTON, Marla, PE, CAE
Executive Director & CEO
Bethesda, MD

National Medical Association (NMA)
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Medical Director-Chief of Tuberculosis Services
Westchester County Department of Health
White Plains, New York

Pediatric Infectious Diseases Society (PIDS)
PAULSEN, Grant, MD
Associate Professor of Pediatrics
Pediatric Infectious Diseases
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Pediatric Infectious Diseases Society (PIDS) (alternate)
ROSS, Shannon A., MD, MSPH
Professor of Pediatrics
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School of Medicine
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Pharmaceutical Research and Manufacturers of America (PhRMA)
YBARRA, MICHAEL, MD, FACEP
Chief Medical Officer and Senior Vice President
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Society for Adolescent Health and Medicine (SAHM)
MIDDLEMAN, Amy B., MD, MSEd, MPH
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Society for Healthcare Epidemiology of America (SHEA)
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Society for Healthcare Epidemiology of America (SHEA) (alternate)
DREES, Marci, MD, MS
Chief Infection Prevention Officer & Hospital Epidemiologist
ChristianaCare
Wilmington, DE
Associate Professor of Medicine
Sidney Kimmel Medical College at Thomas Jefferson University
Philadelphia, PA

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