Exploring Preventable Diseases in Childhood: Implications on Clinical Practice

Air Force Col. (Ret.) Michael Rajnik, M.D.

1145-1245 ET
22 April 2021

"Medically Ready Force…Ready Medical Force"

Presenter

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Dr. Rajnik attended King's College (PA) graduating with a B.S. in Chemistry. He received a USAF Health Professions Scholarship and attended the University of Virginia School of Medicine. He trained in Pediatrics at the San Antonio Uniformed Services Health Education Consortium residency program and Pediatric Infectious Diseases (PEDSID) at the Uniformed Services University of the Health Sciences (USUHS) program, graduating in 2001. Next, he was the Chief of Pediatric Infectious Disease in San Antonio. He returned to USUHS and served as the Program Director for the PEDSID Fellowship Program for ten years. Additionally, he served as the Consultant to the USAF Surgeon General for PEDSID, the President of the Armed Forces Infectious Diseases Society, and chaired the American Academy of Pediatrics Section on Uniformed Services. In 2016, he retired from Active Duty staying at USUHS as the Director of the Division of Pediatric Infectious Diseases.

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- Michael Rajnik has no relevant financial or non-financial relationships to disclose relating to the content of this activity.
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Learning Objectives

At the conclusion of this presentation participants will be able to:

1. Evaluate the key clinical manifestations of the covered vaccine- preventable diseases of childhood.
2. Differentiate between vaccine contraindications and precautions for administering routine ACIP recommended vaccines.
3. Analyze situations where vaccine preventable diseases may re- emerge.
4. Explain the epidemiology of routine vaccine preventable diseases in the U.S. and globally.
5. Illustrate adverse events that may occur following routine immunizations.

