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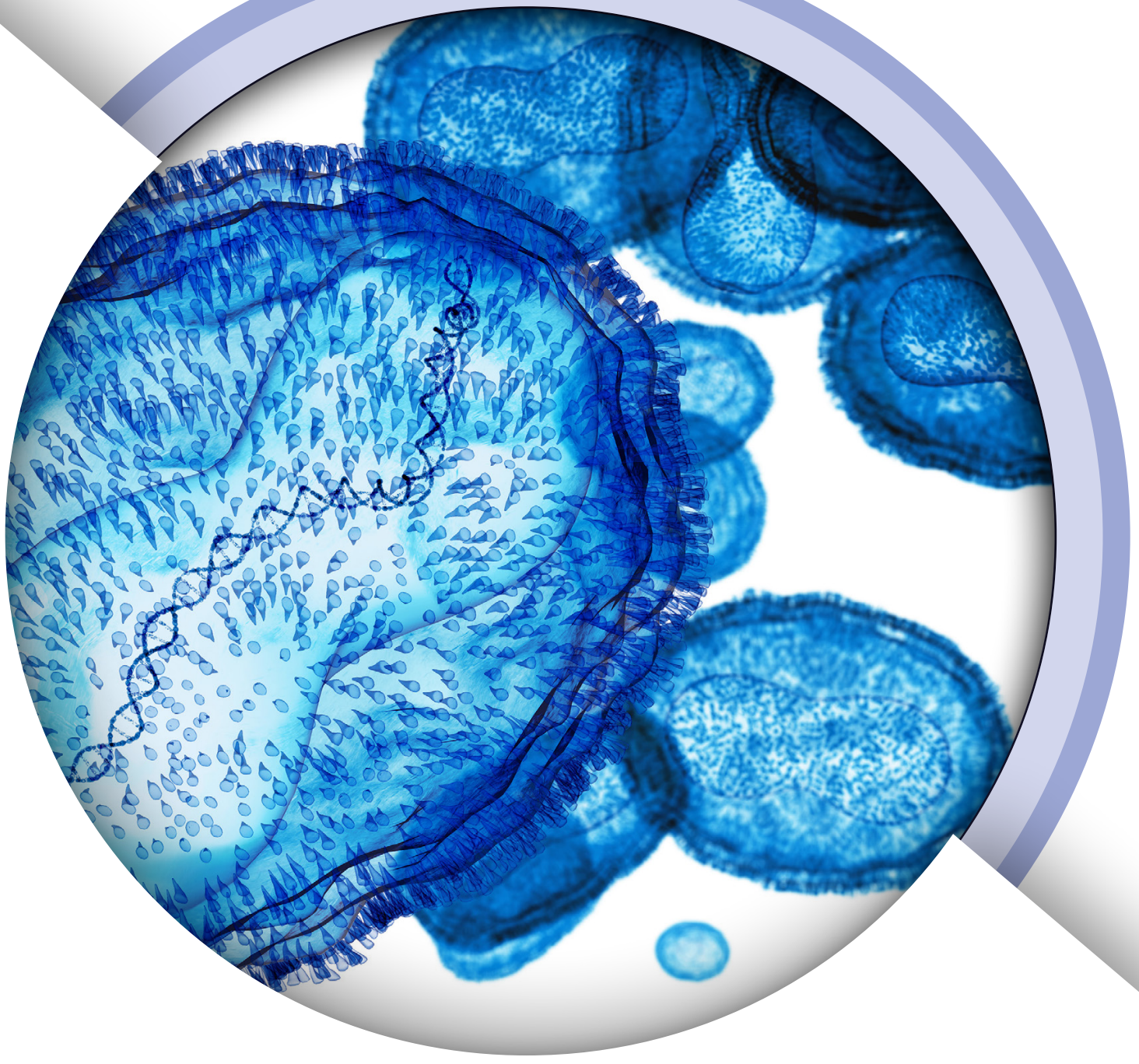

BIOTHERAPEUTICS QUARTERLY

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Diagnostic and Pharmaceutical News for You and Your Medical Practice

BIOTHERAPEUTICS QUARTERLY

Diagnostic and Pharmaceutical News for You and Your Medical Practice

2025/Fall/Volume 61

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Nuvaxovid (COVID-19 Vaccine, Adjuvanted) Injectable Suspension —formerly Novavax COVID-19 Vaccine
Date of Approval: May 16, 2025
Company: Novavax, Inc.
Treatment for: COVID-19
Nuvaxovid (COVID-19 Vaccine, Adjuvanted) is a protein-based, non-MRNA vaccine for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Tryptyr® (acoltremon) Ophthalmic Solution
Date of Approval: May 28, 2025
Company: Alcon Inc.
Treatment for: Dry Eye Disease
Tryptyr (acoltremon) is a first-in-class TRPM8 thermoreceptor agonist indicated for the treatment of the signs and symptoms of dry eye disease.

mNEXSPIKE (COVID-19 VACCINE, mRNA) Injection
Date of Approval: May 30, 2025
Company: Moderna, Inc.
Treatment for: COVID-19
mNEXSPIKE (COVID-19 Vaccine, mRNA) is a vaccine indicated for active immunization to prevent COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Enflonsia (clesrovimab-cfor) Injection
Date of Approval: June 9, 2025
Company: Merck
Treatment for: RSV Vaccination and Immunization
Enflonsia (clesrovimab-cfor) is a respiratory syncytial virus (RSV) F protein-directed fusion inhibitor indicated for passive immunization for the prevention of RSV lower respiratory tract disease in neonates and infants who are born during or entering their first RSV season.

Arynta™ (lisdexamfetamine dimesylate) Oral Solution
Date of Approval: June 16, 2025
Company: Azurity Pharmaceuticals, Inc.
Treatment for: ADHD, Binge Eating Disorder
Arynta (lisdexamfetamine dimesylate) is an oral solution formulation of the approved central nervous system (CNS) stimulant lisdexamfetamine for use in the treatment of ADHD and binge eating disorder.

Yeztugo® (lenacapavir) Tablets and Injection
Date of Approval: June 18, 2025
Company: Gilead Sciences, Inc.
Treatment for: Pre-Exposure Prophylaxis of HIV
Yeztugo (lenacapavir) is a human immunodeficiency virus type 1 (HIV-1) capsid inhibitor for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1.

National Institutes of Health
Turning Discovery Into Health

Monday, June 30, 2025

Breast cancer risk in younger women may be influenced by hormone therapy

NIH study could help to guide clinical recommendations for hormone therapy use among women under 55 years old.

Scientists at the National Institutes of Health (NIH) have found that two common types of hormone therapy may alter breast cancer risk in women before age 55. Researchers discovered that women treated with unopposed estrogen hormone therapy (E-HT) were less likely to develop the disease than those who did not use hormone therapy. They also found that women treated with estrogen plus progestin hormone therapy (EP-HT) were more likely to develop breast cancer than women who did not use hormone therapy. Together, these results could help to guide clinical recommendations for hormone therapy use among younger women.

The two hormone therapies analyzed in the study are often used to manage symptoms related to menopause or following hysterectomy (removal of uterus) or oophorectomy (removal of one or both ovaries). Unopposed estrogen therapy is recommended only for women who have had a hysterectomy because of its known association with uterine cancer risk.

“Hormone therapy can greatly improve the quality of life for women experiencing severe menopausal symptoms or those who have had surgeries that affect their hormone levels,” said lead author Katie O’Brien, Ph.D., of NIH’s National Institute of Environmental Health Sciences (NIEHS). “Our study provides greater understanding of the risks associated with different types of hormone therapy, which we hope will help patients and their doctors develop more informed treatment plans.”

The researchers conducted a large-scale analysis that included data from more than 459,000 women under 55 years old across North America, Europe, Asia, and Australia. Women who used E-HT had a 14% reduction in breast cancer incidence compared to those who never used hormone therapy. Notably, this protective effect was more pronounced in women who started E-HT at younger ages or who used it longer. In contrast, women using EP-HT experienced a 10% higher rate of breast cancer compared to non-users, with an 18%

higher rate seen among women using EP-HT for more than two years relative to those who never used the therapy.

According to the authors, this suggests that for EP-HT users, the cumulative risk of breast cancer before age 55 could be about 4.5%, compared with a 4.1% risk for women who never used hormone therapy and a 3.6% risk for those who used E-HT. Further, the association between EP-HT and breast cancer was particularly elevated among women who had not undergone hysterectomy or oophorectomy. That highlights the importance of considering gynecological surgery status when evaluating the risks of starting hormone therapy, the researchers noted.

“These findings underscore the need for personalized medical advice when considering hormone therapy,” said NIEHS scientist and senior author Dale Sandler, Ph.D. “Women and their health care providers should weigh the benefits of symptom relief against the potential risks associated with hormone therapy, especially EP-HT. For women with an intact uterus and ovaries, the increased risk of breast cancer with EP-HT should prompt careful deliberation.”

The authors noted that their study is consistent with previous large studies that documented similar associations between hormone therapy and breast cancer risk among older and postmenopausal women. This new study extends those findings to younger women, providing essential evidence to help guide decision-making for women as they go through menopause.

About the National Institute of Environmental Health Sciences (NIEHS): NIEHS supports research to understand the effects of the environment on human health and is part of the National Institutes of Health. For more information on NIEHS or environmental health topics, visit www.niehs.nih.gov or subscribe to a news list.

About the National Institutes of Health (NIH): NIH, the nation's medical research agency, includes 27 Institutes and Centers and is a component of the U.S. Department of Health and Human Services. NIH is the primary federal agency conducting and supporting basic, clinical, and translational medical research, and is investigating the causes, treatments, and cures for both common and rare diseases. For more information about NIH and its programs, visit www.nih.gov.

Source: ***https://www.nih.gov/news-events/news-releases/breast-cancer-risk-younger-women-may-be-influenced-hormone-therapy***

Use of JYNNEOS (Smallpox and Mpox Vaccine, Live, Nonreplicating) for Persons Aged ≥18 Years at Risk for Mpox During an Mpox Outbreak: Recommendations of the Advisory Committee on Immunization Practices — United States, 2023

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Abstract

Since the worldwide eradication of smallpox in 1980, orthopoxvirus vaccines had been used nearly exclusively by persons at risk for occupational exposure to orthopoxviruses, including *Monkeypox virus*, the virus that causes mpox. However, during recent years, the epidemiology of mpox has been changing in countries where the animal reservoirs are believed to live and where endemic transmission has been known to occur for decades. CDC issues outbreak-specific vaccination recommendations based on the epidemiology at the time specific cases or clusters are identified; however, because of the increased risk for U.S. mpox outbreaks, the Advisory Committee on Immunization Practices (ACIP) reviewed results from a previously performed modified Grading of Recommendations Assessment, Development, and Evaluation of the 2-dose JYNNEOS (smallpox and mpox vaccine, live, nonreplicating) vaccination series and an Evidence to Recommendations (EtR) framework addressing multiple domains (e.g., benefits, harms, and target population values and preferences). Based on this assessment, ACIP recommended the use of JYNNEOS (a live, replication-deficient vaccinia virus vaccine) for persons aged ≥18 years at risk for mpox during an mpox outbreak (irrespective of clade). Because the cause of future mpox outbreaks and the populations affected by these outbreaks remain uncertain, public health authorities will continue to issue outbreak-specific vaccination guidance when outbreaks occur. A clade IIb mpox outbreak that began in 2022 continued to cause substantial morbidity and mortality >1 year later. Although CDC had issued outbreak-specific vaccination guidance, it was anticipated that the outbreak would be protracted. For this reason, ACIP reviewed a second EtR framework about outbreaks and in 2023 recommended JYNNEOS for persons aged ≥18 years at risk for acquiring mpox during the multinational clade IIb outbreak. As of 2025, cases continue to occur; however, the future need for the recommendation will be reassessed as the outbreak evolves. Mpox vaccination is not routinely recommended for health care personnel during mpox outbreaks, including during the ongoing clade IIb outbreak.

[*] These authors contributed equally to this report.

Introduction

Monkeypox virus and Mpox Disease

Mpox is a zoonotic infection caused by *Monkeypox virus* (MPXV), a double-stranded DNA virus in the *Orthopoxvirus* genus. The disease is endemic in certain West and Central African countries, particularly in remote and forested areas, where the (as yet undetermined) animal reservoirs are believed to live. Infection is spread from person-to-person via direct contact with infectious lesions (including during sex), respiratory secretions, and fomites; infection can result in deep-seated, well-circumscribed, and often painful lesions that can involve various parts of the body including palms and soles. In endemic countries, mpox can spread from infected animals to humans. The first human mpox case was identified in the Democratic Republic of the Congo in 1970 (*1*) and was initially confused with smallpox, a disease also caused by an orthopoxvirus (*Variola virus*), but that was globally eradicated by 1980 (*2*). Two clades (subtypes) of mpox are recognized: clade I (endemic in the Central African Republic, the Democratic Republic of the Congo, Gabon, the Republic of the Congo, and part of Cameroon), and clade II (endemic in Côte d'Ivoire, Liberia, Nigeria, Sierra Leone, and part of Cameroon). Each clade has been further categorized into subclades because of mutations or deletions in the genome (*3*,*4*).

U.S. Mpox Cases Before and During 2022

During 2003, the first mpox outbreak outside of Africa occurred in the United States. The outbreak was caused by clade IIa[†] MPXV and resulted in 47 human cases in six midwestern states, all of which were associated with pet prairie dogs that had previously been housed with small mammals imported from West Africa.[§] Outbreaks associated with exposure to MPXV-infected animals have not reoccurred in the United States; however, other types of mpox outbreaks have occurred. Twice during 2021, unrelated clade IIb cases were recognized

[†] Subclade designations were made after the global clade IIb outbreak in 2022. When the newer sequences were identified as clade IIb, the previous ones were retrospectively designated clade IIa.

