



Shots, Safety, and Science

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Akron Children's Hospital



Objectives

At the conclusion of this activity, participants will be able to:

- **Differentiate** the inactivated, subunit and conjugate, live attenuated, and mRNA platforms by mechanism of antigen presentation, and anticipate the dosing, contraindication, and storage requirements that follow from each
- **Explain** the function of aluminum adjuvants in non-live pediatric vaccines and apply current exposure and safety data when counseling families
- **Describe** how efficacy and safety are established through phased trials, immunobridging, and post-licensure surveillance, and identify what each method can and cannot detect
- **Apply** these principles to MMR, including strain development, immunogenicity and effectiveness by component, and dosing before 12 months and on catch-up





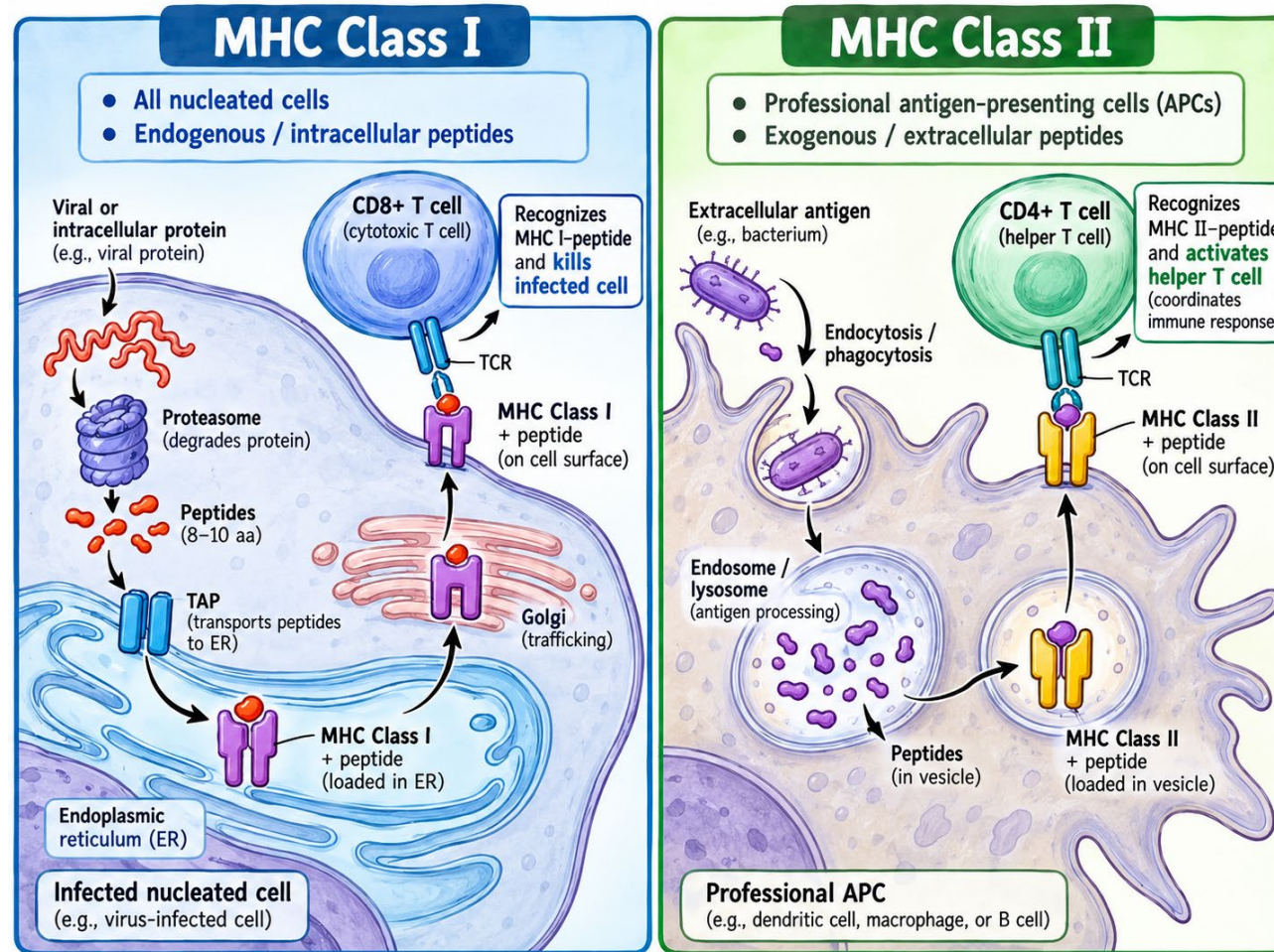
The Basics: how vaccines work

Types of Vaccines

- **Inactivated Vaccines**
- Sub-Component & Conjugated Vaccines
- Live Vaccines
- mRNA Vaccines