Child and Adolescent Immunization Schedule

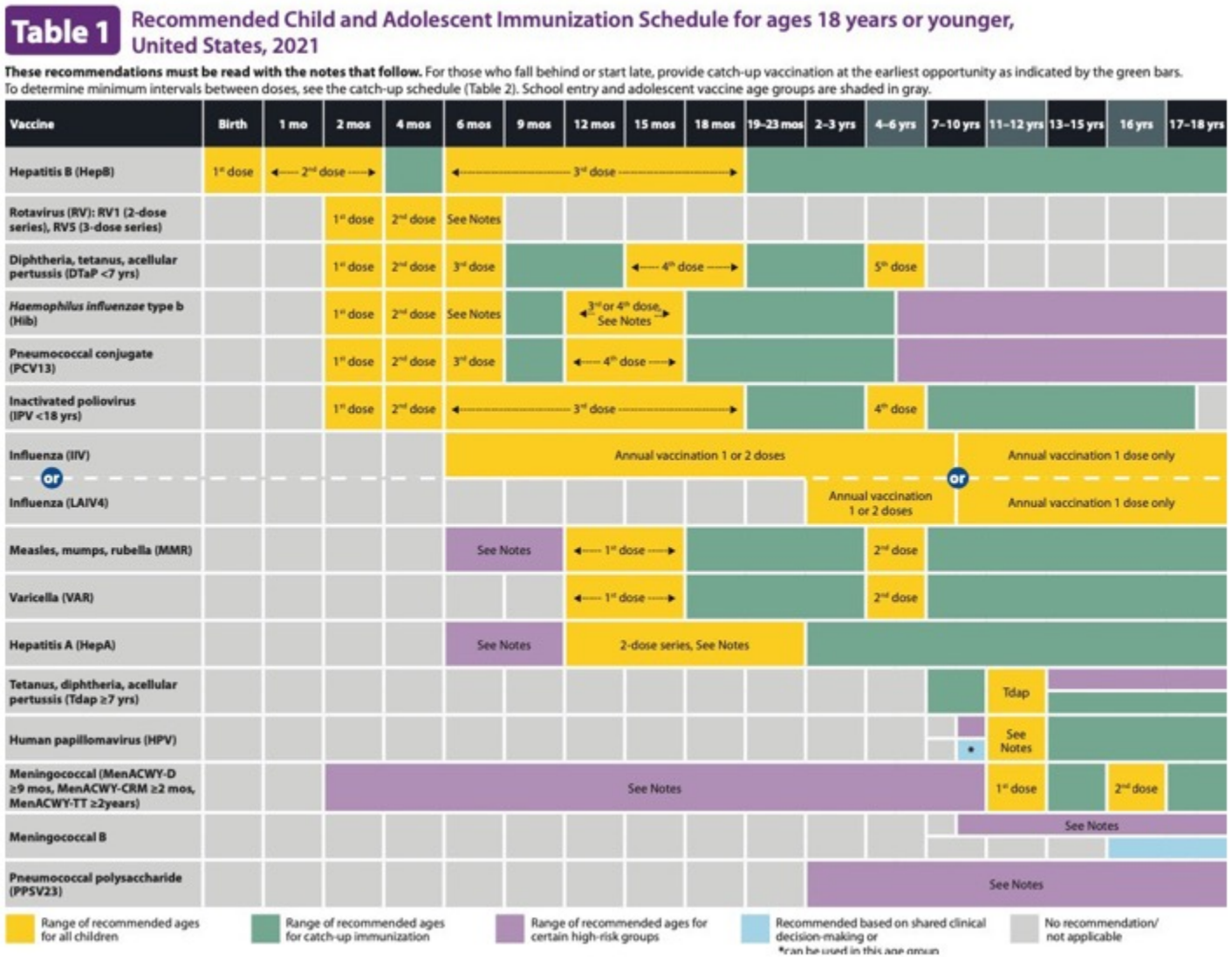


Table 1 Recommended Child and Adolescent Immunization Schedule for ages 18 years or younger, United States, 2021

These recommendations must be read with the notes that follow. For those who fall behind or start late, provide catch-up vaccination at the earliest opportunity as indicated by the green bars. To determine minimum intervals between doses, see the catch-up schedule (Table 2). School entry and adolescent vaccine age groups are shaded in gray.

Vaccine	Birth	1 mo	2 mos	4 mos	6 mos	9 mos	12 mos	15 mos	18 mos	19–23 mos	2–3 yrs	4–6 yrs	7–10 yrs	11–12 yrs	13–15 yrs	16 yrs	17–18 yrs
Hepatitis B (HepB)	1st dose	2nd dose			3rd dose												
Rotavirus (RV): RV1 (2-dose series), RV5 (3-dose series)			1st dose	2nd dose	See Notes												
Diphtheria, tetanus, acellular pertussis (DTaP <7 yrs)			1st dose	2nd dose	3rd dose			4th dose				5th dose					
Haemophilus influenzae type b (Hib)			1st dose	2nd dose	See Notes		3rd or 4th dose, See Notes										
Pneumococcal conjugate (PCV13)			1st dose	2nd dose	3rd dose		4th dose										
Inactivated poliovirus (IPV <18 yrs)			1st dose	2nd dose	3rd dose							4th dose					
Influenza (IIV)					Annual vaccination 1 or 2 doses								Annual vaccination 1 dose only				
or													or				
Influenza (LAIV4)											Annual vaccination 1 or 2 doses		Annual vaccination 1 dose only				
Measles, mumps, rubella (MMR)					See Notes		1st dose					2nd dose					
Varicella (VAR)							1st dose					2nd dose					
Hepatitis A (HepA)					See Notes		2-dose series, See Notes										
Tetanus, diphtheria, acellular pertussis (Tdap ≥7 yrs)														Tdap			
Human papillomavirus (HPV)													*	See Notes			
Meningococcal (MenACWY-D ≥9 mos, MenACWY-CRM ≥2 mos, MenACWY-TT ≥2years)			See Notes											1st dose		2nd dose	
Meningococcal B													See Notes				
Pneumococcal polysaccharide (PPSV23)											See Notes						