[§] Past U.S. Cases and Outbreaks | Mpox | CDC

among travelers from a country with endemic MPXV (*5*,*6*). No secondary cases occurred, but close contacts were monitored for 21 days and postexposure vaccinations considered. In May 2022, a global outbreak caused by clade IIb MPXV began, disproportionately affecting certain gay, bisexual, and other men who have sex with men (MSM) (*7*). Vaccinations were recommended for pre- and postexposure prophylaxis but unlike other mpox outbreaks in the United States, this outbreak has had a protracted course; to date, there have been approximately 35,000 U.S. cases,[¶] and long-term sequelae and deaths have been reported (*8*,*9*).

Coincident with U.S. outbreaks, mpox epidemiology has been changing in countries where the virus is endemic. Cases are 1) no longer restricted to remote and isolated regions, 2) occurring in higher numbers than in previous years, and 3) occurring in certain countries that have not reported a single human MPXV infection in decades (*10*). Reasons for the changes have been hypothesized to include deforestation, demographic changes, population movement, and waning protection after cessation of routine smallpox vaccination (*1*). These epidemiologic patterns have increased the risk for future mpox outbreaks, including in the United States.

Currently Licensed Orthopoxvirus Vaccines and Previous Vaccination Recommendations

Two orthopoxvirus vaccines are currently licensed in the United States. ACAM2000[**] is a live, replication-competent vaccinia virus vaccine licensed in 2007; JYNNEOS (smallpox and mpox vaccine, live, nonreplicating),[††] is a live, replication-deficient vaccinia virus vaccine licensed in 2019. In 2022, ACIP had recommended JYNNEOS, as an alternative to ACAM2000, for persons aged ≥18 years at risk for occupational exposure to orthopoxviruses (*11*). The recommendations were not limited to MPXV and were developed before the 2022 clade IIb outbreak, when U.S. cases were sporadic and fewer persons were at risk for MPXV exposure. A modified Grading of Recommendations Assessment, Development, and Evaluation (GRADE) that had been performed at that time compared JYNNEOS (the more recently licensed vaccine) to ACAM2000 (a derivative of the vaccine used to eradicate smallpox). There were no ACIP recommendations about mpox outbreaks; however, CDC issued interim vaccination recommendations at the time a specific case or cluster of cases was identified. A single U.S. case was considered an outbreak because of the rarity of these occurrences and the substantial resources needed to investigate and offer vaccinations (*5*); however, outbreaks were typically short in duration, so vaccination recommendations were also typically short term. JYNNEOS was available for the first time in the United States during the 2022 outbreak and has a more favorable safety profile and fewer contraindications than does ACAM2000 (*11*); for this reason, JYNNEOS has been the vaccine used nearly exclusively during the 2022 outbreak.

Consideration for JYNNEOS Use During Mpox Outbreaks

Because of increased risk for mpox outbreaks in the United States, ACIP began considering data about the use of JYNNEOS for persons aged ≥18 years at risk for mpox during future mpox outbreaks. The populations at risk differ depending on the epidemiology of a specific outbreak; therefore, public health authorities will continue to issue outbreak-specific guidance, including the populations for whom vaccinations are recommended. However, unlike other U.S. mpox outbreaks, the specific clade IIb outbreak that began in 2022 had continued to cause substantial morbidity and mortality more than 1 year after CDC had recommended JYNNEOS; in addition, only one in four persons recommended to receive the vaccine had received both JYNNEOS doses.[§§] Anticipating a more protracted outbreak than has occurred during previous U.S. outbreaks, ACIP also considered an outbreak-specific recommendation about use of JYNNEOS for persons aged ≥18 years at risk during that specific outbreak.

Methods

ACIP Mpox Work Group

The ACIP Mpox Work Group was constituted to review available evidence (e.g., vaccine effectiveness, safety, and mpox epidemiology); it comprised experts in diverse disciplines, including laboratory, public health, regulatory affairs, preparedness, and various clinical topics (e.g., immunology, vaccine safety, vaccination strategy, infection control, worker safety, occupational health, HIV and other sexually transmitted infections, mpox, obstetrics and gynecology, and pediatrics). Federal partners represented multiple U.S. agencies. During September 30, 2022–October 25, 2023, the work group held 30 weekly or biweekly teleconferences to review the scientific evidence.

Recommendation Considerations

The work group reviewed the 2022 GRADE assessment findings and considered domains within the Evidence to Recommendations (EtR) framework (a process for transparently describing information considered in moving recommendations from evidence to decisions).[¶¶] Data were considered for use of JYNNEOS for persons aged ≥18 years 1) at risk

[¶] U.S. Case Trends: Clade II Mpox | Mpox | CDC
[**] Package Insert - ACAM2000 | FDA
[††] Package Insert - JYNNEOS (Refrigerator) | FDA
[§§] JYNNEOS Vaccine Coverage by Jurisdiction | Mpox | Poxvirus | CDC
[¶¶] Evidence-Based Recommendations for ACIP | ACIP | CDC

for acquiring mpox during any mpox outbreak and 2) at risk during the ongoing global clade IIb outbreak. Evaluated domains included benefits and harms, target population values and preferences, and issues of resource use, acceptability to stakeholders, feasibility of implementation, and anticipated impact on vaccine access. In preparation for a vote, ACIP considered these data and newly collected information from the 2022 outbreak. ACIP also reviewed language about the use of JYNNEOS for persons at occupational risk for exposure to MPXV during an mpox outbreak and considerations for future mpox outbreaks.

Summary of Findings and Rationale for Recommendations

No clinical disease endpoints are available comparing the effectiveness of vaccines against mpox, but prelicensure data involved geometric mean titers and seroconversion data. The 2022 GRADE review*** evaluated these data from three randomized controlled studies and 15 observational studies. After considering the published studies in GRADE, the work group estimated with moderate certainty that the 2-dose JYNNEOS primary series provides a small increase in disease prevention against MPXV compared with that provided by ACAM2000.††† The work group also had low certainty that fewer serious adverse events occur after the JYNNEOS primary series compared with those after the ACAM2000 primary series and that fewer events of myopericarditis occur after the JYNNEOS primary series than after the ACAM2000 primary vaccination. Based on the sum total of their assessment, including the EtR frameworks,§§§,¶¶¶ ACIP voted unanimously in favor of two recommendations.

Recommendations

On February 22, 2023, ACIP voted to recommend the 2-dose JYNNEOS vaccination series**** for persons aged ≥18 years who are considered to be at risk for mpox during an mpox outbreak.†††† On October 25, 2023, ACIP voted to recommend the 2-dose JYNNEOS vaccination series for persons aged ≥18 years who are at risk for acquiring mpox during the ongoing clade IIb outbreak that began in 2022. For the latter vote, persons at risk included 1) MSM§§§§ who, during the past 6 months, have had or anticipate experiencing at least one of the following: a new diagnosis of one or more sexually transmitted infections, more than one sex partner, sex at a commercial sex venue, or sex in association with a large public event in a geographic area where mpox transmission is occurring; 2) sexual partners of persons who have any of these risk factors; and 3) persons who anticipate experiencing any of these risk factors.¶¶¶¶

Clinical Considerations

Clinical considerations have been communicated on the CDC website since the start of the multinational clade IIb outbreak in 2022. These considerations were also reviewed by ACIP and included in this report.

Vaccine Effectiveness

Like other licensed orthopoxvirus vaccines, JYNNEOS contains vaccinia virus, a less virulent orthopoxvirus than either MPXV or variola virus (the causative agent of smallpox). Owing to a high level of protein identity among orthopoxviruses, vaccinia virus vaccines elicit antibodies that provide cross-protection against other orthopoxviruses, including MPXV; this cross-protection was the foundation for the successful global smallpox eradication campaign (*2*). Vaccinia virus and MPXV have a high level (>90%) of nucleotide identity (*12*), and real-world data from the clade IIb outbreak demonstrate vaccine effectiveness (VE) of the 2-dose series ranging from 66% to 89% (*13*–*16*). VE is unlikely to differ across mpox clades because JYNNEOS is a whole-virus vaccine, which elicits an immune response to many vaccinia viral proteins (not to just a subset of viral proteins, as might occur with subunit vaccines). VE might depend on the route of exposure (e.g., mucosal versus other), frequency of exposure, and level of immunocompromise of affected persons. Infections despite vaccination could occur; however, JYNNEOS prevented or decreased the severity of many infections during the ongoing clade IIb outbreak and is expected to be similarly effective during future outbreaks (irrespective of clade).

*** Grading of Recommendations, Assessment, Development, and Evaluation (GRADE): Use of JYNNEOS (orthopoxvirus) vaccine primary series for research, clinical laboratory, response team, and healthcare personnel (Policy Questions 1 and 2) | ACIP | CDC

††† Although this reflects the findings of the analysis, basic science data which are not included in GRADE supports that ACAM2000 would likely be more effective in prevention of mpox (or smallpox) than JYNNEOS.

§§§ Evidence to Recommendations 1

¶¶¶ Evidence to Recommendations 2

**** Dose 2 should be administered 28 days after dose 1.

†††† Public health authorities will determine whether an mpox outbreak is occurring; a single case might be considered an mpox outbreak at the discretion of public health authorities. Other circumstances in which a public health response might be indicated include ongoing risk for introduction of mpox into a community because of disease activity in another geographic area.

§§§§ Wording previously published (Recommended Adult Immunization Schedule for ages 19 years or older-2024 U.S. | CDC) has been amended to comply with Executive Order 14168. Defending Women from Gender Ideology Extremism and Restoring Biological Truth to the Federal Government – The White House

¶¶¶¶ Because there might be stigma associated with affirming risk factors, clinicians should consider vaccinating persons who request vaccination (i.e., self-attest to vaccine eligibility) without requiring specification of the criterion that deems eligibility.

Population Considerations

Future mpox outbreaks might differ epidemiologically by populations affected, numbers of cases, and types of activities for which vaccination is indicated. Because of this inherent variability, public health authorities will issue guidance specific to each outbreak. Vaccination might be advised for preexposure or postexposure protection, for a few persons or many persons, and for persons with only certain exposures or risk factors (e.g., medical, behavioral, or occupational). The specific vaccination recommendations will depend on the epidemiology of the outbreak. For the ongoing clade IIb outbreak, the epidemiology is well understood, and for this reason, ACIP was able to specify persons at risk. However, as epidemiology for this outbreak evolves, public health authorities will continue to issue additional guidance. As of 2025, cases, including deaths, continue to occur. To avoid potential stigma associated with affirming risk factors during the ongoing outbreak, clinicians should consider vaccinating persons who request vaccination (i.e., self-attest to vaccine eligibility) without requiring specification of eligibility criteria. Clinicians and public health authorities should be aware that sexual partners of MSM with a new diagnosis of one or more sexually transmitted infections, more than one sex partner, sex at a commercial sex venue, or sex in association with a large public event in a geographic area where mpox transmission is occurring are recommended to be vaccinated. Such persons might include women. However, MSM without risk factors (e.g., those in a monogamous relationship) are not among the population recommended to be vaccinated.

JYNNEOS is contraindicated in persons with a history of a severe allergic reaction (e.g., anaphylaxis) after a previous JYNNEOS dose or to any component of the vaccine (*17*). Similar to other vaccines, JYNNEOS might be less effective in severely immunocompromised persons, but it has been shown to be safe and immunogenic in persons with well-controlled HIV, atopic dermatitis, eczema, or other exfoliative skin conditions (*18*,*19*). No human data regarding safety of JYNNEOS administration during pregnancy or breastfeeding are available; however, JYNNEOS is a nonreplicating vaccine, and data from animal models, including rats and rabbits, have shown no evidence of harm to a developing fetus (Table 1). CDC does not recommend vaccination for any persons who have recovered from mpox or any other orthopoxvirus infection because recovery from MPXV infection (regardless of clade) likely confers protection from either clade of mpox. Persons who have recovered from mpox can experience reinfection; however, CDC surveillance data suggest this is very rare. Surveillance data through June 2025 suggest that reinfections have occurred in <0.001% of U.S. persons who previously had mpox. In these rare instances, the second infection was generally milder than the initial infection.*****

Health Care Personnel and Laboratorians

For decades, ACIP has recommended that some U.S. persons at occupational risk for exposure to orthopoxviruses receive preexposure vaccination (*20*). Most of these persons have

***** Interim Clinical Considerations for Use of Vaccine for Mpox Prevention in the United States | Mpox | CDC

TABLE 1. Clinical considerations for use of JYNNEOS* in special populations during an mpox outbreak — United States, 2025

Population	Clinical considerations
Persons with atopic dermatitis, eczema, or other exfoliative skin conditions	• No precautions needed. • Studies described in the package insert have indicated JYNNEOS is safe and effective in these circumstances.
Persons with immunocompromising conditions†	• No precautions needed. • JYNNEOS is safe in these persons because although it is a live virus vaccine, the virus is nonreplicating; it therefore acts like a nonlive vaccine but similar to other vaccines, JYNNEOS might be less effective in persons with severe immunocompromise • Affected persons should be counseled so that preventing exposures remains a high priority regardless of vaccination status.
Pregnant women	• Available data on JYNNEOS administered during pregnancy are insufficient to determine vaccine-associated risk in pregnancy; however, the package insert describes data involving animal models (e.g., rat and rabbit models) that have shown no evidence of harm to the developing fetus.
Breastfeeding women	• The safety and efficacy of JYNNEOS during breastfeeding have not been evaluated. • No studies have evaluated whether JYNNEOS affects milk production or safety to breastfed infants. However, because JYNNEOS is replication-deficient, it likely does not present a risk of transmission to breastfed infants and can be administered to the mother if vaccination is indicated based on risks.
Persons aged <18 years§	• Data currently do not indicate any safety signals. • Vaccination is permitted for children aged <18 years who are at risk for mpox • VIGIV (purified immunoglobulin from persons vaccinated with ACAM2000) should be considered in lieu of JYNNEOS if postexposure vaccination is indicated for infants aged <6 months. • ACIP is continuing to assess available data and will make changes to recommendations as needed.