Review: the antigen presentation engines





Where the antigen is made decides everything

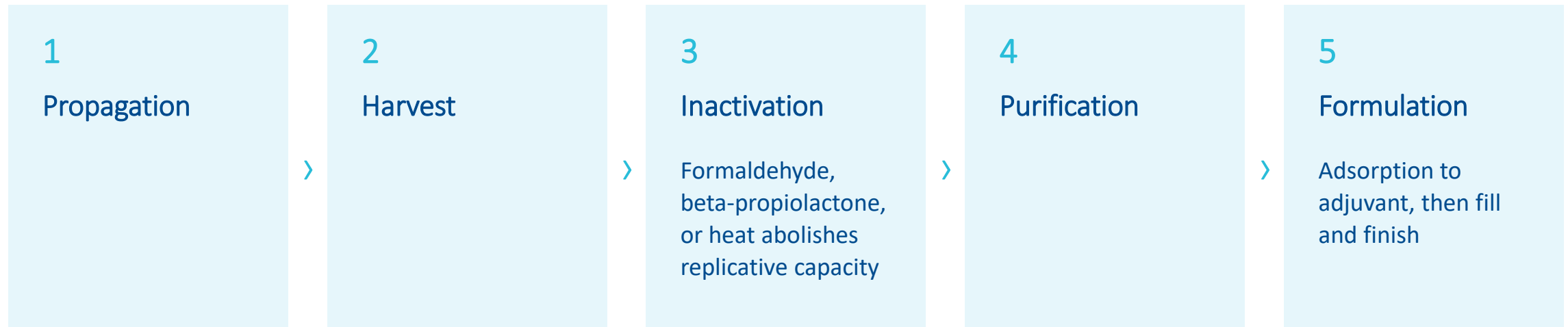
	MHC class I	MHC class II
Found on	Every nucleated cell	Dendritic cells, macrophages, B cells
Peptides from	Proteins made INSIDE the cell	Material taken up from OUTSIDE the cell
Read by	CD8 cytotoxic T cells	CD4 helper T cells
Question	Is this cell making something foreign?	What is out there?
Consequence	Kill the infected cell	License B cells; activate macrophages

Where the antigen is introduced affects which pathway it enters, and that affects what kind of immunity results





Inactivated vaccines: definition and manufacture



Release testing must demonstrate the absence of residual infectivity in every lot.

Goal: abolish infectivity, preserve the key antigen epitopes





Antigen Presentation & Immune Response

Antigen Presentation

- Antigen is delivered in non-replicating form
- Uptake by antigen presenting cells
- Peptides displayed on MHC class II
- Important Limitations:
 - Limited entry into the cytosol -> poor MHC class I loading
 - Antigen quantity is fixed
 - Antigen is rapidly cleared (days)



Immune Response

- B-Cell and CD4 T-Cell activation
- Class switching and affinity maturation (CD4 dependent)
- Final Immune State: Circulating IgG, long-lived plasma cells, memory B cells
- Important Limitations
 - Limited CD8 response
 - No mucosal IgA

The platform determines the pathway, and the pathway determines the effector profile: antibody-dominant immunity with limited cytotoxic and mucosal components.





Common Properties of Inactivated Vaccines

- **Multi-dose schedules**
 - Affinity maturation and long-lived plasma cell generation require repeated antigen exposure over time, not a larger single dose
- **Adjuvant dependence**
 - Prolongs antigen availability and supplies the innate activation that a non-replicating antigen cannot provide
- **Waning immunity**
 - Booster doses are required; duration of protection is measured in years rather than decades
- **Cannot revert or spread**
 - Permissible in immunodeficiency, in pregnancy, and in household contacts of immunocompromised patients
- **Antibody-dominant profile**
 - Limited cytotoxic T cell priming and, with intramuscular delivery, limited mucosal immunity
- **Formulation stability**
 - Substantially less vulnerable to cold chain excursion than live attenuated products



Key Limitations of Whole Inactivated Vaccines

- Off-Target Antigens
 - Reactogenicity (Whole-Cell Pertussis)
 - Non-neutralizing antibody (Inactivated RSV)
 - Molecular mimicry (Men-B Vaccines)
- Polysaccharide Antigens
 - T-Cell Independent Response
 - Less durable
 - Very limited under 2 years of age



Types of Vaccines

- Inactivated Vaccines
- **Sub-Component & Conjugated Vaccines**
- Live Vaccines
- mRNA Vaccines



Sub-Component Vaccines: Avoiding Off-Target Effects

- Concept
 - Do not include the whole organism
 - Produce only the antigens required for neutralizing antibody
- Examples
 - Acellular pertussis
 - Decreased reactogenicity
 - Cost: TH2 instead of TH1 & TH17 response
 - Men B
 - Avoid molecular mimicry by targeting protein sub-component





Conjugation: Smuggling in a T-Cell to help a B-Cell

1

A B cell recognizes polysaccharide antigen also ingests the conjugated protein



2

Processes attached PROTEIN and displays on MHC II



3

CD4 helper T cells recognize protein antigen and deliver help



4

B cell making anti-polysaccharide antibody receives help it could never have recruited alone

Hib has: class switching to IgG, affinity maturation, memory, a real booster response, protection in infants — and reduced nasopharyngeal carriage, which protects the unvaccinated.