Range of recommended ages for all children

Range of recommended ages for catch-up immunization

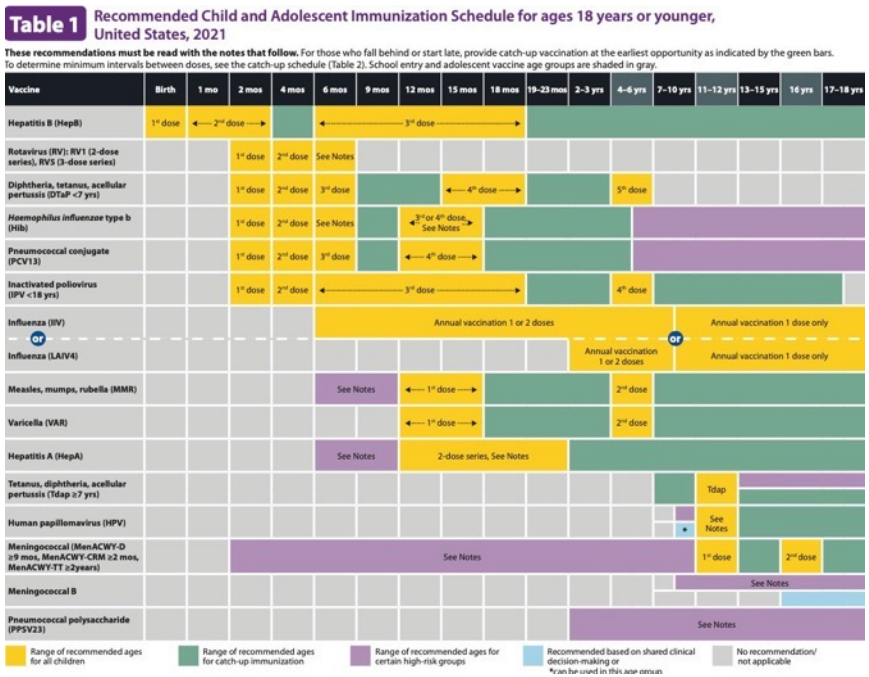
Range of recommended ages for certain high-risk groups

Recommended based on shared clinical decision-making or

*can be used in this age group

No recommendation/ not applicable

We will need to be a bit more focused



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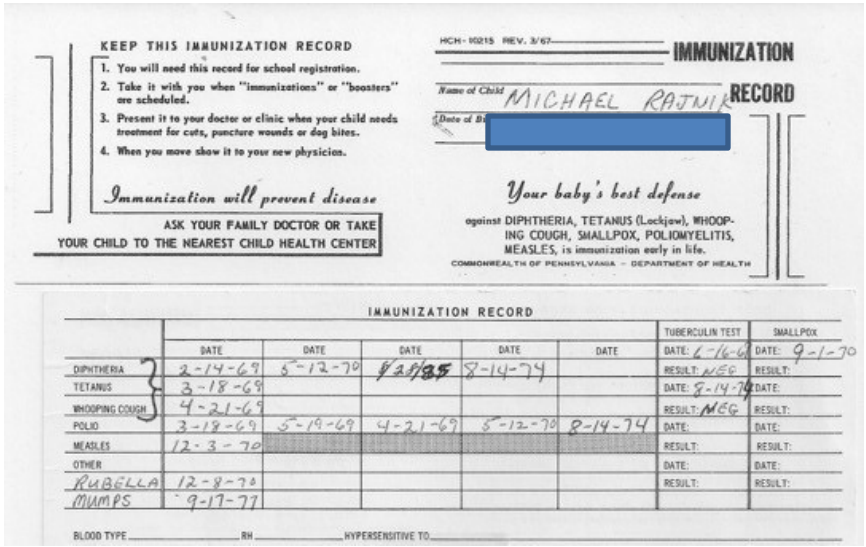
Range of recommended ages for all children | Range of recommended ages for catch-up immunization | Range of recommended ages for certain high-risk groups | Recommended based on shared clinical decision-making or | No recommendation/ not applicable



KEEP THIS IMMUNIZATION RECORD

1. You will need this record for school registration.
2. Take it with you when "immunizations" or "boosters" are scheduled.
3. Present it to your doctor or clinic when your child needs treatment for cuts, puncture wounds or dog bites.
4. When you move show it to your new physician.

Immunization will prevent disease

ASK YOUR FAMILY DOCTOR OR TAKE YOUR CHILD TO THE NEAREST CHILD HEALTH CENTER

HCH-10215 REV. 3/67

IMMUNIZATION RECORD

Name of Child MICHAEL RAJNIK

[redacted]

Your baby's best defense

against DIPTHERIA, TETANUS (Lockjaw), WHOOPING COUGH, SMALLPOX, POLIOMYELITIS, MEASLES, is immunization early in life.

