

Kaiser Permanente Research Brief

Vaccines

This brief summarizes the contributions of Kaiser Permanente Research since 2007 on the topic of vaccines. This includes vaccinations delivered in early childhood as well as those delivered to adolescents and adults.

Although the development of vaccinations against communicable diseases dates back to the 18th century, the creation of modern vaccines and their widespread use in the United States began in the 20th century.¹ Today, the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention provides national recommendations for 15 vaccines, including pertussis (whooping cough) shots for pregnant women and numerous vaccinations delivered to children, adolescents, and adults (see figure below).² Although vaccination has largely eliminated diseases such as measles and rubella in the United States,¹ these and others are still found frequently in countries with lower rates of vaccine coverage,³ and the ease of global travel has led to cases in which unvaccinated persons from well-vaccinated nations have contracted these infections.⁴ Moreover, diseases such as pertussis,¹ varicella (chicken pox)⁵ and human papillomavirus (HPV)⁶ still occur frequently in the United States.

In addition to the direct effect of immunizing patients against dangerous diseases, vaccination also benefits society more broadly through so-called “herd immunity” effects. Through herd immunity, higher rates of effective vaccination for a given illness at a population level confer protection to unvaccinated individuals by making encounters with infected individuals increasingly rare. For example, increased uptake of the pediatric pneumococcal vaccine has been associated with decreased rates of the disease among adults, many of whom have not, until recently, received this vaccine.^{7,8} The level of vaccination coverage required to create herd immunity for a given disease depends on both the

Kaiser Permanente Publications Related to Vaccines since 2007



Source: Kaiser Permanente Publications Library and PLUM metrics, as of October 19, 2020.

a Number of citing journal articles, according to Scopus.

b Number of references in PubMed guidelines.

c Citations in DynaMed Plus, a point-of-care clinical reference tool.

This brief summarizes a selection of the publications contained within the Kaiser Permanente Publications Library, which indexes journal articles and other publications authored by individuals affiliated with Kaiser Permanente. The work described in this brief originated from across Kaiser Permanente's 8 regions and was supported by a wide range of funding sources including internal research support as well as both governmental and nongovernmental extramural funding.

vaccine's effectiveness and how easily the disease is transmitted between unvaccinated persons.

Vaccination is an active area of study for Kaiser Permanente Research. Scientists across the organization have used our rich, comprehensive, longitudinal data to advance knowledge in the areas of understanding risk, improving patient outcomes, and translating research findings into policy and practice. We have published nearly 600 articles related to vaccines since 2007. Together, these articles have been cited approximately 14,000 times.

These articles are the product of observational studies, randomized controlled trials, meta-analyses, and other studies led by Kaiser Permanente scientists. Our unique environment, which includes our fully integrated care and coverage model, lets our research scientists, clinicians, medical groups, and health plan leaders collaborate to contribute generalizable knowledge on vaccines, and many other topics of research.

Understanding Risk

Kaiser Permanente researchers have contributed to understanding vaccine safety and the risks of acquiring vaccine-preventable diseases.

Who is at risk of acquiring vaccine-preventable communicable diseases?

Any person who has not been vaccinated against a particular disease and encounters a person infected with that disease is at risk of infection themselves. Additionally, no vaccine is 100% effective in preventing disease transmission, so vaccinated persons may continue to be at risk.^{9,10} In children, undervaccination (either delaying or not receiving vaccines) appears to be increasingly common.¹¹ Parental refusal of vaccines has been associated with outbreaks of measles, pertussis, varicella, Haemophilus influenzae type b (Hib), and pneumococcal disease,¹² and our recent studies have linked parental hesitancy with significantly higher rates of pertussis,¹³ varicella,¹⁴ and pneumococcal disease.¹⁵ Another study conducted by our scientists found lower rates of vaccination in children diagnosed with autism spectrum disorder, as well as their younger siblings.¹⁶ Our researchers also have found

higher rates of infection in children who failed to complete all courses of multicourse vaccines.¹⁷ In some instances, delaying vaccinations can increase the risk of side effects. For example, delayed receipt of measles-mumps-rubella (MMR) or measles-mumps-rubella-varicella (MMRV) vaccine has been associated with a higher risk of febrile seizures.¹⁸ Infants too young to be vaccinated against particular diseases are also at risk of acquiring those diseases; research has found that preterm infants may have lower immune