Pollard AJ, Bijker EM. Nat Rev Immunol. 2021;21(2):83-100 · Warfel JM, et al. Proc Natl Acad Sci U S A. 2014;111(2):787-792



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Types of Vaccines

- Inactivated Vaccines
- Sub-Component & Conjugated Vaccines
- **Live Vaccines**
- mRNA Vaccines



Not a new idea

- 1st Vaccine (Jenner/Vaccinia)
 - Attenuated by nature
 - Still resulted in effective immunity
- Pasteur (Chicken Cholera/*Pasteurella multocida*)
 - Attenuated intentionally by culture technique
 - Still resulted in effective immunity
- Calmette & Guerin (BCG/*Mycobacterium bovis*)
 - Attenuated by serial passaging
 - Conceptually closest to the modern viral vaccine attenuation techniques





Live attenuated vaccine basics

What replication adds

- Antigen self-amplifies (no adjuvant)
- Viral protein inside host cells: MHC class I, CD8 response
- Full antigenic repertoire, native conformation
- Durable, often lifelong after one or two doses

What replication costs

- **Immunosuppression:** Symptomatic infection (e.g., measles inclusion body encephalitis)
- **Pregnancy:** Theoretical potential for fetal infection
- **Reversion to Wild Type:** Vaccine-derived poliovirus
- **Interference:** Response sensitive to IG or other live-vaccine co-administration
- **Fragile:** Improper storage fails silently

Note: Durable immunity from vaccination is most likely when infection with the wild-type organism also produces durable immunity

Pollard AJ, Bijker EM. Nat Rev Immunol. 2021;21(2):83-100 · ACIP. MMWR Recomm Rep. 2013;62(RR-4):1-34



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Types of Vaccines

- Inactivated Vaccines
- Sub-Component & Conjugated Vaccines
- Live Vaccines
- **mRNA Vaccines**





mRNA: features of both ends

	Inactivated	mRNA	Live attenuated
Antigen made inside host cells	No	Yes	Yes
MHC class I / CD8 response	Minimal	Yes	Yes
Agent replicates	No	No	Yes
Can revert or disseminate	No	No	Yes
Safe in immunocompromise	Yes	Yes	No
Needs a separate adjuvant	Usually	No	No

Live-vaccine antigen presentation with killed-vaccine safety. The LNP is self-adjuvanting, which is why reactogenicity is high

Pollard AJ, Bijker EM. Nat Rev Immunol. 2021;21(2):83-100



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Why adjuvants exist

The immune system does not respond to foreignness alone. It responds to foreignness plus evidence that something is wrong. A purified protein delivers the first without the second.

- **Possible/Proposed Explanations:**
- **Depot effect.** Proposed 1926. Largely discredited: adsorbed antigen desorbs rapidly, and stable adsorption is not required for adjuvanticity
- **Enhanced uptake.** Particulate antigen is phagocytosed far more efficiently than soluble protein
- **Danger signals.** Local cell injury releases DAMPs including host DNA and uric acid
- **NLRP3 inflammasome.** Real, but necessity disputed; NLRP3-deficient mice still respond to alum
- **Chemokine recruitment.** Monocytes and dendritic cells drawn to the injection site

Aluminum has been in use for nearly a century and the mechanism is still contested. Its consequence is a Th2-polarized, antibody-dominant response

Zhu M, et al. *Pharmaceutics*. 2023;15(6):1756 · He P, et al. *Hum Vaccin Immunother*. 2015;11(2):477-488



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Aluminum in the pediatric schedule

Contains aluminum

- DTaP, Tdap, DT, Td
- Hepatitis A and B
- HPV
- Pneumococcal conjugate
- Meningococcal B
- Hib (some formulations)

AT BIRTH

~384 µg body burden from in utero exposure

FROM DIET

~0.03 mg/day breast milk, ~0.15 mg/day formula, under 1% absorbed

Contains none

- MMR
- MMRV, varicella
- Rotavirus
- IPV
- Most influenza vaccines

ACROSS YEAR ONE

Vaccines add somewhat more than diet. Modelled burden stays below the minimal risk level

No live vaccine contains an adjuvant. Replication supplies what the adjuvant would.