COMMONWEALTH OF PENNSYLVANIA – DEPARTMENT OF HEALTH

IMMUNIZATION RECORD

	DATE	DATE	DATE	DATE	DATE	TUBERCULIN TEST	SMALLPOX
DIPTHERIA	2-14-69	5-12-70	8-25-75	8-14-74		DATE: 7-16-69	DATE: 9-1-70
TETANUS	3-18-69					RESULT: NEG	RESULT:
WHOOPING COUGH	4-21-69					DATE: 8-14-74	DATE:
POLIO	3-18-69	5-19-69	4-21-69	5-12-70	8-14-74	RESULT: NEG	RESULT:
MEASLES	12-3-70					DATE:	DATE:
OTHER						RESULT:	RESULT:
RUBELLA	12-8-70					DATE:	DATE:
MUMPS	9-17-71					RESULT:	RESULT:

BLOOD TYPE _____ RH _____ HYPERSENSITIVE TO _____

Measles, Mumps and Rubella

MMR and MMRV

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Measles

- Measles (Rubeola) virus is a Paramyxovirus.
  - 24 serotypes but all behave as 1 immunologically
- It is spread via large droplets and inhaled aerosolized droplets
  - Infects respiratory epithelia
  - Spreads throughout the body via the lymph nodes and infects other lymphoid tissue
- It is one of the most infectious agents
  - R_0 is 12-18 for measles, COVID-19 – 1.4-3.9 (R_0 – Expected cases per one exposure)
- Clinical manifestations occur following 7-21 days of incubation

EPIDEMIOLOGY

- Prior to the measles immunization, about 500,000 cases annually in the U.S.
  - In 2000, U.S. declared measles – eliminated
  - Recent outbreaks related to globalization and decreased U.S. vaccine coverage
- Globally, a huge push for immunizations dropped annual cases

Year	Cases	Deaths
2000	29 million	650,000
2016	6.5 million	90,000

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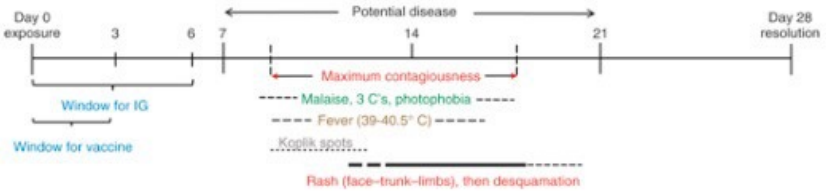
Measles – Clinical Manifestations & Complications

Clinical Manifestations * Ill appearing

- Onset begins with onset of fever and malaise
- 10 days post-exposure
  - Brassy cough, coryza, conjunctivitis (3 C's) and photophobia
  - Koplik spots will occur during this time
  - Maculopapular rash
    - Face -> Trunk -> Limbs
- Fevers begin with the prodrome and lasts for 4 days into the rash



Complications

Pneumonitis
- 6% with Bacterial Pneumonia

Otitis Media
- 7%

Diarrhea
- 8%

Immunosuppressed patients may develop fatal pneumonia

Malnourished Children at high risk for complications

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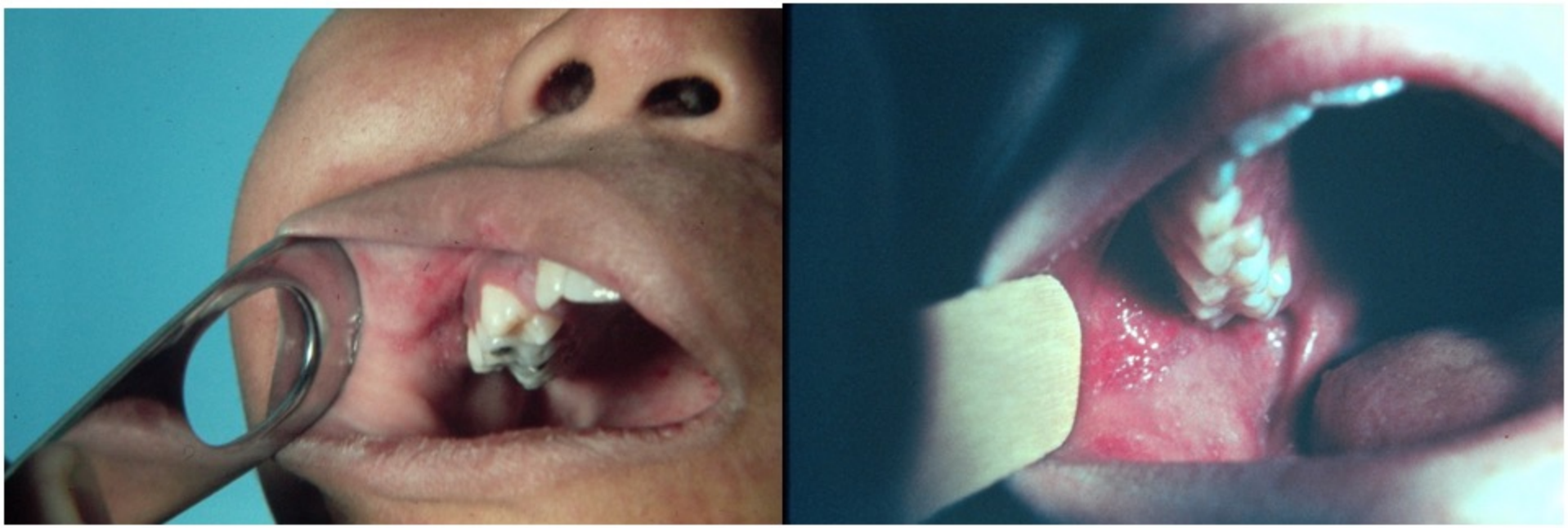
Koplik Spots