The CDC's Advisory Committee on Immunization Practices sets national guidelines for recommended vaccines.²

Childhood

(BIRTH TO 10 YEARS)

- Pertussis (during pregnancy)
- Diphtheria, Tetanus and Pertussis
- Hepatitis A, Hepatitis B
- Polio
- Pneumococcal
- Haemophilus Influenza Type B (Hib)
- Measles, Mumps, Rubella and Varicella
- Rotavirus
- Annual Flu (beginning at 6 months)



Adolescence

(11 TO 18 YEARS)

- Human Papillomavirus (HPV)
- Meningococcal Conjugate
- Tetanus, Diphtheria and Pertussis
- Annual Flu



Adulthood

(19+ YEARS)

- Annual Flu
- Tetanus and Diphtheria (with/without Pertussis)
- Herpes Zoster (at Age 50)



Kaiser Permanente scientists have developed and tested programs that address parental concerns about vaccinating their young children.



Beginning during pregnancy and continuing through infancy, physicians should provide information about vaccines, and work actively to build trust with hesitant parents¹⁰¹⁻¹⁰³

A website featuring vaccine information and social capabilities that allows parents to communicate and share information is associated with improved vaccination rates¹⁰⁶⁻¹⁰⁸



responses to vaccines,¹⁹ while neonatal intensive care unit-treated infants may not receive all appropriate vaccines.²⁰

In adults, our research has found higher risks of herpes zoster²¹ and influenza²² among the unvaccinated, and cervical cancer may be more common among women who do not receive HPV vaccination during adolescence.²³ Individuals with weakened immune systems also are at higher risk of acquiring vaccine-preventable diseases. For example, reactivation of latent herpes zoster infection is more likely to occur in patients using immunosuppressive drugs.²⁴

How safe are vaccines?

Because vaccines are, by definition, delivered to large numbers of healthy individuals, they are judged by very strict standards of safety, and regulatory approval is only granted to vaccines with extremely low observed risks. Kaiser Permanente researchers have been involved in studying the safety of meningococcal,²⁵⁻³⁵ pneumococcal,^{36,37} HPV,³⁸⁻⁴² MMR,⁴³ MMRV,⁴⁴⁻⁴⁶ tetanus-diphtheria-pertussis (Tdap),⁴⁷⁻⁵⁰ diphtheria-tetanus-pertussis (DTaP)-polio,⁵¹⁻⁵³ flu,⁵⁴⁻⁶⁸ shingles,⁶⁹ pertussis,⁷⁰

hepatitis A^{71,72} and hepatitis B⁷³ vaccines, among others.⁷⁴⁻⁷⁹ Nevertheless, the rarity of problems with vaccine safety makes the prediction of these risks challenging, and requires considerable research expertise^{80,81} and ongoing surveillance.⁸²⁻⁸⁴

Allergic reactions such as swelling or soreness at the vaccination site,⁸⁵⁻⁸⁸ and complications such as febrile seizures^{89,90} or fevers,^{91,92} are known side effects of vaccines, though these are rarely associated with long-term health problems.⁹³ Our scientists have led studies linking febrile seizure risks to specific vaccines, including the MMRV⁹⁴⁻⁹⁷ and influenza⁹⁸ vaccines. Elderly patients have also experienced higher rates of adverse effects from the shingles⁸⁶ and tetanus-diphtheria-pertussis (Tdap)⁹⁹ vaccines, although these risks are arguably outweighed by the benefits of these vaccines, such as prevention of neuralgic pain and tetanus or diphtheria infection.

Improving Patient Outcomes

What strategies are effective in increasing vaccination rates?