Splitting the shots usually means more aluminum

Same coverage at the 2-month visit	Aluminum per dose
Vaxelis (hexavalent)	0.32 mg
Infanrix + Engerix-B + PedvaxHIB + IPOL	0.98 mg
Daptacel + Engerix-B + ActHIB + IPOL	0.58 mg
Pediarix (covers only DTaP, HepB, IPV)	0.70 mg

Not because combining reduces aluminum. Content tracks FORMULATION, not valency — Pediarix covers less and contains more





The evidence, and the conversation

Danish nationwide cohort, 2025: 1,224,176 children born 1997-2018, cumulative vaccine aluminum by age 2, 50 chronic conditions across autoimmune, atopic and neurodevelopmental categories.

- **Adjusted hazard ratios.** 0.98 autoimmune · 0.99 atopic/allergic · 0.93 neurodevelopmental
- **For most outcomes,** upper confidence bounds were incompatible with relative increases above 10%, and for nearly all, above 30%
- **But most point estimates fall BELOW 1.0,** several significantly: food allergy 0.84, ADHD 0.90. Aluminum is not protective against ADHD

This study excludes moderate-to-large harm. It does not demonstrate zero effect. The sub-1.0 pattern is a signature of residual confounding





The four questions you will actually be asked

- ***"How much aluminum is my baby getting?"***
 - Background diet, what the schedule adds, where the total sits against an independently set threshold.
- ***"Why is it in there at all?"***
 - Not a preservative, not a filler. It is what makes a non-live vaccine work.
- ***"Can I get the vaccine without it?"***
 - No. The aluminum-free version is not a purer product; it is one that does not work.
- ***"So many at the same time?"***
 - Glanz 2018, VSD: cumulative antigen exposure and non-vaccine-targeted infections, OR 0.94 (0.84-1.07).

Antigen load has FALLEN: ~3,000 antigens on the 1980 schedule, ~150-160 today. The honest exception: IIV with PCV13 and DTaP at one visit modestly raises febrile seizure risk





Licensing a genuinely new vaccine

Phase	N	Primary question
Preclinical	—	Does it work in animals? Can it be made consistently?
Phase 1	Tens	Safety
Phase 2	Hundreds to low thousands	Safety; dose and schedule selection
Phase 3	Thousands to tens of thousands	Efficacy AND safety
Post-licensure	Millions	Rare events, effectiveness, waning

A 1-in-100,000 event is invisible to any phase 3 trial ever run





Three surveillance systems, three questions

	What it answers	What it cannot do
VAERS Passive; anyone may report	Is there a signal worth investigating?	Establish causation. No denominator, no control group
Vaccine Safety Datalink Active, defined populations	Does the rate differ from the unvaccinated or differently vaccinated?	Detect events too rare even for millions
CISA Clinical consultation network	What happened to this patient, and can they be revaccinated?	Population-level inference

VAERS asks the question. VSD answers it. The febrile seizure interaction was found exactly this way





When the classical trial is impossible

Four situations: the disease is gone · placebo would be unethical · age or population extension · formulation or manufacturing change.

- **The substitute is immunobridging.** Measure the immune response instead of the disease, and argue that a comparable response implies comparable protection
- **Measles.** Correlate of protection established at 120 mIU/mL. The bridge is solid
- **Rubella.** Correlate established at 10 IU/mL. Solid
- **Mumps.** NO established correlate of protection. The 10 IU/mL figure is a seroconversion threshold standing in for a protection threshold nobody has determined





MMR as a worked example

Rubella: clinical characteristics

AGENT

Rubivirus, Matonaviridae

RESERVOIR

Humans, the only natural host

INCUBATION

17 days (range 12-23)

INFECTIOUS PERIOD

The week before and after rash

Postnatal rubella

- Up to half of infections are subclinical
- Maculopapular rash starting on the face, generalizing within 24 hours, median 3 days
- Posterior auricular and suboccipital lymphadenopathy 5-8 days
- **Arthralgia and arthritis.** Rare in children, common in adolescent and adult women
- **Encephalitis 1 in 6,000.** Thrombocytopenia 1 in 3,000

Congenital rubella syndrome

- Cataracts, pigmentary retinopathy, congenital glaucoma
- PDA, peripheral pulmonary artery stenosis
- Sensorineural hearing loss
- Microcephaly, developmental disability
- **Risk highest in the first 12 weeks of gestation, rare after 20**

The mother who transmits may never have had a rash. Protection has to be in place before conception.