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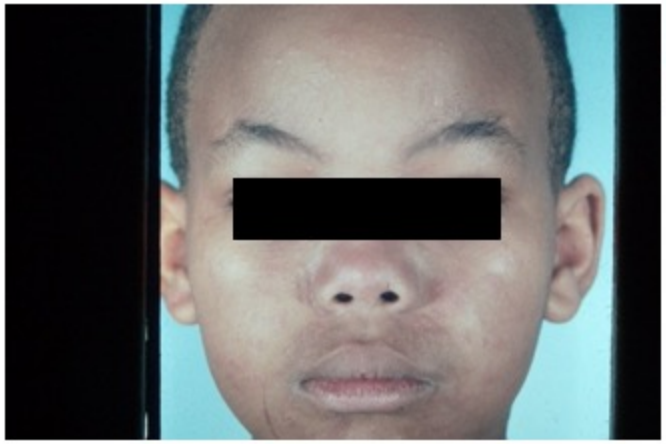
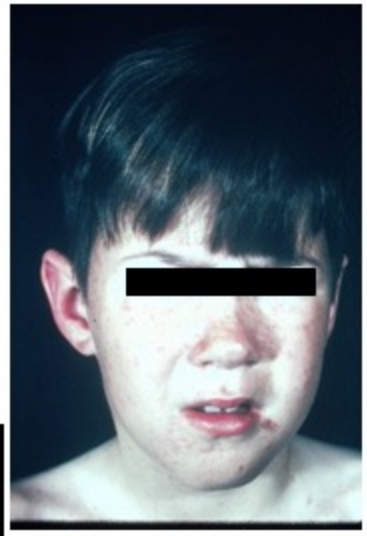
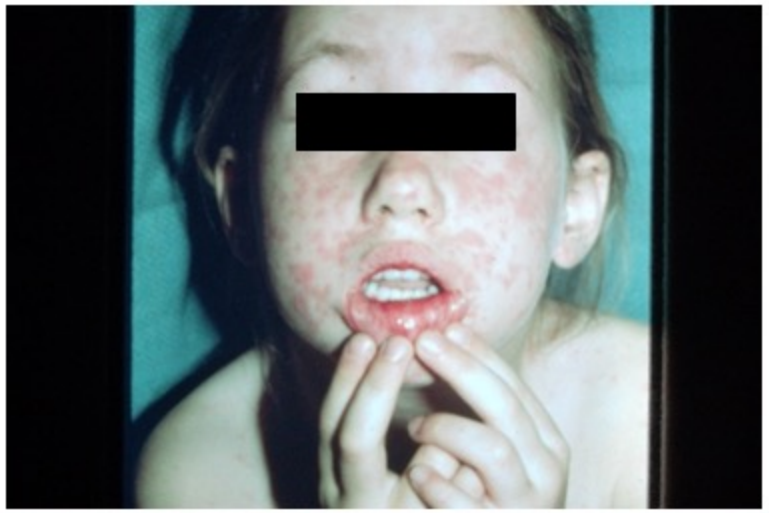
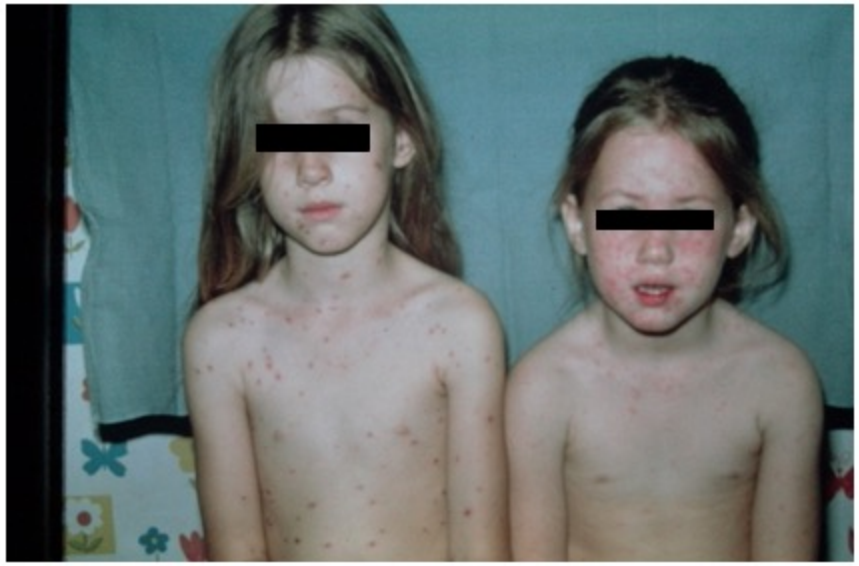
Cutaneous Measles