Abbreviations: ACIP = Advisory Committee on Immunization Practices; VIGIV = vaccinia immune globulin intravenous.
* Package Insert - JYNNEOS (Refrigerator) | FDA
† Altered Immunocompetence | Vaccines & Immunizations | CDC
§ CDC recommendations for use of JYNNEOS during mpox outbreaks for persons aged <18 years is outlined at Interim Clinical Considerations for Use of Vaccine for Mpox Prevention in the United States | Mpox | CDC

been research laboratory personnel who work with orthopoxviruses; however, some clinical laboratory personnel who work in Laboratory Response Network laboratories (a network of domestic and international laboratories established to respond to biologic and chemical threats and emerging infectious diseases[†††††]) were included for smallpox preparedness, and since the early 2000s, when the concern for biothreats (e.g., due to anthrax) was at its peak, some jurisdictions began maintaining limited cadres of vaccinated health care personnel as well.[§§§§§]

At the time the 2022 ACIP recommendations for JYNNEOS were being developed, mpox cases rarely occurred in the United States, and data regarding transmission in health care settings were primarily from countries with endemic MPXV, where personal protective equipment (PPE) is inconsistently available. A single occupationally acquired case had been reported in a health care provider in the United Kingdom; however, this case was associated with inadequate PPE (*21*).

With the onset of the 2022 outbreak, transmission of mpox in U.S. health care settings was evaluated. Few occupationally acquired cases occurred among health care personnel (fewer than 25 cases, accounting for <0.08% of all U.S. cases), and no cases among laboratorians. Because infection prevention and control practices were found to be effective in preventing transmission, CDC has not routinely recommended vaccination of clinical laboratory personnel or health care personnel who care for patients during the ongoing outbreak. ACIP agreed that the 2022 recommendations regarding use of JYNNEOS for persons at occupational risk for orthopoxvirus infections apply for persons at risk whether or not an active mpox outbreak is occurring. However, for health care personnel and clinical laboratorians at occupational risk exclusively during an mpox outbreak, the committee concurred that data support JYNNEOS not being routinely recommended. Vaccination of a small number of these persons could be considered on a case-by-case basis if site- and activity-specific biosafety risk assessments during an outbreak suggest that vaccination is warranted; however, these are expected to be rare (Table 2).

Vaccination Schedule and Duration of Protection

JYNNEOS is recommended as a 2-dose subcutaneous vaccination series, with the second dose administered 28 days after the first. Similar to other multidose vaccines, the second dose could be administered up to 4 days[¶¶¶¶¶] before the recommended 28-day interval (i.e., 24–27 days after the first dose). If the second dose is not administered during the recommended interval, it should be administered as soon as possible; however, there is no need to restart the series if the interval between doses is prolonged (e.g., >1 year). The duration of protection after the 2-dose series is still being studied, but recently published data indicate protection might be >5 years (*22*). At this time, persons who have been vaccinated with the 2-dose JYNNEOS series do not require an additional dose, nor do they need to be revaccinated during a future outbreak. Although the 2-dose JYNNEOS series may not be as effective in severely immunocompromised persons, it is not known whether additional doses will improve effectiveness; in addition, some data have suggested that more than 2 doses may cause increased reactogenicity (*22*) and for this reason, additional doses are not recommended. As more data become available, CDC might provide additional guidance.

Timing of Administration of Other Vaccines and of Immunoglobulin Products

JYNNEOS is a live virus vaccine. However, because the vaccinia virus component is nonreplicating, it is managed in nearly every situation as if it were a nonlive vaccine. Unlike other live virus vaccines, no minimum interval is required between receipt of JYNNEOS and other vaccines; however, at this time, theoretical considerations regarding temporal proximity of administration of JYNNEOS and COVID-19 vaccines, and JYNNEOS and

[†††††] About the Laboratory Response Network | The Laboratory Response Network Partners in Preparedness | CDC

[§§§§§] CDC interim guidance for revaccination of eligible persons who participated in the US civilian smallpox preparedness and response program

[¶¶¶¶¶] Timing and Spacing of Immunobiologics | Vaccines & Immunizations | CDC

TABLE 2. Advisory Committee on Immunization Practices preexposure vaccine recommendations for persons at occupational risk for exposure to orthopoxviruses only during an mpox outbreak, including the clade IIb outbreak that began in 2022 — United States, 2025

Population	Recommendation on a case-by-case basis
Health care personnel who care for patients infected with mpox	• Recommended infection prevention and control practices are effective in preventing transmission. • ACIP recommends use of JYNNEOS (as an alternative to ACAM2000) based on shared clinical decision-making, i.e., vaccination can be offered based on site- and activity-specific biosafety risk assessments (e.g., inadequate availability of personal protective equipment during humanitarian missions for mpox in endemic countries).
Clinical laboratory personnel who handle specimens* that during an mpox outbreak, might have a higher possibility of containing replication-competent *Monkeypox virus*	• ACIP recommends use of JYNNEOS (as an alternative to ACAM2000) based on shared clinical decision-making. • Recommended infection prevention and control practices are effective in preventing transmission.

Abbreviation: ACIP = Advisory Committee on Immunization Practices.
* Specimens include lesion material, throat swabs, oral swabs, and rectal swabs. Science Brief: Detection and Transmission of Mpox (Formerly Monkeypox) Virus During the 2022 Clade IIb Outbreak | CDC Archive

TABLE 3. Clinical considerations for temporal administration of other vaccines and of immunoglobulin products in relation to JYNNEOS vaccine administration*

Vaccine or immunoglobulin	Guidance
Vaccine	
Live, replicating virus vaccines (e.g., yellow fever, measles, and varicella virus vaccines)	• No required interval between JYNNEOS vaccine and live, replicating virus vaccines, because unlike other live virus vaccines, JYNNEOS does not replicate to induce an immune response. • For the purposes of planning administration of other vaccines, JYNNEOS may be considered similar to nonlive virus vaccines.
COVID-19 vaccines	• No required minimum interval between receiving any COVID-19 vaccine and JYNNEOS vaccine (e.g., for mpox prevention), regardless of which vaccine is administered first. • Persons (particularly adolescent and young adult males) who are recommended to receive both vaccines might consider waiting 4 weeks between vaccines, because of the observed risk for myocarditis and pericarditis after receipt of ACAM2000 orthopoxvirus vaccine and COVID-19 vaccines and the hypothetical risk for myocarditis and pericarditis after JYNNEOS vaccine. • If a patient's risk for mpox or severe disease due to COVID-19 is increased, administration of JYNNEOS and COVID-19 vaccines should not be delayed. • This guidance might be revised if the concern for myocarditis and pericarditis abates.
Immunoglobulin products	
Antibody containing preparations (e.g., blood products, IVIG) except VIGIV	• No minimum interval between most immune globulins and JYNNEOS vaccine; the former are not associated with mpox prevention but might be administered because of other medical problems. • Antibodies to measles and varicella are high in immune globulin products; administration of these in close temporal proximity to the measles and varicella live virus vaccines can prevent the vaccine virus from entering cells and being effective; however, unlike for measles and varicella, antibodies to orthopoxviruses including *Monkeypox virus,* are believed to be low in most antibody containing products, including during the ongoing outbreak.
VIGIV (purified immunoglobulin from persons vaccinated with ACAM2000)†,§	• VIGIV is the only known antibody-containing preparation that could potentially interfere with JYNNEOS vaccine. This is because antibody in VIGIV might interfere with entry of the vaccine virus into cells, As a live virus vaccine, entry into cells is essential to effectiveness. • Because VIGIV could interfere with immune response to JYNNEOS necessitating an additional JYNNEOS dose at a later time, VIGIV should not be administered in temporal proximity to JYNNEOS, and JYNNEOS should be delayed if VIGIV was recently administered. The duration for which it should be delayed is currently unknown. CDC can be consulted for case-specific guidance. • During outbreaks, it is acceptable for VIGIV and JYNNEOS to have been administered in temporal proximity (e.g., if JYNNEOS vaccine was administered to a patient as postexposure prophylaxis but the patient went on to develop a severe manifestation of mpox for which VIGIV is recommended). • Public health authorities oversee access to VIGIV and can provide additional guidance if indicated.

Abbreviations: IVIG = intravenous immune globulin; VIGIV = vaccinia immune globulin intravenous.

* JYNNEOS is a live virus vaccine but because it is replication-deficient, guidance differs from that for other live virus vaccines (e.g., yellow fever, measles, and varicella vaccines)

† VIGIV is maintained by the U.S. Department of Health and Human Services' Center for the Strategic National Stockpile and only available under certain circumstances and via consultation with CDC's on-call poxvirus subject matter experts (CDC Emergency Operations Center: 404-639-3311). Indications for VIGIV are outlined in the Investigational New Drug protocol. Expanded Access IND Protocol: Use of Vaccinia Immune Globulin Intravenous (VIGIV, CNJ-016) for Treatment of Human Orthopoxvirus Infection in Adults and Children | CDC

§ Interim Clinical Treatment Considerations for Severe Manifestations of Mpox — United States, February 2023 | MMWR | CDC

vaccinia immune globulin intravenous (VIGIV), are recognized. Although JYNNEOS has not been reported to be associated with myopericarditis, ACAM2000 (a live, replication-competent smallpox and mpox vaccine) is known to be associated with myocarditis.****** Because some COVID-19 vaccines have also been associated with myocarditis,†††††† persons (particularly adolescent and young adult males) who are recommended to receive COVID-19 and JYNNEOS vaccines might consider waiting 4 weeks between vaccines out of an abundance of caution. If there is a need for VIGIV to be administered in close temporal proximity to JYNNEOS vaccination, CDC should be consulted for case-specific guidance§§§§§§ (Table 3).

****** ACAM2000 (Smallpox Vaccine) Questions and Answers | FDA

†††††† CDC. Clinical considerations: myocarditis after COVID-19 vaccines

§§§§§§ VIGIV is maintained by the U.S. Department of Health and Human Services' Center for the Strategic National Stockpile and only available under certain circumstances and via consultation with CDC's on-call poxvirus subject matter experts (CDC Emergency Operations Center: 404-639-3311). Investigational New Drug protocol | CDC

Strategies for Consideration During Outbreaks

During the 2022 U.S. outbreak of clade IIb MPXV, initial demand for vaccination was high, and supplies were limited. To address this shortage, intradermal administration of JYNNEOS was advised as a dose-sparing strategy; intradermal administration required one fifth of the subcutaneous dose and assessments indicated VE comparable to JYNNEOS administered subcutaneously (*14*). Although the intradermal vaccination technique is similar to that used for application of tuberculin skin tests, not all providers were comfortable with this technique. In addition, intradermal JYNNEOS vaccination was associated with a visible nodule or hyperpigmentation at the site of administration, which was stigmatizing for some persons.

Individual jurisdictions implemented measures including mass vaccination sites and other efforts to make vaccines available to communities with either a high mpox incidence

Summary

What is already known about this topic?

CDC provides interim vaccination guidance for self-limited mpox outbreaks; however, a clade IIb outbreak that began in 2022 has had a protracted course, and the risk for U.S. mpox outbreaks has increased.

What is added by this report?

In 2023, the Advisory Committee on Immunization Practices (ACIP) recommended JYNNEOS (smallpox and mpox vaccine, live, nonreplicating) for persons aged ≥18 years who are at risk for mpox during any mpox outbreak and who are at risk for mpox during the ongoing clade IIb outbreak.

What are the implications for public health practice?

ACIP recommends JYNNEOS during outbreaks to improve vaccination coverage and limit the scope of outbreaks. As of 2025, the clade IIb outbreak has continued; the need for vaccinating persons at risk will be reassessed as the outbreak evolves.

or limited access to health care. Some jurisdictions prioritized first doses and delayed administration of the second dose until adequate supplies were available (*23*).

At this time, there is an abundance of JYNNEOS vaccine supply; therefore, vaccine doses should be administered subcutaneously. However, if a shortage occurs, JYNNEOS can be administered intradermally. Regardless of vaccine supply and strategy, decisions about vaccine administration during an outbreak should ensure fair and prudent distribution of doses. Vaccinated persons should be advised that peak antibody response is achieved 2 weeks after receipt of the second dose, but that even a single dose provides some protection (*13–16*). Vaccinations should be provided along with counseling that breakthrough infections could still occur and the importance of other prevention strategies.

Reporting Adverse Events

Adverse events following vaccination can be reported to the Vaccine Adverse Event Reporting System (VAERS). Reporting is encouraged for any clinically significant adverse event, even if it is unclear whether the vaccine caused the event. Information on how to submit a report to VAERS is available at Vaccine Adverse Event Reporting System (VAERS) or by telephone at 1-800-822-7967.

Future Research

Because the proportion of immunocompromised persons has increased in the United States (*24*), information about VE of JYNNEOS among severely immunocompromised persons (e.g., persons with advanced HIV) will be critical to guiding future recommendations. In addition, if more mpox outbreaks occur in the United States, it will be important to know whether there is durable protection after JYNNEOS vaccination or after resolved infection, and if not, when a booster dose might be needed. Because JYNNEOS behaves like a nonlive virus vaccine and is recommended as a 2-dose series, its role as postexposure prophylaxis is poorly understood; studies are ongoing to understand VE of JYNNEOS postexposure vaccination.