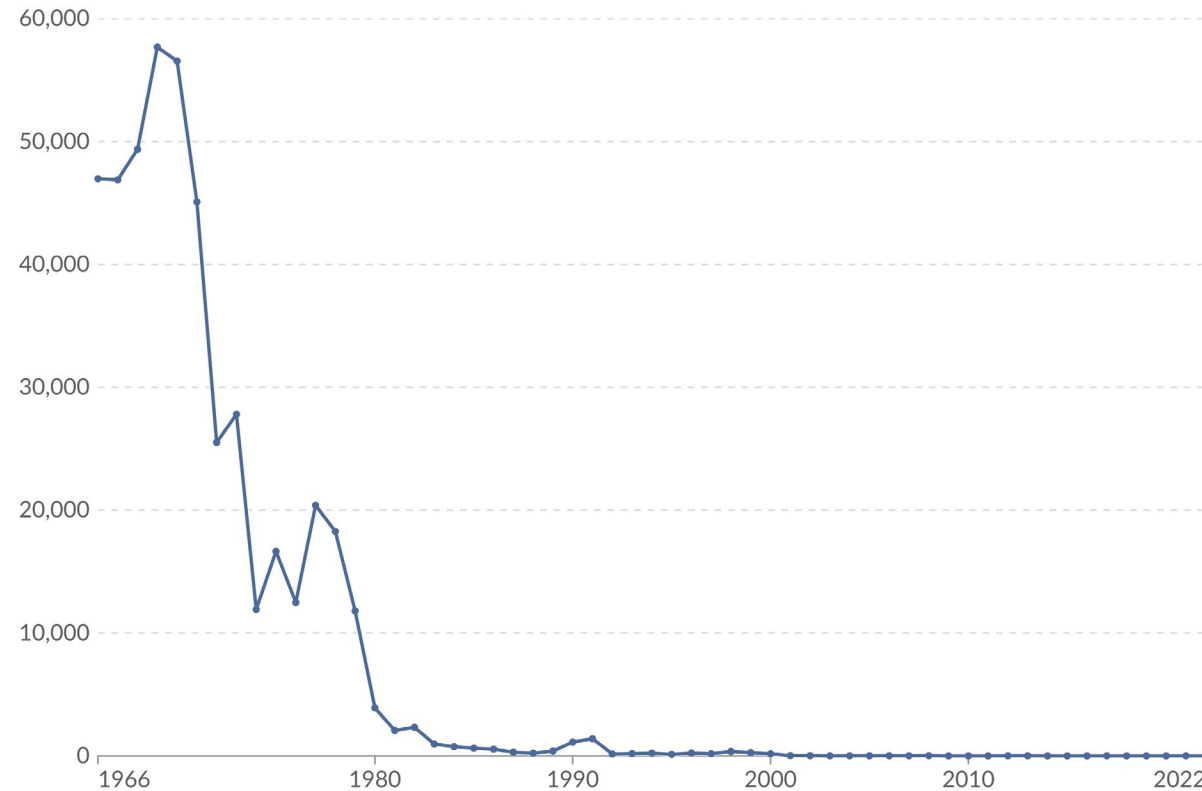
AAP. Red Book. 33rd ed. 2024:735-741 · ACIP. MMWR Recomm Rep. 2013;62(RR-4):1-34



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Rubella: epidemiology



- **Prevaccine.** Epidemics every 6-9 years. The 1964-65 epidemic: ~12.5 million cases, 11,250 fetal deaths, 2,100 neonatal deaths, 20,000 infants born with CRS
- **Vaccine era.** Licensed 1969. Cases fell 78%, from 57,686 to 12,491 by 1976. CRS fell 69%
- **Resurgence 1989-91.** Unvaccinated adolescents, young adults, and religious communities with low coverage. Two clusters of ~20 CRS cases
- **Since 2012,** every reported US case has had evidence of acquisition abroad

20,000

infants with CRS in the 1964-65 epidemic

78%

fall in cases, 1969 to 1976

2004

elimination declared





Mumps: clinical characteristics

AGENT	INCUBATION	INFECTIOUS PERIOD	ISOLATION
Orthorubulavirus, Paramyxoviridae, 12 genotypes	16-18 days	From 2 days before parotitis	5 days after swelling onset

Acute illness

- The only known cause of epidemic parotitis
- **Parotitis in ~95% of symptomatic cases**, initially unilateral, contralateral involvement in 70%
- About one fifth of infections in unvaccinated people are asymptomatic