Our researchers have explored a variety of approaches for increasing vaccination rates. In general, the approaches used for early-childhood vaccination are very different from those used for other types of vaccines. Successful interventions for increasing vaccine uptake in young children include physician-oriented approaches to address parental hesitancy,¹⁰⁰⁻¹⁰⁵ tailored messages delivered via social media,¹⁰⁶⁻¹⁰⁹ school-based vaccination,¹¹⁰⁻¹¹³ and community-based education (for example, public-service announcements).^{114,115} In contrast, outreach approaches that have been shown to increase adolescent and adult uptake of vaccines include workplace vaccination programs^{116,117} and reminders placed in the electronic health records of patients or parents.^{110,118,119}

How effective is vaccination in preventing the transmission of communicable diseases?

Kaiser Permanente researchers have been actively involved in research on vaccine effectiveness, including herd immunity effects^{13,120-122} and pro-

tection of vulnerable populations, including the elderly,¹²³⁻¹²⁶ infants,¹²⁷⁻¹³³ those with suppressed immune systems,^{24,134} and people with certain chronic diseases.^{135,136} Other Kaiser Permanente research has identified shortcomings in vaccine effectiveness. Numerous studies of annual flu vaccinations have identified waning effects over time,¹³⁷⁻¹³⁹ differences in effectiveness between vaccine types,^{140,141} and variable effectiveness from year to year.^{22,142,143} More recently, we have repeatedly found evidence of the waning effectiveness of the pertussis¹⁴⁴⁻¹⁴⁹ and herpes zoster^{150,151} vaccines. This work contributed directly to changes in the ACIP's recommendations regarding immunization for these conditions. Finally, our scientists are actively involved in randomized trials evaluating the effectiveness of co-administering multiple vaccines to adolescents⁷⁷ and adults.⁷⁹

How does vaccination affect a person's health?

Vaccine-preventable diseases carry serious and well-known health risks, including cervical cancer from HPV, liver failure from hepatitis, meningitis from Hib, and death from illnesses such as influenza, pertussis, or hepatitis. Vaccination affects health in numerous ways beyond the transmission of communicable diseases. For example, vaccination in pregnant women has been shown to transmit immunity to their children,¹⁵²⁻¹⁵⁴ and annual flu vaccinations appear to have small but statistically significant effects on mortality and hospitalization rates,^{123,155-158} and on numbers of outpatient visits.¹⁵⁹

Translating Research Findings Into Policy and Practice

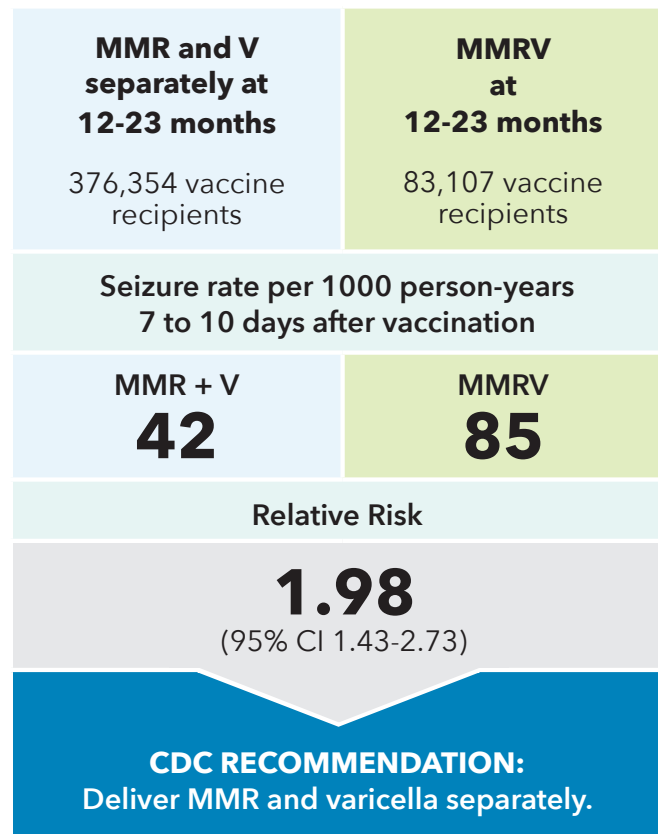
How has Kaiser Permanente research on vaccines contributed to changes in policy and practice?