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PREVENTING CHRONIC DISEASE
PUBLIC HEALTH RESEARCH, PRACTICE, AND POLICY
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ESSAY

Eliminating Cervical Cancer: the Impact of Screening and Human Papilloma Virus Vaccination

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PEER REVIEWED

Cervical cancer is a vaccine-preventable disease that is a significant public health concern because of its considerable impact on disease and death among women (1). The National Cancer Institute estimated that as of 2021 approximately 295,000 women in the US had been diagnosed with this cancer, with 7.6 per 100,000 women newly diagnosed per year (2). Cervical cancer is unique among cancers because of its well-defined pathogenesis (3). Approximately 99.7% of these cancers are due to untreated or chronic infection with human papillomavirus (HPV), a sexually transmitted virus that directly infects the squamous cell epithelium on mucosal surfaces (3). The 5-year relative survival rate of cervical cancer is 67.4%, but when diagnosed at an early stage, the survival rate rises significantly, to 91% (2). Early vaccination against HPV has proven successful in preventing this cancer, with early vaccination resulting in a 40% reduction in cervical precancers and more than an 80% reduction in the overall risk of developing the disease (4,5). Prevention and early detection are critical to improving survival (6).

The elimination of cervical cancer is primarily dependent on increasing HPV vaccination rates, implementing cervical cancer screening programs, and increasing education. However, several barriers stand in the way, including health care access, insurance status, vaccine hesitancy, limited public education, stigma, and cost.

HPV Vaccination

Unlike many other cancers, HPV infections and the risk of cervical cancer can be eliminated (5). As of 2019, the US Food and Drug Administration had approved 3 HPV vaccines: Gardasil-9 (9-valent/9vHPV), Gardasil (quadrivalent/4vHPV), and Cervarix (bivalent/2vHPV), to prevent HPV infections (7). While all 3 vaccines are effective against HPV types 16 and 18, the most prevalent strains in cancer development, the US administers only Gardasil-9 because of its broad-spectrum protection against multiple HPV types (7–9). Still, all 3 vaccines have been proven highly effective in preventing cervical cancer by preventing infection with HPV (10).

The Centers for Disease Control and Prevention (CDC) recommends that people receive an HPV vaccination between ages 9 through 26 years, with earlier vaccination preferred as it prevents future HPV infections (5). As of 2022, the overall vaccination rate (at least 1 HPV dose) for US adolescents aged 13 to 17 years was 76% (11). However, rates vary among states, with several reporting that less than 70% of adolescents have had at least 1 HPV vaccine and less than 55% were up to date with HPV vaccination (11).

Barriers to HPV Vaccination and Cervical Cancer Screening

Given the existence of an established vaccine for preventing HPV infection and thereby reducing cervical cancer risk, incidence of that cancer should be significantly reduced. However, barriers such as limited health care access, insurance status, vaccine hesitancy, limited public education, stigma, and cost diminish the impact of the vaccine (12–14).

Cost and lack of insurance coverage have been consistently cited as major obstacles to HPV vaccination (15). Although increased vaccination rates have been linked with increased screening, studies show that only 68% of people in the US are aware of HPV, its relationship to certain cancers, and the availability of vaccines to prevent infection (16,17). This knowledge gap is greater among African American and Hispanic populations than among their White counterparts, potentially contributing to the racial disparities observed in vaccination rates (7). A 2021 study found that although 48% of White women received the HPV vaccine, only 38% of African American women and 30% of Hispanic women

received it (17). A large proportion of Hispanic women reported not having undergone cervical cancer screening because they did not know that they needed it (18). Furthermore, women without health insurance reported 7 times more often that they could not receive screening because of lack of access compared with women with private health insurance (18). Many of these barriers were further compounded by the COVID-19 pandemic, which saw a decrease in HPV vaccine delivery and administration because of the shift to pandemic-related health priorities (19,20). The pandemic also affected the ability of children and adults to schedule routine visits, and a higher proportion of those who were unable to schedule visits were from racial and ethnic minority groups or were living below the poverty level (21). Also, vaccine hesitancy and refusal increased during the COVID-19 pandemic, which further limited the impact of the HPV vaccination (19,22). These disparities highlight the need for programs that provide information to minority and socioeconomically marginalized populations, alleviate the structural barriers that prevent patients from obtaining screening and vaccination, and ensure adherence to national vaccination and screening guidelines.

Preventive Measures for Reducing Cervical Cancer

While HPV vaccination plays a critical role in reducing the risk of cervical cancer, several other preventive measures are important. The World Health Organization (WHO) has established the Cervical Cancer Elimination Initiative, which outlines a plan for all countries to maintain an incidence rate less than 4 women per 100,000 by 2030 (23). The plan is based on a 90–70–90 target: 90% of girls fully vaccinated with the HPV vaccine by the age of 15, 70% of women screened with a high-performance test by the age of 35 years and again by the age of 45, and 90% of women with precancer treated and 90% with invasive cancer managed (23). WHO supports many primary prevention measures, such as sexual and reproductive health education, education about protective sex practices, and programs that promote healthy lifestyles in children and adolescents (23). The success of these measures hinges on understanding social, cultural, and societal barriers that can affect the success of HPV vaccination (23). WHO also supports secondary prevention measures related to the reduction of cervical cancer incidence and mortality, the identification and treatment of precancerous lesions (23).

The Papanicolaou (Pap) test, a cervical cytology test, samples and analyzes cells from the vagina and cervix to detect abnormalities (10). This test has become the standard in cervical cancer screening in developed countries and has led to a 70% decrease in incidence and mortality from this cancer (10). For high-risk women aged 30 years or older, WHO recommends HPV–DNA testing along with a Pap test (10). Application of these guidelines is most successful in areas with established health care infrastructure where patients can receive follow-up care. In areas with low health care resources and among rural populations, the benefit of routine Pap tests is limited due to low sensitivity and specificity (23). Instead, self-sampling, rapid HPV testing, and visual inspection of the cervix with acetic acid have been more successful, which is likely due to availability of HPV rapid testing self-test kits (23). If precancerous lesions are identified, treatment depends on their severity and can include various ablation methods or surgical excision (10).

Initiatives to Increase HPV Vaccination and Cervical Cancer Screening

Several countries have established programs in response to WHO's initiatives to help increase cervical cancer screening and HPV vaccination rates. For example, Australia has implemented an aggressive HPV vaccination program for children and adolescents that achieved an 80% full vaccination rate among girls aged 15 years or younger (24). In addition, 67% of women aged 45 to 49 years were screened, and 86% of precancerous lesions were treated under this program within 6 months of diagnosis (24). In India, mobile health education interventions among women from low socioeconomic backgrounds achieved a significant increase in knowledge about cervical cancer and HPV vaccination and a 5% increase in screening after the educational intervention (25).

In the US, initiatives such as Alabama's Operation Wipeout (26) and CDC's National Breast and Cervical Cancer Early Detection Program (NBCCEDP) (27) are providing HPV vaccination and cervical cancer screening to women in low-income regions of the US. Operation Wipeout is a partnership among Alabama's public, private, academic, and nonprofit sectors started by researchers at the University of Alabama at Birmingham. The initiative established goals that model the WHO's 90–70–90 targets and aims to increase the initiation of HPV vaccination (receipt of a single dose) to 90% among children aged 9 to 12 years and 85% among adolescents aged 13 to 17 years, to increase HPV vaccination dose completion (receipt of 3 doses) to 80% in both age groups, to increase compliance with screening guidelines to 90%, and to increase adherence to cervical cancer treatment and follow-up to 90% (26). NBCCEDP is a federally funded program that provides Pap tests, HPV tests, and pelvic examinations to women who are uninsured, underinsured, or living below the poverty line (27). In 2023, the NBCCEDP provided cancer screening and diagnostic services to approximately 129,000 women in the US (27). As a result of that program, 87 invasive cervical cancers and approximately 6,200 precancerous cervical lesions were detected (28).

While these initiatives show promise, outcomes still fall short of the targets set by WHO. Social, cultural, and societal norms affected these initiatives in cervical cancer. Black, Latina, and Chinese American women with cervical cancer reported feeling self-blame and experiencing both internalized and public stigmas related to their diagnosis, leading to isolating behaviors and negative health outcomes (29). Additionally, fear, embarrassment, and anxiety are often cited as major barriers to adherence to screening guidelines (15). Addressing these psychological barriers, in addition to socioeconomic challenges that prevent women from getting adequate care, is essential to improving screening rates and outcomes for women with cervical cancer.

Conclusion

The US has the resources necessary to provide widespread access to HPV vaccination and cervical cancer screening. However, disparities in health care access persist, especially among women in racial and ethnic minority communities and rural areas and among women of low socioeconomic status. Initiatives like NBCCEDP and Operation Wipeout can help address these disparities by providing free or low-cost screening and HPV vaccinations and by providing educational resources tailored to medically underserved communities (26,27). Culturally relevant educational materials can help reduce the stigma associated with cervical cancer screening. Telehealth can enhance health care accessibility by distributing educational resources and improving health care access among women in low-income and rural areas. Most importantly, initiatives, both domestically and internationally, have shown the impact of proper funding and management in increasing rates of HPV vaccination and screening. For the long-term success of these strategies, the US must continue to fund programs and advance policies that emphasize minority and disadvantaged populations to reach the goals established by WHO and eliminate cervical cancer.

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Mycoplasma pneumoniae Infections in Hospitalized Children — United States, 2018–2024

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Abstract

Mycoplasma pneumoniae is a common bacterial cause of respiratory infection and a leading cause of childhood community-acquired pneumonia (CAP). Increases in *M. pneumoniae* infection occur every 3–5 years. In the United States, *M. pneumoniae* prevalence decreased during and immediately after the COVID-19 pandemic. Information from 42 U.S. children's hospitals that provided information to the Pediatric Health Information System, a database of clinical and resource use information, was used to identify discharge diagnostic codes for 2018–2024 indicating *M. pneumoniae* infection. *M. pneumoniae*–associated CAP incidence among children aged ≤18 years was significantly higher in 2024 (12.5 per 1,000 hospitalizations) than during 2018–2023 (2.1). During the study period, an *M. pneumoniae* diagnostic code was listed in 11.5% of pediatric CAP hospitalizations, peaking at 53.8% in July 2024. Among pediatric *M. pneumoniae* CAP cases, the highest percentage occurred among children aged 6–12 years (42.6%), followed by children aged 2–5 years (25.7%) and 13–18 years (21.1%). The lowest occurred among those aged 12–23 months (6.4%) and 0–11 months (4.2%). *M. pneumoniae* infections in 2024 were not more severe than 2018–2023 infections, as assessed by length of hospitalization and percentage of patients admitted to an intensive care unit. The increase in *M. pneumoniae* infections in the United States in 2024 might be higher than previous periodic increases because the susceptible population was larger after sustained low incidence during and immediately after the COVID-19 pandemic. Health care providers should be aware of the periodicity of *M. pneumoniae* CAP and consider testing for this pathogen as a cause of respiratory illness among children of all ages.

Introduction

Mycoplasma pneumoniae is a common cause of bacterial respiratory infections, including community-acquired pneumonia (CAP). Most *M. pneumoniae* infections are mild, although some patients develop pneumonia requiring hospitalization (*1*). *M. pneumoniae* infections affect all age groups; however, the highest percentages of cases have historically been reported among children and adolescents aged 5–17 years. Previous studies have estimated that *M. pneumoniae* accounts for approximately 10%–30% of hospitalized pediatric CAP cases (*1*,*2*). No vaccine is available to prevent *M. pneumoniae* infection. Macrolide antibiotics such as azithromycin, clarithromycin, and erythromycin are the first-line treatment for infection.* Macrolide-resistant *M. pneumoniae* infections are widespread in some regions of the world but remain relatively uncommon in the United States, accounting for <10% of cases (*3*,*4*).

* CDC | Clinical care of *Mycoplasma pneumoniae* infection

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Historically, *M. pneumoniae* infections have increased approximately every 3–5 years, which mathematical modeling suggests is due, in part, to changes in predominant strain types and associated increases in susceptible populations resulting from waning immunity after infection (*1*,*5*). During the COVID-19 pandemic, *M. pneumoniae* infections were rarely detected (*6*). In 2023, *M. pneumoniae* infections increased in other countries but remained low in the United States (*7*). *M. pneumoniae* infections in the United States began to increase sharply in April 2024, as indicated by an increase in the percentage of positive test results and syndromic surveillance data from emergency departments.† This report describes the epidemiology of *M. pneumoniae* and characterizes infections among patients aged ≤18 years (referred to as children in this report) discharged from pediatric hospitals during 2024 compared with previous years.

Methods

Population and Data Source

The Pediatric Health Information System (PHIS)§ contains clinical and resource use data for patients aged ≤18 years. Children treated at one of 42 U.S. children's hospitals that consistently contributed data to PHIS were eligible for inclusion. The PHIS database was queried for *International Classification of Diseases, Tenth Revision* (ICD-10) discharge diagnostic codes indicating CAP¶ and *M. pneumoniae* infection.** Data were used to identify the total number of CAP cases, *M. pneumoniae*–associated CAP cases, and CAP cases with administration of an antimicrobial agent effective against *M. pneumoniae*†† during January 2018–December 2024. ICD-10 codes used to identify *M. pneumoniae* CAP were validated by comparing discharge diagnosis codes with laboratory results at one hospital (Primary Children's Hospital, Salt Lake City, Utah).