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Measles Immunization - Development

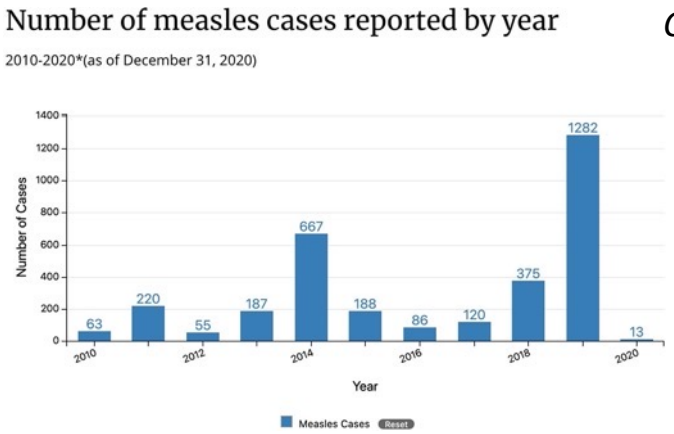
- John Enders
  - First investigator to cultivate the measles virus (previously poliovirus)
  - He developed a live-attenuated viral vaccine which proved to be effective
    - Isolated from John Edmonston – became known as the Edmonston strain
- Maurice Hilleman further attenuated the vaccine
  - Edmonston-Enders Strain (Moraten)
  - This is the strain used for all measles vaccines since 1968

- Post-vaccine
  - Measles cases dropped precipitously in the U.S.
  - Goal was to eliminate from U.S. by 1982
    - Had achieved a greater than 80% reduction
  - 1989 – U.S. outbreak among school-aged children
    - Led to 2nd vaccine dose
  - 2000 – Measles declared eliminated from U.S.

Measles Immunization Controversy

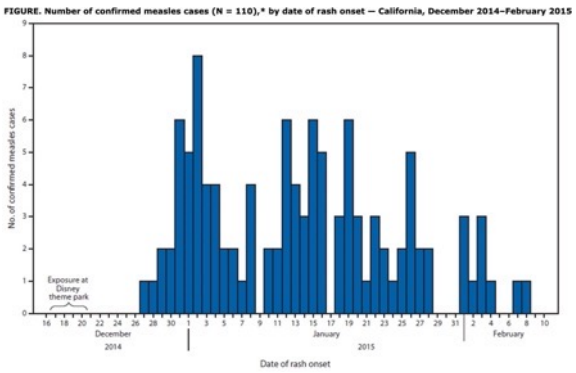
- Wakefield – Autism
  - Published a paper noting that colonic lesions associated with measles vaccine virus allowed for neurotoxic proteins to get to the blood stream and CNS
- Additional reports citing the finding of the virus in various tissues
- Political and celebrity proponents of the vaccine-autism link joined in
- Wakefield's article was redacted
- Next turned to the presence of thimerasol
- All of these efforts resulted in decreasing vaccine rates in developed countries

- Outbreaks



CDC.gov

Outbreak after introduction to an amusement park in CA *MMWR* 64:153-154



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Measles Recommedations

- Children
  - First dose at 12 to 15 months of age
  - Second dose at 4 to 6 years of age
    - (Separated by at least 28 days)
- Post-High School Ed. Institutions
  - 2 doses separated by 28 days if not evidence of immunity
- Adults
  - Immune if born before 1957
  - If 1957 or after, need one dose if non-immune