As part of a learning health care organization that uses research to inform and improve practice, our research, clinical, and operational partners have tested a range of interventions to increase uptake of recommended vaccines. Pediatricians in Kaiser Permanente have worked to address

parental vaccine hesitancy,^{101,160,161} leading to the development and evaluation of messaging interventions.^{102,107} This work was subsequently expanded to flu and HPV vaccination. Reminders placed in Kaiser Permanente's electronic health record system have been used to inform changes in vaccination policies,^{84,162-165} including a change in herpes zoster vaccines. Our scientists have also explored multicomponent programs for increasing rates of HPV vaccination.¹⁶⁶

Collectively, research from Kaiser Permanente authors has been cited more than 200 times in recent consensus statements, and in the vaccination guidelines for influenza,¹⁶⁷ HPV,¹⁶⁸ herpes zoster,¹⁶⁹ Tdap¹⁷⁰ and MMRV¹⁷¹ published by the CDC's Morbidity and Mortality Weekly Report. Our research has also directly influenced national vaccines policies. One study of febrile seizure risks associated with the first injection of MMRV versus MMR separately from varicella found that

The Vaccine Safety Data link demonstrated increased seizure risk with MMRV versus delivering MMR and varicella in separate injections.⁹⁴



those receiving MMRV were twice as likely to experience seizures 7 to 10 days after vaccination.⁹⁴ This led the CDC to recommend that the first MMR and varicella shots be given separately (unless the parent wishes their child to receive MMRV).^{18,171} Work questioning the durability of the pertussis vaccine delivered to children^{145,149} led to increased emphasis on prenatal vaccination,¹⁵² and other work¹⁵⁰ prompted uptake of a newer zoster vaccine.¹⁵¹

Kaiser Permanente has also shown considerable leadership in the field of vaccine research. Our researchers are leaders in the CDC's Vaccine Safety Datalink, or VSD, an ongoing effort to use data from large health care organizations to evaluate vaccine safety.^{172,173} In the VSD, which began in 1990, 5 of our regions contribute electronic patient data that are used to study rare but serious adverse reactions, and monitor the safety of new vaccines or changes in vaccine recommendations. Vaccine safety in pregnancy is an emphasis of VSD research, along with the development of new research methods and rapid cycle analysis techniques for promptly notifying the public of possible risks.¹⁷⁴⁻¹⁷⁷ We are also involved in the U.S. Flu Vaccine Effectiveness Network, which provides interim and annual estimates of the effectiveness of each year's flu vaccine by studying individuals entering health care facilities during flu season.¹⁷⁸⁻¹⁸⁴ Our researchers continue to be involved in early-stage vaccine development through the large, long-standing vaccine clinical trials program in the Northern California Vaccine Study Center, and through the National Institutes of Health's Vaccine and Treatment Evaluation Network.¹⁸⁵ The VTEU, based in Kaiser Permanente's Washington Region, is the only such unit in the country housed in an integrated health system. Finally, our scientists are part of numerous vaccine clinical trials in response to the COVID-19 pandemic. The VTEU was the lead site for the first-ever trial of a COVID-19 vaccine, evaluating the vaccine developed by Moderna Therapeutics and the National Institute of Allergy and Infectious Diseases.^{186,187} Our researchers were involved in several late-phase efficacy trials, including trials of the vaccines developed by Pfizer, Inc. and BioNTech, Moderna/NIAID, and Johnson & Johnson.¹⁸⁸

Kaiser Permanente's nearly 170 research scientists and more than 1,600 support staff are based at 8 regional research centers and 1 national center. There are currently more than 2,400 studies underway, including clinical trials. Since 2007 our research scientists have published more than 12,000 articles in peer-reviewed journals. Kaiser Permanente currently serves more than 12.4 million members in 8 states and the District of Columbia.

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