† CDC | *Mycoplasma pneumoniae* infections have been increasing

§ Children's Hospital Association | Leverage your data with CHA's Pediatric Health Information System

¶ Influenza due to identified novel influenza A virus with pneumonia (J09.X1); influenza due to other identified influenza virus with pneumonia (J10.00–10.01 and J10.08); influenza due to unidentified influenza virus with pneumonia (J11.00 and J11.08); viral pneumonia, not elsewhere classified (J12.0–12.3 and J12.8–12.9); pneumonia due to *Streptococcus pneumoniae* (J13); pneumonia due to *Haemophilus influenzae* (J14); bacterial pneumonia, not elsewhere classified (J15.0–15.9); pneumonia due to other infectious organisms, not elsewhere classified (J16.0 and J16.8); pneumonia in diseases classified elsewhere (J78); bronchopneumonia, unspecified organism (J18.0–18.2 and J18.8–18.9); acute respiratory distress syndrome (J80); Legionnaires disease (A48.1); and acute bronchitis due to *M. pneumoniae* (J20.0).

** Pneumonia due to *M. pneumoniae* (J15.7); acute bronchitis due to *M. pneumoniae* (J200); *Mycoplasma* infection, unspecified site (A493); and *M. pneumoniae* as the cause of diseases classified elsewhere (B960).

†† Antibiotics considered effective against *M. pneumoniae*, with *Current Procedural Terminology* codes and exclusions, include azithromycin (122421, excluding ophthalmic 1224214568000 and 1224214568064); clarithromycin (122425); doxycycline (123115, excluding topical 1231154041000, 1231154042000, and 1231154045652); minocycline (123131); levofloxacin (123215, excluding inhalation 1232154242272 and excluding ophthalmic 1232154565000, 1232154565064, 1232154565114, and 1232154569000); and moxifloxacin (123225, excluding ophthalmic 1232254539000, 1232254539591, 1232254539861, 1232254539941, 1232254565000, 1232254565074, and 1232254565114).

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Analysis

To determine whether the severity of *M. pneumoniae* infections during 2018–2023 (before, during, and immediately after the COVID-19 pandemic) differed from the severity of infections in 2024, as measured by intensive care unit admission and length of hospital stay, the number and rate (cases per 1,000 hospitalizations) of *M. pneumoniae* cases during 2018–2024, 2018–2023, and 2024 were analyzed. The number and percentage of cases during each period were reported by age group, sex, race and ethnicity, and characteristics of hospitalization. Chi-square and Wilcoxon rank-sum tests were used to compare demographic and clinical characteristics of patients with infections during 2018–2023 and 2024, with p-values <0.05 considered statistically significant. Statistical testing was performed using SAS (version 9.4; SAS Institute). This activity was reviewed by CDC, deemed not research, and was conducted consistent with applicable federal law and CDC policy.[§§]

Results

Prevalence of CAP-Associated Pediatric Hospitalizations

Among 5,631,734 hospitalized children, 141,955 (2.5%) received a CAP diagnosis (Figure 1), including 111,064 (2.3%) of 4,760,521 during 2018–2023 and 30,891 (3.5%) of 871,213 in 2024. Seasonal increases in CAP occurred annually during the fall and winter, except during 2020–2021. The annual number of CAP cases ranged from 10,221 in 2020 to 30,891 in 2024.

Percentage of Pediatric CAP Cases with an *M. pneumoniae* Diagnostic Code

Overall, among all hospitalized pediatric patients with CAP, an *M. pneumoniae* diagnostic code was listed for 16,353 of 141,955 (11.5%); 94.4% of identified *M. pneumoniae* infections had a CAP diagnosis. *M. pneumoniae* accounted for <5% of total hospitalized CAP cases annually during 2021–2023, then increased to 33% in 2024, peaking at 53.8% in July 2024 (Figure 1). Among 16,353 *M. pneumoniae*–related hospital discharges (representing 4.45 per 1,000 hospitalizations), a total of 6,055 (2.12 per 1,000) occurred during 2018–2023, and 10,298 (12.49 per 1,000) occurred in 2024 (Table).

Demographic and Clinical Characteristics of Children Hospitalized with *M. pneumoniae* and CAP

The number of hospital discharges for *M. pneumoniae*–associated CAP decreased in early 2020, remained low through 2023, and increased in all age groups in 2024 (Figure 2). The highest total number and proportion of *M. pneumoniae* CAP cases occurred among children aged 6–12 years (6,959; 42.6%), followed by those aged 2–5 years (4,210; 25.7%) and 13–18 years (3,448; 21.1%); the lowest proportion was among children aged 12–23 months (1,046; 6.4%) and 0–11 months (690; 4.2%) (Table). The peak monthly proportion of CAP cases attributed to *M. pneumoniae* was highest among children aged 13–18 years (67.2%), followed by those aged 6–12 years (60.8%), 2–5 years (53.4%), 0–11 months (52.0%), and 12–23 months (44.8%) (Figure 2). In 2024, compared with 2018–2023, the proportion of CAP attributed to *M. pneumoniae* increased the most among children aged 12–23 months (increased 8.5 times), followed by 0–11 months (8.1 times), 2–5 years (7.7 times), 13–18 years (4.5 times), and 6–12 years (4.1 times). Compared with 2018–2023, the length of hospital stay in 2024 was shorter (2 days [range: 1–4 days] versus 3 days [range: 2–6 days]), and the percentage of patients admitted to an intensive care unit was lower (19.5% versus 26.0%). Forty-four (0.3%) deaths occurred among children with *M. pneumoniae* CAP, including 29 (0.5% of *M. pneumoniae* CAP cases) during 2018–2023 and 15 (0.1%) in 2024. The median age of patients who died from *M. pneumoniae* CAP was 12 years (IQR: 2.0–16.5 years).

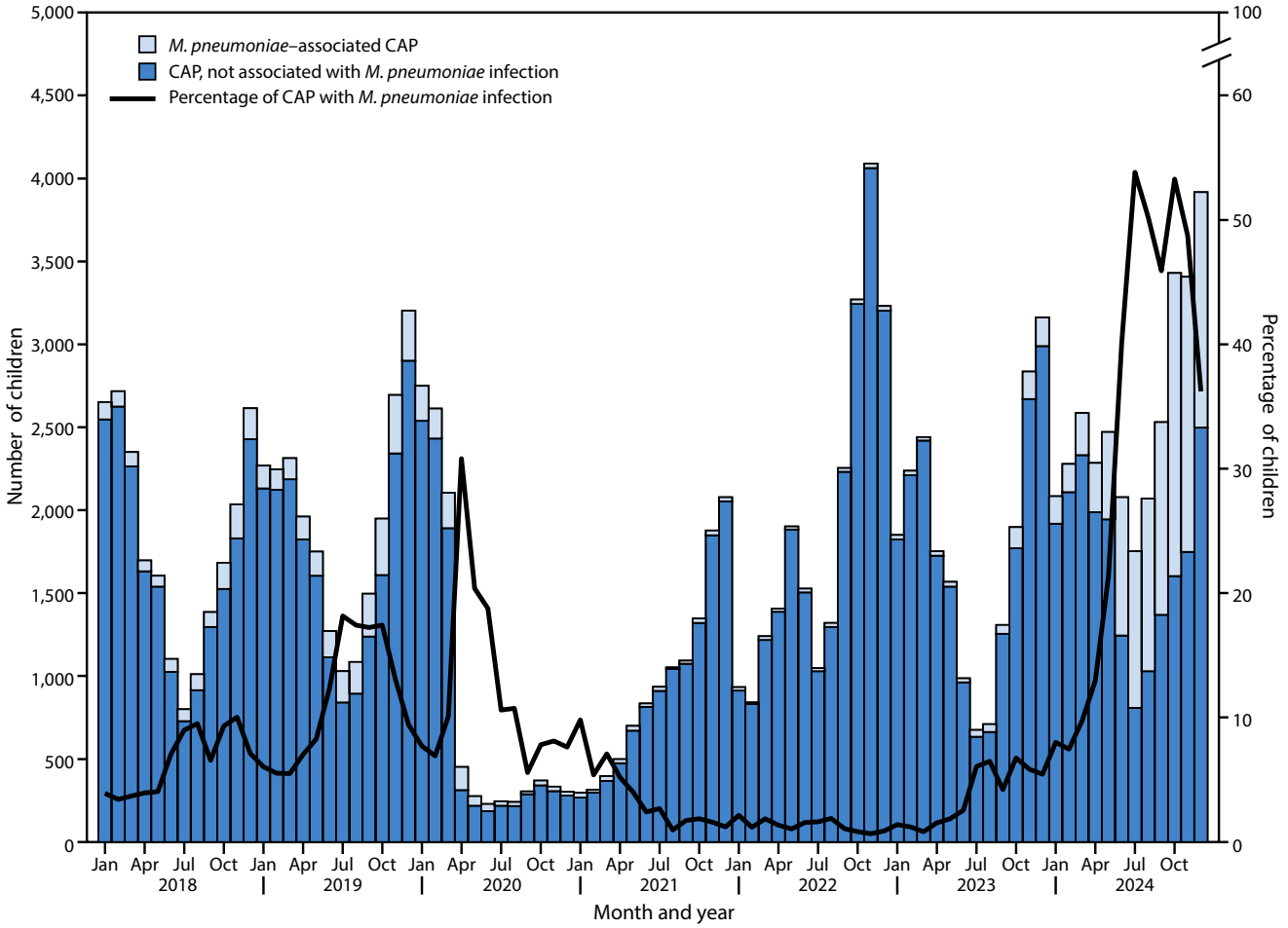
ICD-10 codes used for identifying *M. pneumoniae* CAP were validated by comparing discharge diagnosis codes with laboratory results from one hospital (Primary Children's Hospital, Salt Lake City, Utah) for 2018–2024. A positive polymerase chain reaction test result for *M. pneumoniae* was recorded for 86% of discharges coded as *M. pneumoniae* pneumonia; 14% of cases did not have an *M. pneumoniae*–specific test result code recorded. Code J15.7 (pneumonia due to *Mycoplasma pneumoniae*) was recorded for 84% of discharges coded as *M. pneumoniae* CAP. During the study period in all 42 hospitals, 22.0% of all CAP inpatients and 95.9% of *M. pneumoniae* CAP inpatients received an antibiotic typically considered effective against *M. pneumoniae* (i.e., a macrolide antibiotic); the proportion of *M. pneumoniae* CAP patients who received these antibiotics was slightly higher in 2024 (96.2%) than during 2018–2023 (95.4%) (Table).

Discussion

Consistent with recently reported trends worldwide (*6*,*7*), analyses of data from 42 U.S. children's hospitals indicate that discharges for *M. pneumoniae* CAP decreased in early 2020, remained low through 2023, and increased in all age groups in 2024. During July–December 2024, *M. pneumoniae* ICD-10 codes were listed for approximately one half of CAP hospitalizations at U.S. children's hospitals, the highest level

[§§] 45 C.F.R. part 46.102(l)(2), 21 C.F.R. part 56; 42 U.S.C. Sect. 241(d); 5 U.S.C. Sect. 552a; 44 U.S.C. Sect. 3501 et seq.

FIGURE 1. Hospitalized children with community-acquired pneumonia, associated and not associated* with *Mycoplasma pneumoniae*, by month — Pediatric Hospital Information System,† United States, 2018–2024



Abbreviation: CAP = community-acquired pneumonia.
* The number of CAP cases that were not associated with *M. pneumoniae* infection was calculated by subtracting the number of *M. pneumoniae* CAP cases from the total number of CAP cases.
† Forty-two hospitals.

in 6 years. Increases in *M. pneumoniae* CAP were not observed during annual seasonal increases in overall CAP during 2021–2023.

Increases in *M. pneumoniae* infection occur approximately every 3–5 years, likely due to variations in strain predominance (*5*). The 2024 increase in the United States and other countries was higher than most previously reported periodic increases (*1*,*2*). Surveillance data and mathematical modeling suggest that this increase might reflect increased population susceptibility after low levels of *M. pneumoniae* circulated worldwide during and immediately after the COVID-19 pandemic (*7*–*9*). Despite the increased population susceptibility, pediatric *M. pneumoniae* infections requiring hospitalization in 2024 did not appear to be more severe than those during the previous 5 years.

Historically, the highest percentage of *M. pneumoniae* infections have been reported among children aged 5–17 years (*1*,*10*). In this study, children aged 6–12 years similarly accounted for the highest number and percentage of *M. pneumoniae* CAP cases. However, comparing 2024 with 2018–2023, the proportion of CAP attributed to *M. pneumoniae* increased the most among children aged <5 years. In addition, although the number of *M. pneumoniae* infections among children aged <2 years was lower than that in older children and adolescents, *M. pneumoniae* accounted for approximately one half of CAP among children aged 0–11 months and 12–23 months at peaks in November and July 2024, respectively.

TABLE. Demographic and clinical characteristics of children hospitalized with *Mycoplasma pneumoniae*–associated community-acquired pneumonia — Pediatric Hospital Information System, United States, 2018–2024

Characteristic	2018–2024 Rate* (95% CI): 4.45 (4.38–4.52) No. (%)	2018–2023 Rate* (95% CI): 2.12 (2.07–2.18) No. (%)	2024 Rate* (95% CI): 12.49 (12.26–12.74) No. (%)	p-value†
Total	**16,353 (100)**	**6,055 (100)**	**10,298 (100)**	**<0.001**
Age group, yrs				
<1	690 (4.2)	285 (4.7)	405 (3.9)	<0.001
1	1,046 (6.4)	384 (6.3)	662 (6.4)	
2–5	4,210 (25.7)	1,491 (24.6)	2,719 (26.4)	
6–12	6,959 (42.6)	2,474 (40.9)	4,485 (43.6)	
13–18	3,448 (21.1)	1,421 (23.5)	2,027 (19.7)	
Sex				
Female	7,192 (44.0)	2,726 (45.0)	4,466§ (43.4)	0.07
Male	9,159 (56.0)	3,329 (55.0)	5,830§ (56.6)	
Race and ethnicity				
Asian, non-Hispanic	843 (5.2)	308 (5.1)	535 (5.2)	<0.001
Black or African American, non-Hispanic	2,027 (12.4)	750 (12.4)	1,277 (12.4)	
Hispanic or Latino	4,192 (25.6)	1,553 (25.6)	2,639 (25.6)	
White, non-Hispanic	8,223 (50.3)	2,959 (48.9)	5,264 (51.1)	
Other	1,068 (6.5)	485 (8.0)	583 (5.7)	
Clinical characteristics and outcomes				
Length of hospitalization stay, median (IQR)	2 days (1–4 days)	3 days (2–6 days)	2 days (1–4 days)	<0.001
CAP diagnosis¶	15,440 (94.4)	5,549 (91.6)	9,891 (96.0)	<0.001
Admitted to intensive care unit	3,586 (21.9)	1,577 (26.0)	2,009 (19.5)	<0.001
Received antibiotics for *M. pneumoniae***	15,682 (95.9)	5,774 (95.4)	9,908 (96.2)	0.008
Died††	44 (0.3)	29 (0.5)	15 (0.1)	<0.001

Abbreviation: CAP = community-acquired pneumonia.