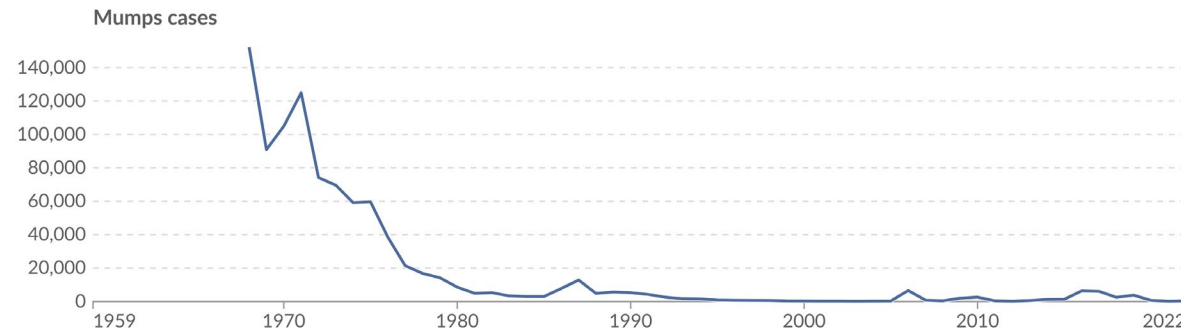
Complications, prevaccine vs vaccinated

- **Orchitis 12-66% prevaccine, 3-11% vaccinated.** Roughly half of affected testes atrophy. Sterility uncommon even with bilateral involvement
- **CSF pleocytosis in more than half of cases;** symptomatic meningitis in fewer than 1%
- **Aseptic meningitis 0.2-10% prevaccine, under 1% vaccinated**
- **Encephalitis 0.02-0.3% prevaccine, under 0.3% vaccinated**

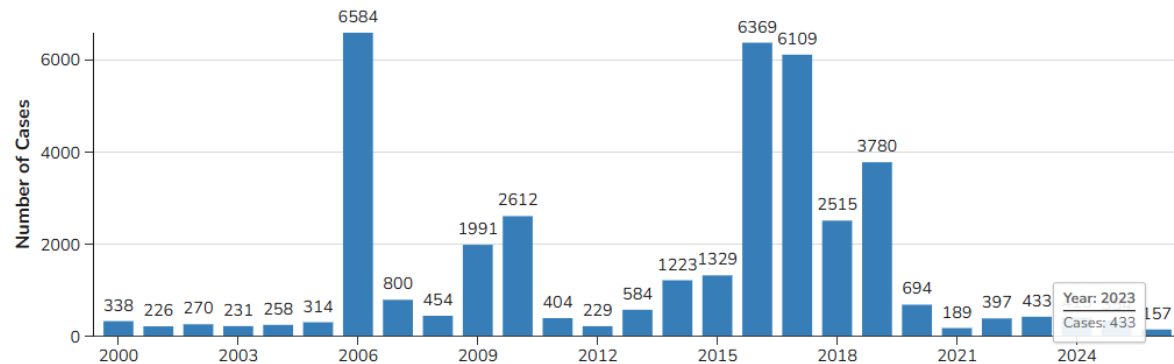
Vaccination lowers every complication rate on this slide. It does not drive any of them to zero.



Mumps: epidemiology



Detail: reported cases, 2000-2026



152,209

cases reported in 1968

99%

decline after the two-dose policy

70%

of 2016-17 outbreak cases had received two doses

- **Prevaccine.** Universal disease of childhood; most children infected by 14
- **Licensed 1967**, routine 1977, second dose arrives 1989 as a byproduct of the two-dose measles policy. Fewer than 300 cases per year, 2000-2005
- **Then it comes back in vaccinated people.** 2006: 6,584 cases in midwestern colleges. 2016-17: over 6,000 each year. 2019: over 3,500
- **Jan 2016 to Jun 2017:** 150 outbreaks, 9,200 cases, half in universities, median age 21. Circulating genotype is G; the vaccine strain is genotype A





Measles: clinical characteristics

AGENT

Morbillivirus, Paramyxoviridae, one serotype

TRANSMISSION

Airborne

INCUBATION

11-12 days to prodrome, 14 to rash

INFECTIOUS PERIOD

4 days before through 4 days after rash

Acute illness

- **Attack rate 90% in susceptible close contacts.** Population immunity of 95% or higher is required to interrupt transmission
- **Common complications.** Otitis media 7%, pneumonia 6%, diarrhea 8%
- **Encephalitis ~1 in 1,000.** Death 1-3 per 1,000 reported cases in the postelimination United States

Delayed consequences

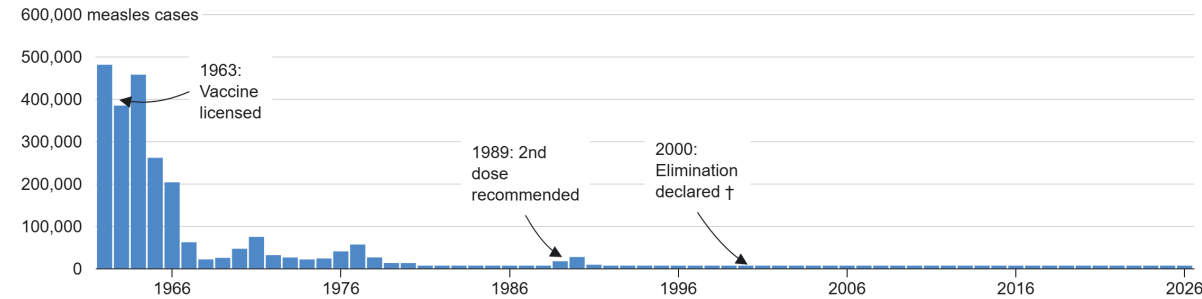
- **SSPE 4-11 per 100,000 cases**, onset typically 7-11 years later, highest in children infected before age 2
- **MIBE** in immunocompromised hosts, within a year, high mortality
- **Immune amnesia.** Suppression of cell-mediated immunity with increased susceptibility to other pathogens for years afterward

SSPE and immune amnesia are counted years after the acute illness has resolved.