* Number of cases per 1,000 hospitalizations.

† Chi-square (for categorical variables) and Wilcoxon rank-sum (for continuous variables) tests were used to compare demographic and clinical characteristics of patients with infections during 2018–2023 and 2024.

§ Missing values (2) in 2024.

¶ Influenza due to identified novel influenza A virus with pneumonia (J09.X1); influenza due to other identified influenza virus with pneumonia (J10.00–10.01 and J10.08); influenza due to unidentified influenza virus with pneumonia (J11.00 and J11.08); viral pneumonia, not elsewhere classified (J12.0–12.3 and J12.8–12.9); pneumonia due to *Streptococcus pneumoniae* (J13); pneumonia due to *Haemophilus influenzae* (J14); bacterial pneumonia, not elsewhere classified (J15.0–15.9); pneumonia due to other infectious organisms, not elsewhere classified (J16.0 and J16.8); pneumonia in diseases classified elsewhere (J78); bronchopneumonia, unspecified organism (J18.0–18.2 and J18.8–18.9); acute respiratory distress syndrome (J80); Legionnaires disease (A48.1); and acute bronchitis due to *M. pneumoniae* (J20.0).

** Antibiotics considered effective against *M. pneumoniae*, with *Current Procedural Terminology* codes and exclusions, include azithromycin (122421, excluding ophthalmic 1224214568000 and 1224214568064); clarithromycin (122425); doxycycline (123115, excluding topical 1231154041000,1231154042000, and 1231154045652); minocycline (123131); levofloxacin (123215, excluding inhalation 1232154242272 and excluding ophthalmic 1232154565000, 1232154565064, 1232154565114, and 1232154569000); and moxifloxacin (123225, excluding ophthalmic 1232254539000, 1232254539591, 1232254539861, 1232254539941, 1232254565000, 1232254565074, and 1232254565114).

†† The median age of children with *M. pneumoniae* CAP who died was 12.0 years (IQR: 2.0–16.5 years).

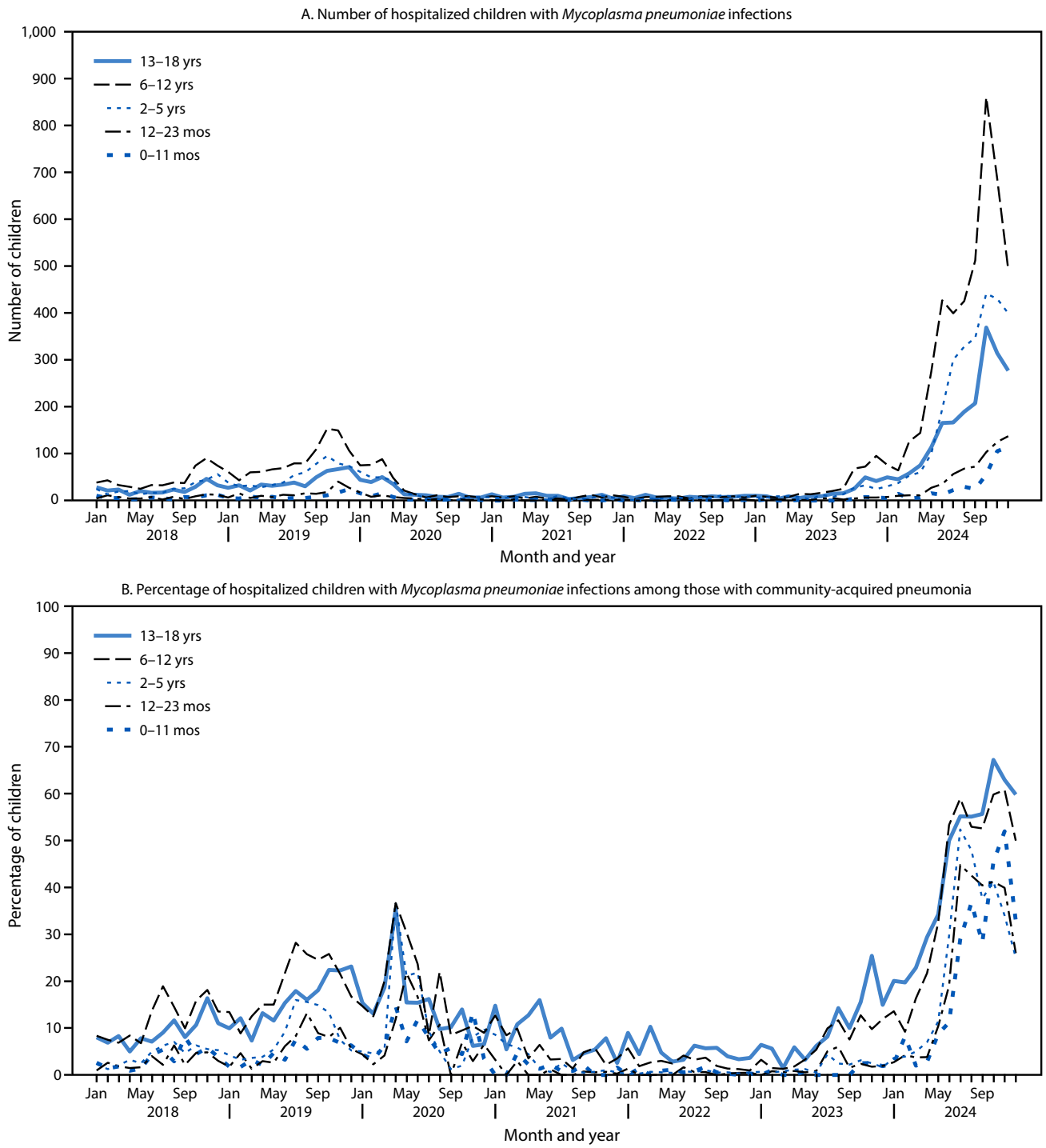
These findings suggest that during periodic increases in *M. pneumoniae* infections, this pathogen might account for a substantial proportion of CAP among children of all ages, including those aged <5 years. Widespread use of multiplex laboratory tests for detection of respiratory pathogens could contribute to improved recognition of infections, including *M. pneumoniae* infections, in younger patients. The high percentage of patients with an *M. pneumoniae*–associated ICD-10 code with confirmatory laboratory evidence at one reporting site suggests that discharge code data at children's hospitals can be used to accurately track infection trends over time.

Health care providers should be aware of increases in *M. pneumoniae* CAP, which might occur in summer and fall when circulation of other common respiratory pathogens is low (*1*). Because *M. pneumoniae* infection cannot be identified based on physical examination alone, providers should consider and test for this pathogen as a cause of respiratory illness among children of all ages, especially during periods of high transmission. Confirmation of *M. pneumoniae* infection by laboratory testing helps guide patient treatment because first-line antibiotic treatment of *M. pneumoniae* CAP differs from that for CAP of other bacterial etiologies.

Limitations

The findings in this report are subject to at least four limitations. First, passively collected resource use data are subject to possible biases from test ordering and medical coding practices. A limited evaluation at a single hospital indicated that most *M. pneumoniae*–associated discharges were supported

FIGURE 2. Number of hospitalized children with *Mycoplasma pneumoniae* infections (A) and percentage of children with *M. pneumoniae* infections among those with community-acquired pneumonia (B), by month and age group — Pediatric Hospital Information System,* United States, 2018–2024



* Forty-two hospitals.

Summary

What is already known about this topic?

Mycoplasma pneumoniae is a common cause of community-acquired pneumonia (CAP) in school-aged children. In the United States, *M. pneumoniae* infection prevalence decreased during the COVID-19 pandemic and remained low through 2023.

What is added by this report?

The number of hospital discharges of children with *M. pneumoniae*–associated CAP from U.S. pediatric hospitals increased sharply in 2024, accounting for approximately one half of hospitalized children with CAP. This number included children aged <5 years, a group in which *M. pneumoniae* infections have historically been less commonly reported. Data on length of hospitalization and intensive care unit admissions indicate that *M. pneumoniae* infections in 2024 were not more severe than 2018–2023 infections.

What are the implications for public health practice?

Increased awareness among health care providers might improve diagnosis and could guide treatment of *M. pneumoniae* infections among children of all ages, especially during periodic increases in *M. pneumoniae* circulation and among children requiring hospitalization.

by laboratory testing; however, this might not be generalizable to all facilities and might result in an underestimation of cases. Second, coinfections and underlying conditions were not evaluated, which might affect comparison of clinical characteristics between study periods. Third, laboratory results for characterization of *M. pneumoniae*, including antimicrobial susceptibility testing, were not available for cases included in this analysis, which could also affect study period comparisons. Finally, because most *M. pneumoniae* infections are mild, cases requiring hospitalization likely accounted for a small proportion of infections during the study period.

Implications for Public Health Practice

Increased awareness among health care providers might improve diagnosis and could guide treatment of *M. pneumoniae* infections among children of all ages, especially during periodic increases in *M. pneumoniae* circulation and among children requiring hospitalization. In addition, ongoing surveillance of *M. pneumoniae* infections is important to detect periodic increases and improve mathematical modeling to predict the timing and magnitude of future increases. Characterization of circulating *M. pneumoniae* strains is needed to monitor predominant genotypes, emergence of variants, and antimicrobial resistance patterns.

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ESSAY

Confronting the Crisis: Actions to Address Maternal Morbidity and Mortality Among Black Women in Rural Georgia

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PEER REVIEWED

Maternal mortality remains a public health crisis in the US, disproportionately affecting Black women, who face substantially higher risks compared with their White counterparts (1–3). In 2021, the national maternal mortality rate was 32.9 deaths per 100,000 live births (1). However, the rate among non-Hispanic Black women was 69.9 per 100,000 live births — nearly 2.6 times higher than of the rate among non-Hispanic White women (1). In Georgia, the maternal mortality rate is 66.3 per 100,000 live births, the second highest rate in the US (2). Women in rural areas (ie, <50,000 people) face maternal mortality risks up to 50% higher than their urban counterparts; of Georgia's 159 counties, 120 are classified as rural (4). The disparities are even more pronounced among Black women in rural Georgia, whose maternal mortality rate is double that of their rural White counterparts and 30% higher than that among Black women in urban areas (4). These statistics underscore the urgent need for focused, targeted interventions to address maternal mortality among Black women, particularly in the rural communities of Georgia.

Why Is the Maternal Morbidity and Mortality Health Crisis a Challenge in Rural Georgia?

Rural Georgia faces substantial health care infrastructure challenges, including a shortage of hospitals and specialized maternal care providers (4). Economic barriers, including high poverty rates, further limit women's ability to access transportation, resulting in delayed or missed health care appointments that often affect maternal health (3). Cultural and language barriers also persist, as many health care providers lack the cultural competency needed to effectively engage with Black women, which discourages them from seeking care (3). High rates of postpartum depression and anxiety worsen maternal morbidity and mortality, as limited mental health resources leave many women in medically underserved areas to struggle in silence, which affects both maternal and infant health (5). Additionally, the shortage of health care providers, coupled with the high turnover rate of providers in rural communities, disrupts continuity of care, making it difficult for women to establish long-term, trusting relationships with their health care providers (4).

Existing and Historical Policy Shortcomings

US federal policies

Historically, federal programs like the Maternal and Child Health Services Block Grant, the National Health Service Corps, and the Healthy Start program have been designed to improve maternal health outcomes, especially for underserved populations (4,6). However, these policies have fallen short of addressing the needs of Black women, particularly in rural areas. Despite the intent, underfunding and inconsistent implementation have limited their effectiveness. The National Health Service Corps, which offers loan repayment incentives for health care providers to work in medically underserved areas, has struggled with high turnover rates in rural regions, preventing continuity of care (4,5). The Healthy Start program, meant to provide services like home visits and early screenings, often fails to reach remote communities due to geographic barriers and resource limitations (4).

State of Georgia policies

Medicaid expansion, shown to reduce maternal mortality rates in states that adopted it, would have provided low-income women with critical prenatal and postpartum care. However, Georgia's de-

cision not to expand Medicaid leaves many women without health insurance, forcing them to forgo necessary care. The state's lack of culturally competent care and a shortage of health care professionals, especially in rural areas, continue to perpetuate disparities.

Furthermore, Georgia's 6-week abortion ban has substantially affected the Black maternal health crisis by exacerbating existing disparities and limiting reproductive choices. The ban restricts access to abortion services for Black women, who already face systemic barriers to comprehensive health care. This restriction forces some women to carry unwanted pregnancies to term, increasing the risk of maternal complications and adverse health outcomes. The ban also imposes additional financial and emotional burdens, particularly on those in rural areas with limited resources. By reducing access to safe and timely reproductive care, the policy further deepens the challenges.