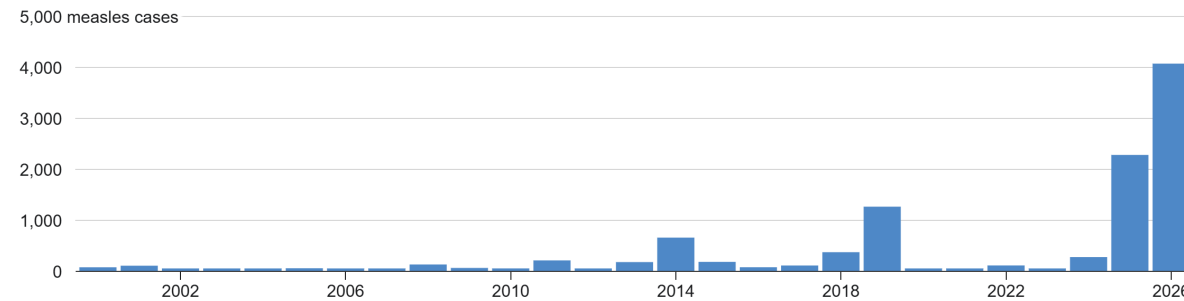


Measles: epidemiology

Reported Measles Cases in the United States from 1962-2026*



Detail: reported cases, 2000-2026, as of 8 October 2026



- **Prevaccine.** 3-4 million infections annually; ~500,000 reported, 48,000 hospitalized, 1,000 with permanent brain damage, 400-500 deaths each year
- **1989-91 resurgence.** ~55,000 cases, 120 deaths. Drives the two-dose recommendation and the Vaccines for Children program. Elimination declared 2000
- **2024: 285. 2025: 2,289. 2026: 4,080 through 8 October**, with 95% outbreak-associated
- **Of 2024 cases**, 40% were hospitalized, rising to 52% of children under 5

3,471

cases in 2026 through 17 September

92.4%

kindergarten MMR coverage, down from 95.2% in 2019-20

89%

of 2024 cases unvaccinated or unknown status





When the platform is wrong: inactivated measles vaccine

March 1963: two measles vaccines licensed on the same day. Merck's live attenuated Rubeovax, and Pfizer's formalin-inactivated Pfizer-Vax Measles-K.

- **Live.** Antibody in over 95% of susceptible children, but 30-40% developed fever and rash. Blunted by coadministering gamma globulin
- **Inactivated.** Minimal immediate side effects. Lower antibody titers, duration unknown beyond six months
- **1965-67.** Children given killed vaccine and later exposed to wild measles developed a severe illness Fulginiti named atypical measles. Immunity had waned by six months
- **MRC trial, 36,000+ British children.** Single-dose live gave better two-year protection (95%) than killed-followed-by-live (89%). Conclusion: live vaccine alone
- **Practical residue.** Inactivated measles vaccine was available in the US 1963-1967. Recipients are considered unvaccinated and require revaccination

The inactivated vaccine was the safer-looking product. Reactogenicity is not the same as risk, and absence of reactogenicity is not evidence of safety





Building the three strains

Component	Strain	Substrate	Origin
Measles	Enders' Edmonston, further attenuated (Moraten)	Chick embryo cell culture	Isolated by Enders and Peebles, 1954, from a boy named David Edmonston
Mumps	Jeryl Lynn (B level)	Chick embryo cell culture	Isolated from Maurice Hilleman's daughter
Rubella	Wistar RA 27/3	WI-38 human diploid lung fibroblasts	Isolated by Plotkin from a fetus infected with congenital rubella





What M-M-R II actually is

Lyophilized preparation of three live attenuated viruses, reconstituted with supplied sterile diluent. Approximately 0.5 mL per dose. Initial US approval 1978.

- **Minimum potency per dose.** Measles $\geq 3.0 \log_{10}$ TCID₅₀ · mumps $\geq 4.1 \log_{10}$ TCID₅₀ · rubella $\geq 3.0 \log_{10}$ TCID₅₀
- **Route: intramuscular or subcutaneous** per the package insert revised November 2025. PRIORIX is subcutaneous only. Several widely used references still say subcutaneous only and are out of date
- **Storage.** -50°C to $+8^{\circ}\text{C}$, protected from light. Reconstituted vaccine used immediately or held at $2-8^{\circ}\text{C}$ in the dark for up to 8 hours
- **MMRV differs.** Stored frozen -50°C to -15°C , and discarded within 30 minutes of reconstitution
- **Monovalent measles, mumps, and rubella vaccines** are no longer commercially available in the United States





WI-38 and RA 27/3: two fetal origins

RA 27/3: the virus

- Isolated by Stanley Plotkin
- From a fetus infected with congenital rubella
- This is the rubella vaccine strain itself

WI-38: the cell substrate

- Derived by Leonard Hayflick at the Wistar Institute, 1962
- Human diploid lung fibroblasts
- From the lungs of a female fetus following a legal elective abortion in Sweden
- The substrate in which the rubella component is grown

Two separately sourced components, from two different fetuses.



WI-38 and RA 27/3: two questions

Why a human cell line at all?

- The alternative was primary monkey kidney cells
- Frequently contaminated with simian viruses, especially SV40
- SV40 produced tumors in animals and transformed human cells
- A single-donor human strain could be frozen, characterized and tested before use in manufacture

Was consent obtained?

- No contemporaneous documentation exists
- The principals in Sweden are dead; Hayflick did not know
- Located decades later by a journalist, the mother said she had not been asked
- Helsinki 1964, Karolinska ethics committee mid-1960s, US human subjects regulations 1974. All after 1962

Further reading: Pontifical Academy for Life (2005) · Dignitas Personae n. 35 (2008) · CDF note (December 2020)





Immunogenicity and effectiveness

	Seroconversion, 1 dose	VE, 1 dose	VE, 2 doses	Duration
Measles	96% (84-100)	93% (39-100)	97% (67-100)	≥11 yr / ≥15 yr
Rubella	99% (95-100)	97% (94-100)	—	≥16 yr / ≥15 yr
Mumps	94% (89-97)	78% (49-92)	88% (66-95)	≥10 yr / ≥15 yr

Median (range). ACIP 2013, Table 1.





Licensing a vaccine when you cannot run an efficacy trial

M-M-R II's own efficacy evidence comes from controlled trials run between 1962 and 1972.

- **Approved June 2022.** Compared with M-M-R II for immunogenicity and safety, not efficacy
- **Evidence base.** 13 randomized trials for humoral immunity; 4 at licensed US potency for serious adverse events; observational studies for febrile seizures, aseptic meningitis and ITP
- **Result.** Fully interchangeable with M-M-R II, including off-label uses with no direct evidence

WHAT THE SEROLOGY WAS JUDGED AGAINST

Component	Threshold used	What that threshold is
Measles	200 mIU/mL	Above the established correlate of protection, 120 mIU/mL
Rubella	10 IU/mL	An established correlate of protection
Mumps	10 IU/mL	Seroconversion only. No correlate of protection exists





Dosing before 12 months, and catch-up

DOSE 1	DOSE 2	MINIMUM INTERVAL	CATCH-UP
12-15 months	4-6 years	28 days for MMR, 90 days for MMRV	Two doses, at least 28 days apart

A dose at 6-11 months, for international travel or during an outbreak, does not count. Two further doses are required.

Why it does not count

- **Residual maternal antibody** neutralizes vaccine virus before it can replicate sufficiently
- **Age-related immaturity of the humoral response**, demonstrable at 6 months and independent of maternal antibody

What it still does

- **Cell-mediated responses** appear equivalent at 6, 9 and 12 months regardless of passive antibody
- **Priming without protection**





True versus false contraindications

TRUE contraindications

- Anaphylaxis to a vaccine component, including neomycin or gelatin
- Immunosuppression
- Pregnancy
- Moderate or severe febrile illness
- Active untreated tuberculosis

NOT contraindications

- Egg allergy (skin testing is not predictive and is not required)
- Contact dermatitis to neomycin
- Mild illness with or without low-grade fever
- Breastfeeding
- Pregnant household contact
- Immunocompromised household contact

PRODUCT CHOICE

AAP permits either MMRV or MMR with varicella. CDC specifies separate injections.





Safety: three categories, not two

1 · EVIDENCE SUPPORTS A CAUSAL RELATION

Event	Rate, and what it is measured against
Anaphylaxis	1.8-14.4 per million doses. Attributed to gelatin or neomycin, not egg
Febrile seizures	~1 per 3,000-4,000 doses
Febrile seizures, MMRV dose 1 at 12-23 months	One additional per 2,300-2,600 children versus MMR and varicella given separately. No excess at 4-6 years
Thrombocytopenic purpura	~1 per 40,000 doses. Natural rubella: 1 per 3,000

Also in this category: transient arthralgia · MIBE in the immunodeficient

2 · EVIDENCE FAVORS REJECTION

Autism and other autistic spectrum disorders, inflammatory bowel disease, type 1 diabetes

3 · EVIDENCE INADEQUATE TO ACCEPT OR REJECT

ADEM, afebrile seizures, chronic arthritis, encephalopathy, Guillain-Barre, transverse myelitis, and roughly a dozen others





Questions?

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