Proposed Solutions and Innovative Strategies

Solutions for addressing the challenges exist at many levels. We suggest ways to link solution ideas to levels of leadership (Figure).

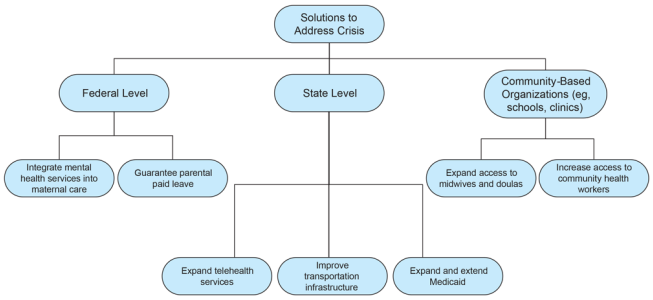

Figure. Hierarchy of leadership levels and solutions to address existing challenges in maternal health among Black women in rural Georgia.

Community-based organizations

To address the disparities in Black maternal health, expanding access to midwives and doulas is essential. Midwifery care reduces preterm births and cesarean delivery rates and improves breastfeeding outcomes, particularly among Black mothers. Doulas provide invaluable emotional and physical support during pregnancy and childbirth, mitigating racial biases and fostering trust in the health care system (3). Programs like Morehouse School of Medicine's rural doula initiative have demonstrated effectiveness in improving maternal health outcomes in Georgia and could serve as a model for expansion statewide. Additionally, implementing policies that streamline doula reimbursement and simplify administrative paperwork is crucial to removing barriers, supporting doula workforce sustainability, and enhancing access to these vital services (3).

Increasing the availability of community health workers (CHWs) is also a vital strategy. CHWs play a pivotal role in bridging gaps between medically underserved populations and health care providers, offering culturally competent care; guiding patients through the health care system; providing prenatal education; and assisting with transportation, which can be challenging in rural areas where long travel distances often delay care (7). Strengthening CHW programs would help ensure that Black women in rural Georgia receive the necessary support to improve maternal health outcomes.

Solutions at the state level

Telehealth offers a promising solution for enhancing access to maternal care in rural Georgia. Virtual consultations, remote monitoring, and postpartum care provide timely access to specialists, especially in areas lacking obstetricians and family physicians (8). However, for telehealth to be effective, substantial investment in infrastructure is needed, including expanding broadband and high-speed internet access to underserved rural areas.

Expanding Medicaid would also provide access to comprehensive health care coverage for many low-income women, helping to reduce pregnancy-related complications and mortality rates (6). Additionally, extending Medicaid postpartum coverage to one year is crucial for addressing mental health and chronic conditions that contribute to maternal mortality rates (3,6). Evidence from other states that have expanded Medicaid shows marked improvements in maternal health outcomes.

Improving transportation infrastructure and implementing mobile health clinics are crucial to addressing the maternal mortality crisis in rural Georgia. Many rural counties lack adequate hospital facilities, requiring women to travel long distances — often more than 50 miles — to access essential care (4). Expanding public transit options, offering shuttle programs, or partnering with ride-share services can help alleviate these logistical barriers. Mobile health clinics can further reduce access gaps by delivering essential maternal health services, such as prenatal checkups, screenings, and education, directly to medically underserved areas, ensuring women receive the care they need promptly (9).

Solutions at the federal level

Integrating mental health services into maternal care is critical to addressing the mental health challenges faced by Black women in rural Georgia. By embedding mental health screenings and treat-

ment within prenatal and postpartum care, the health care system can better address these issues (5). Expanding Medicaid to cover mental health services would ensure that Black women have access to comprehensive care, improving both their physical and mental health before, during, and after pregnancy.

Guaranteeing paid leave to new parents is a critical policy change, particularly for Black women, who are disproportionately affected by a lack of paid leave options. Currently, only 30% of Black rural women have access to paid leave (10). Implementing paid leave would allow women to recover from childbirth and care for their families without risking their financial security. Because many Black mothers serve as the primary breadwinners in their households, paid leave would improve maternal and child health outcomes by allowing women the time they need for postpartum recovery, ultimately supporting their health and economic stability (10).

Who Would Benefit From These Solutions?

These innovative solutions are designed to bring substantial improvements to Black women in rural Georgia, who disproportionately face challenges related to maternal health. Expanding access to midwifery care, doulas, and CHWs would provide these women with personalized, culturally competent care at every stage of pregnancy, during childbirth, and postpartum. This comprehensive support ensures that Black women receive the attention and resources they need in a manner that is sensitive to their unique cultural and health needs. Additionally, rural health care providers stand to benefit from enhanced support for maternal health professionals. By addressing existing provider shortages and improving health care access, we can reduce the strain on the system and enhance job satisfaction among providers, ultimately leading to better outcomes for all involved.

Future Outlook

If effectively implemented, these innovative approaches could transform maternal health care in rural Georgia, reducing maternal mortality and morbidity while strengthening the state's health care system and fostering greater equity and inclusivity. A more integrated and comprehensive health care system would guarantee that women, particularly Black women in rural areas, have access to continuous, culturally competent care throughout pregnancy, childbirth, and the postpartum period. Moreover, this approach could serve as a framework for other states facing similar challenges, promoting nationwide change and improving maternal health outcomes across the country.

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Notes from the Field

Early-Season Human Plague Transmitted from an Infected Cat — Oregon, January 2024

Emilio DeBess, DVM[1]; Kelly Coyle, MS[2]; Richard Fawcett, MD[2]; Ali K. Hamade, PhD[1]; Paul R. Cieslak, MD[1]

Summary

What is known about this topic?

Plague is caused by the bacterium *Yersinia pestis,* which is transmitted primarily through fleas from rodents. This case highlights an off-season transmission of plague. Plague is most often identified during May–August.

What is added by this report?

An Oregon man sought care at an emergency department for signs and symptoms of plague on January 30, 2024, the earliest calendar date of plague recorded in the state's history, possibly indicating a shift in the seasonality of plague incidence. The patient did not have direct contact with rodents, but did have contact with his infected cat after cutting his finger.

What are the implications for public health practice?

Public health messaging and diagnostic efforts regarding plague are warranted year-round in areas with endemic disease.

Plague is caused by the bacterium *Yersinia pestis*. *Y. pestis* is transmitted primarily through the bite of an infected rodent flea or handling of infected animals. Plague is a rare but potentially life-threatening illness in the western United States, occurring in bubonic, septicemic, or pneumonic forms, primarily affecting rural populations, and is treatable with antibiotics if diagnosed early.

Investigation and Outcomes

On January 19, 2024, a 2-year-old cat began receiving veterinary care in Central Oregon for a neck abscess and vomiting. The cat was initially treated with an oral antibiotic. On January 24, the abscess was excised and drained by a veterinarian.

On January 25, the cat's owner, a man aged 73 years, cut his right index finger with a kitchen knife and sought treatment at an urgent care facility in Central Oregon. The wound was irrigated and sutured, and the man returned home. That same day, the man had close contact with his cat, which was still under veterinary care. On January 26, the man noticed a new, tender, raised ulcer on his right wrist, and 4 days later he sought care at an emergency department. His signs and symptoms included cellulitis and lymphadenitis extending up to his right axilla, originating from the ulcerated wrist lesion. He was admitted to the hospital and initially treated with empiric intravenous ceftriaxone and metronidazole for bacterial lymphangitis. *Y. pestis* was detected by blood culture evaluated at the hospital microbiology laboratory and was confirmed by polymerase chain reaction (PCR) and bacteriophage-lysis testing at the Washington State Public Health Laboratory on February 6. At the time the isolate was identified, Oregon State Public Health Laboratory was undergoing renovations and Washington State Public Health Laboratory agreed to support and perform pathogen testing by PCR as needed.

Based on culture results, antibiotic therapy was changed to intravenous gentamicin and intravenous levofloxacin, which resulted in improvement in the patient's cellulitis, lymphangitis, and lymphadenitis. On February 7, he was discharged and prescribed a 9-day course of oral levofloxacin. At his follow-up appointment on February 15, he appeared to have made a full recovery, with only mild residual fatigue.

The owner was not able to give the cat its antibiotics after surgery, and the cat died on January 31. The Washington State Public Health Laboratory reported the man's positive *Y. pestis* test results to the Oregon State Public Health Laboratory and Oregon's public health veterinarian, who contacted CDC to request confirmatory testing of the cat. CDC's Diagnostic and Reference Laboratory in Fort Collins, Colorado, requested tissue sections from the cat's liver and spleen and subsequently confirmed the presence of *Y. pestis* via PCR and tissue culture.

This project is classified as a public health surveillance activity conducted, supported, requested, ordered, required, or authorized by a public health authority (e.g., Oregon Health Authority). Per federal regulations, this activity does not constitute research involving human subjects and is therefore not subject to institutional review board review.

Conclusions and Actions

This human case of plague occurred earlier in the calendar year than the other 18 cases reported in Oregon during the previous 90 years. Vectorborne diseases can emerge or reemerge with changes in climate, soils, forest cover, and land use (*1*). Temperate climates of California's Central Valley and the Pacific Northwest can be conducive to flea emergence year-round, and various factors, such as unseasonal warm temperatures during the winter, can extend the flea life cycle and potentially promote enzootic transmission (*2*). Flea eggs can hatch in temperatures as low as 50°F (10°C) (*3*), which was close to the average temperature in Central Oregon

when the cat became ill. The effect of environmental factors, including climate, on plague transmission remains an area of active research (*2*,*4*).

Y. pestis can be transmitted to humans through exposure to ill pets, especially cats (*5*). Regular treatment of pets and their surroundings for fleas might reduce the risk for infection with pathogens transmitted by fleas. *Y. pestis* infection was not considered during the cat's veterinary screening. Had it been, the pet owner could have been counseled about the risks of animal-to-human plague transmission, potentially preventing zoonotic spread. Veterinarians and medical personnel should maintain a high index of suspicion for *Y. pestis* infection in patients with a febrile illness associated with animal exposure in areas where *Y. pestis* is enzootic, regardless of season.

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Precision Medicine for IBS: A novel, IBS-specific immune response guided dietary therapy

Insights from a randomized, sham-controlled, multicenter trial that significantly reduced IBS symptoms

Author: Astrid Starke, Dr.sc.nat. – Marketing Director, Biomerica

Introduction

Understanding IBS and the Role of Diet

Irritable Bowel Syndrome (IBS) is a chronic, often debilitating disorder of gut-brain interaction marked by altered bowel habits including symptoms such as abdominal pain, bloating, diarrhea and constipation. IBS symptoms negatively impact the patient´s quality of life; 1 in 4 patients report missing work, many relate to a decreased work productivity and suffer from drastic impacts on their social lives.

80-90% of IBS sufferers report food as a trigger. While IBS affects up to 9% of the global population, effective and personalized treatment options remain limited. With the rise of precision medicine, there's increasing interest in dietary interventions tailored to the individual.

Limitations of Current Dietary Therapies

The most recognized among these is the low-FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) diet, a restrictive protocol that eliminates fermentable carbohydrates. The diet is nutritionally complex, time-consuming, often difficult for patients to adhere to long-term and costly. While effective for about 50% of the patients, it is difficult to predict beforehand who will benefit.

Precision Nutrition and the Evolution of Dietary Approaches

Precision nutrition emphasizes individualized dietary interventions based on biological markers. By identifying immune-reactive foods through a validated diagnostic assay, guesswork is minimized. Instead of eliminating entire food groups, it targets specific food triggers unique to each individual. This personalized approach reduces unnecessary restrictions while potentially enhancing therapeutic outcomes.

Advancing IBS Care with Individualized Antibody-Based Elimination Diets

Immune Responses to Foods and IBS Symptoms

The gut immune system plays a crucial role in detecting and responding to foreign antigens, including those derived from dietary proteins. In some individuals, these food antigens may pass through a compromised gastrointestinal barrier, eliciting a hypersensitive immune response. While IgE-mediated food allergies are well described and understood, and elicit an immediate adverse reaction to the culprit food, research suggests that non-IgE mediated immunological pathways (IgG-mediated) may also play a role in the development or trigger of adverse reactions to food. IBS patients can experience these delayed gastrointestinal symptoms such as bloating, abdominal pain, or irregular bowel movements. Identifying foods that provoke such a delayed immune hypersensitivity and guide food elimination could offer a pathway to alleviating these symptoms.

A novel approach – an IBS-specific elimination diet based on an elevated IgG antibody response to certain foods, provides a science-backed, individualized method for targeting food-related symptoms. This approach represents a significant step toward precision-based dietary therapy in IBS.

A Novel Diagnostic Tool: Identification of IBS-Specific Trigger Foods with an IgG Assay

Overview of the Assay's Development

The foundation of this personalized dietary therapy is a novel diagnostic test—a discriminatory p-value-based IgG food specific assay (inFoods IBS). Developed through rigorous statistical analysis, the IgG antibody responses to a range of common foods in IBS patients versus healthy controls were compared. Foods that triggered IgG reactions significantly more often in IBS patients were identified, ensuring only statistically significant "IBS-specific foods" were selected for the assay.

In a second step, the discriminatory p-value method distinguishes between elevated and normal IgG antibody level to these preselected "IBS-specific foods". Foods were only included into the assay if the IBS patient's IgG response lies outside the 95th percentile compared to healthy controls and demonstrated statistical significance. This ensures that the food elimination diet is both statistically significant and personalized, minimizing the risk of unnecessary exclusions. Moreover, the assay's discriminatory power was verified through multiple adjustment models, including False Discovery Rate (FDR) corrections ensuring that only foods with genuine clinical significance were targeted, setting a new standard in personalized dietary guidance.

A Randomized, Sham-Controlled Clinical Study to Prove the Efficacy of the inFoods IBS Test

Recruitment and Eligibility Criteria

The multicenter, randomized, double-blind, sham-controlled trial enrolled subjects from 8 centers in the US including Mayo Clinic Jacksonville & Scottsdale; Beth-Israel Deaconess Medical Center Boston (Harvard Medical School); Michigan Medicine; University of Texas Health Science Center, San Antonio; Houston Methodist Hospital; Cleveland Clinic Ohio.

This clinical trial screened 556 adults diagnosed with IBS according to Rome IV criteria, and finally 223 subjects could be included in the intent-to treat statistical analysis. Patients were enrolled in a 10-week clinical study. They entered a two-week run-in period and were required to report moderate-to-severe abdominal pain and other gastrointestinal parameters. Patients were excluded if they had other gastrointestinal diseases, IgE food allergy, recent use of conflicting medications, or prior engagement with restrictive diets like low-FODMAP. Patients with a negative test results, i.e. no elevated IgG level to the foods in the assay, were excluded.

Intervention Framework and Dietary Assignment

At the end of the run-in period, all participants with a positive test result were randomly assigned to receive either the diet based on the inFoods IBS test, i.e. they eliminated positive foods or a sham-controlled diet. To ensure blinding, foods removed in the sham group were selected to mirror the types and frequency of foods eliminated in the experimental group - participants actually had negative results for these foods.

Statistical Rigor and Methodological Strengths

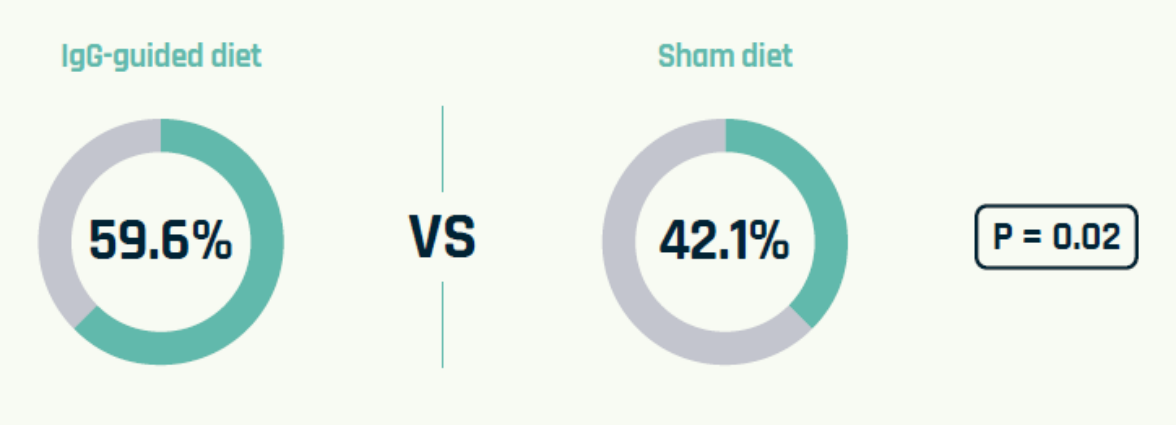
Mixed Models and Multivariate Adjustments

To ensure validity, the study employed a modified intent-to-treat (mITT) analysis alongside a rigorous per-protocol assessment. Generalized linear mixed models adjusted for baseline symptom scores, number of foods excluded, IBS subtype, study site, age, and sex. This multivariate approach minimized confounding and ensured the observed outcomes were a result of the intervention itself. Binary outcomes, such as responder status for abdominal pain and global improvement, were analyzed using mixed logistic regression, while continuous outcomes like bloating and IBS-SSS scores were assessed through general linear models with interaction terms for time and treatment group.

Efficacy Outcomes of the IgG-guided Diet

Significant Reduction in Abdominal Pain Intensity

The primary outcome was the proportion of participants who achieved a ≥30% reduction in abdominal pain intensity (API, FDA-responder endpoint) for at least two of the final four weeks.



More IBS patients on the IgG-guided elimination diet met the primary outcome.

Secondary Outcomes and Global Improvement Metrics

Patients on the IgG-guided diet compared to the sham-diet also experienced improvements in:

- **IBS Symptom Severity Score (IBS-SSS)**: Mean reduction of -73.3 points vs. -61.3
- **Global Improvement Scale (GIS)**: Significant improvement of 1.4 vs. 1.0; *p=0.03*
- **Adequate Relief (IBS-AR)**: 57.5% vs. 46.8% (*trend p=0.06*)
- **Subject Global Assessment (SGA)**: More responders in the IgG-guided diet (18.1% vs. 8.8%, *p=0.04*)

These outcomes support the efficacy of the IgG-guided diet in alleviating IBS symptoms.

Further Explanation to the Clinical Relevance of Response Thresholds

Crucially, response thresholds were established according to FDA and clinical consensus guidelines. A 30% reduction in API is widely recognized as a meaningful improvement for IBS patients. Additional thresholds, such as 50-point and 100-point reductions in IBS-SSS, provided further information for clinical interpretation.

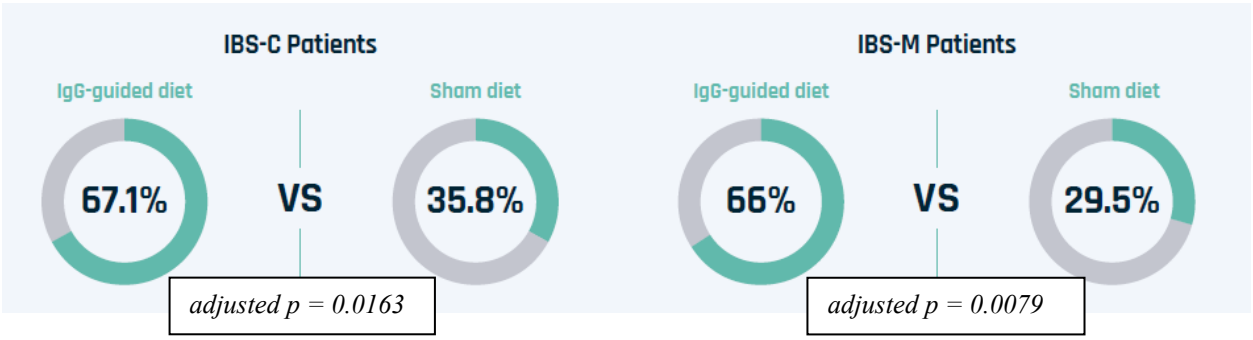
In these additional endpoints, the IgG-guided diet also outperformed the control group:

- **50-point IBS-SSS reduction**: 67% vs. 47.2% (*adjusted p = 0.0451*)
- **100-point IBS-SSS reduction**: 29% vs. 16.2% (*adjusted p = 0.0808*)

Subgroup and Sensitivity Analyses

Impact by IBS Subtype (IBS-C, IBS-D, IBS-M)

Subgroup analyses by IBS subtype revealed that patients with constipation-predominant (IBS-C) and mixed-type IBS (IBS-M) experienced the greatest clinical benefits, e.g. abdominal pain reduction (≥30%), with the IgG-based elimination diet.



These results demonstrate that inFoods IBS could be a first therapeutic approach for IBS-M patients who may particularly benefit from the precision dietary intervention.

IBS-D (diarrhea-predominant) patients showed a minimal difference between the experimental and sham group. The reasons are not clear but may suggest a different pathophysiological profile where diet may be less effective or where other factors like microbiome imbalance may be more prominent. However, the IBS-D patient recrement was not enhanced and had similar number of bowl movements as the IBS C patients.

Compliance and Per-Protocol Findings

Diet compliance was monitored through daily self-reported logs, with per-protocol analysis focusing on participants who completed the diary on at least 70% of days. In the compliant cohort, 63.3% in the IgG-guided diet met the primary endpoint (≥ 30% reduction in API) versus 45.7% in the sham group (not significant). This reinforces one important message: adherence to the elimination diet is required for and enhances the therapeutic effect of symptom relief.

Safety Profile and Tolerability

Adverse Events and Participant Feedback

Adverse events were rare and distributed equally across both groups and unrelated to the intervention; i.e. no serious adverse events, and mild (e.g., common colds, transient headaches).

Dietary Burden and Adherence Challenges

Although the IgG-based elimination diet was generally well-tolerated, some participants noted the social and logistical challenges of following a restrictive diet. However, many participants who achieved symptom relief, reported a willingness to continue the diet long term. Personalized meal plans, educational materials, and nutritionist support are instrumental in maintaining adherence to the elimination diet and crucial for symptom relief.

Discussion

Clinical Implications of Personalized Dietary Therapies

This trial marks a significant advancement in the management of IBS through personalized dietary intervention. By identifying specific food triggers using inFoods IBS, clinicians can now offer personalized dietary plans backed by clinical and statistical evidence.

Particularly for IBS-C and IBS-M patients, this novel approach offers a breakthrough. Traditional treatments often leave these patients underserved, with few interventions that provide consistent relief. The IgG-guided diet addresses this gap, offering both clinical efficacy and a manageable implementation strategy.

Comparison with Traditional Approaches like Low-FODMAP

The low-FODMAP diet remains a cornerstone in IBS management, but has its drawbacks—it's broad, burdensome, and may disrupt the gut microbiome. More importantly, clinicians cannot currently predict who will benefit.

In contrast, the IgG-guided diet offers:

- A diagnostic assay to identify possible responders (i.e. patients with positive food(s)).
- Targeted elimination of specific personalized foods.
- Less disruption to overall diet due to an implementable solution.

The precision and personalization make it not only clinically effective but also sustainable to relief patient´s symptoms and improve quality of life. .

Limitations and Future Research

Need for Objective Compliance Tracking

A limitation of this study lies in its reliance on self-reported adherence. While daily logs provided basic compliance data, this binary approach—simply reporting whether or not participants

followed the diet each day—offered limited nuance. It couldn't capture partial compliance, deviations in quantity or frequency, or the nature of accidental exposures to restricted foods.

Future research should incorporate objective tracking methods. Digital tools, including app-based food diaries, barcode scanners, and real-time meal photography, could offer deeper insights into how participants engage with their diet. Biomarkers indicating exposure to specific food antigens might also be explored as a way to independently verify adherence.

Understanding real-world compliance is crucial not just for study integrity, but also for refining educational tools, tailoring support systems, and ultimately enhancing long-term outcomes in patients and clinical practice.

Broader Application and Larger Trials

Though this trial is the largest on IgG elimination diet in IBS, it is still an early step of IgG-guided dietary therapy in clinical routine. Recruitment was impacted by the COVID-19 pandemic, resulting in slightly underpowered subgroup analyses. Furthermore, the study duration—eight weeks—may not capture the sustainability of the intervention.

Key future directions:

- **Long-term studies** assessing durability of symptom relief and reintroduction of eliminated foods
- **Larger, stratified trials** specifically targeting IBS subtypes
- **Translational studies** to identify how immune responses to food drive symptoms in IBS patients
- **Treatment trials** comparing IgG-guided dietary therapy with low-FODMAP diet and pharmaceutical treatments
- **Hybrid therapies** combining IgG-guided diet with gut-directed psychotherapies or microbiome-modulating interventions

Additionally, real-world validation in clinical practice is invaluable in demonstrating feasibility, scalability and sustainability.

Conclusion

This randomized, double-blind, multicenter trial provides robust evidence supporting the use of a personalized IgG-guided diet for the management of IBS. The IgG-based diet (inFoods IBS) significantly reduced abdominal pain in IBS patients and improved global symptom scores, particularly among patients with IBS-C and IBS-M.

By shifting away from generalized dietary exclusions toward data-driven, individualized therapy, the IgG-guided diet marks a new frontier in IBS management. It merges the rigor of laboratory

diagnostics with the flexibility of nutritional therapy, offering a tailored approach that takes into consideration patient`s immunological diversity and clinical complexity.

As healthcare continues to embrace personalization, this strategy exemplifies how statistical precision and patient-centered care can converge—delivering better outcomes, fewer side effects, and a more empowered experience for patients navigating the challenges of IBS.

References:

A Novel, IBS-Specific IgG ELISA-Based Elimination Diet in Irritable Bowel Syndrome: A Randomized, Sham-Controlled Trial. Singh, Prashant et al. Gastroenterology, Volume 168, Issue 6, 1128 - 1136.e4

FAQs

1. What is an IgG-guided diet in IBS?
An IgG-guided diet is a personalized dietary treatment that eliminates foods identified as elevated above normal through a lab assay (inFoods IBS). The test is based on IgG responses statistically linked to IBS and aims to alleviate symptoms.

2. How does the inFoods IBS (discriminatory p-value assay) work?
The assay compares food-specific IgG in IBS patients to healthy controls. Foods that trigger significantly (p-value) higher IgG levels than the normal IgG level of healthy controls are considered positive to ensure only the most clinically relevant foods are eliminated.

3. Which IBS patients benefit most from this approach?
Patients with constipation-predominant (IBS-C) and mixed-type IBS (IBS-M) experienced the most clinical benefit in the study. These groups showed the highest symptom reduction rates, particularly in abdominal pain and global improvement scores.

4. How is inFoods IBS different from the low-FODMAP diet?
Unlike the low-FODMAP diet, which restricts broad carbohydrate groups, the IgG-based diet targets specific foods based on the individual`s immune reactivity. This leads to fewer food restrictions and a more personalized, sustainable intervention.

5. What are the next steps for implementing this diet in practice?
The study published in Gastroenterology highlights the benefit of dietary treatment without side effects and offers a new option for practitioners to treat IBS patients who believe their symptoms are triggered by foods. Additionally, training for healthcare providers, development of patient-friendly tools, and integration into clinical routine will be essential for widespread clinical adoption.

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