- International Travel
  - Infants 6 - 11 months – one dose*
  - Children > 12 months of age# should have 2 doses separated by 28 days
  - Teenagers and adults without evidence of immunity should have 2 doses if non-immune
  - Healthcare workers must show evidence of immunity

* MMR does not count towards primary series

MMRV may be used, separated by at least 3 months

Measles – Post Exposure Prophylaxis

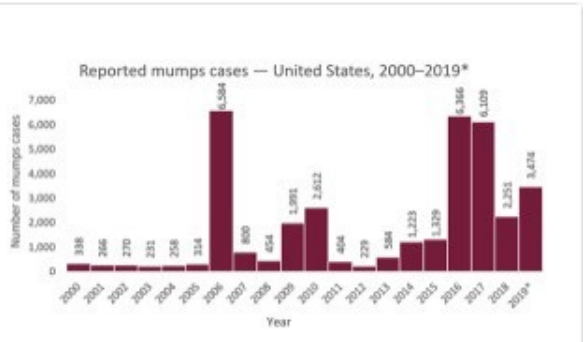
- Measles immunizations can be given within 72 hours of an exposure
  - MMR
- After 72 hours, immunoglobulin (IVIG) may be given

Mumps

- Mumps virus is a Paramyxovirus It is inactivated by many chemicals, UV light, heat
- It is spread via aerosolized droplets
- Incubation period is 16-18 days
- It infects the nasopharynx and regional lymph nodes
  - Secondary viremia takes virus to the CNS and other glandular tissue
  - CNS infection is common with the virus spreading to CNS via the choroid plexus
  - Orchitis occurs via direct infection with the virus

EPIDEMIOLOGY

- Prior to the mumps immunization, about 186,000 cases annually
- Began routine use in 1977 and further decline occurred in 2003 after use of a second dose
  - 99% reduction
  - Cases in the hundreds/year
- Outbreaks continue to occur in U.S. as immunization is not 100% effective
  - Usually in people 18-24 years of age
  - Universities, athletic teams, religious groups



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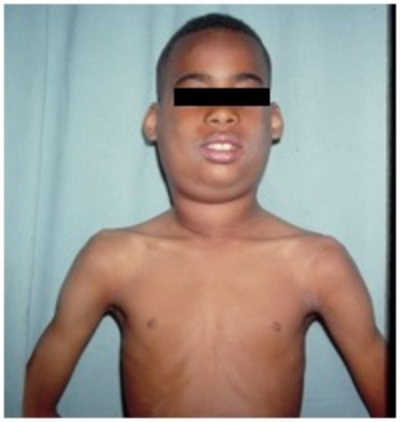
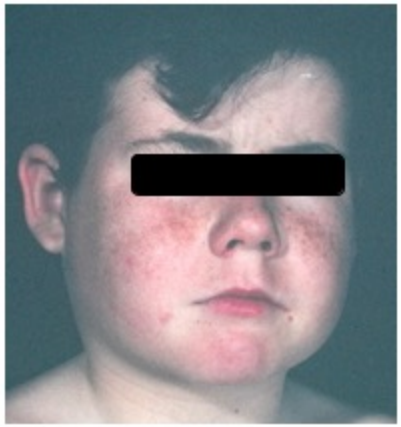
Mumps – Clinical Manifestations & Complications

Clinical Manifestations

- 1/3 of cases have a respiratory tract infection
  - Prodrome of HA, anorexia, abdominal pain
- Parotitis will begin unilateral and 70% become bilateral (7-10 days)





Complications

- CNS
  - Pleocytosis > 50% of cases, with symptoms in up to 10%
  - Male >> Female
  - Meningitis >> Encephalitis
- Orchitis
  - 24 – 35% of males aged 15 to 29 years
  - Usually unilateral – results in testicular atrophy
  - Infertility is rare
- Glomerulonephritis
  - Hematuria and Proteinuria
  - Self-resolving
- Arthritis – 3 weeks after parotitis

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Mumps Immunization

- Maurice Hilleman
  - 1963 – Cultured the mumps virus from his daughter Jeryl Lynn
  - 1967 – Developed the first mumps from an attenuated version of this
    - Jeryl Lynn Strain
    - Still Used in todays Mumps immunizations
  - In 1971, introduced the first combination vaccine – MMR
  - 40 vaccines have been attributed to his development

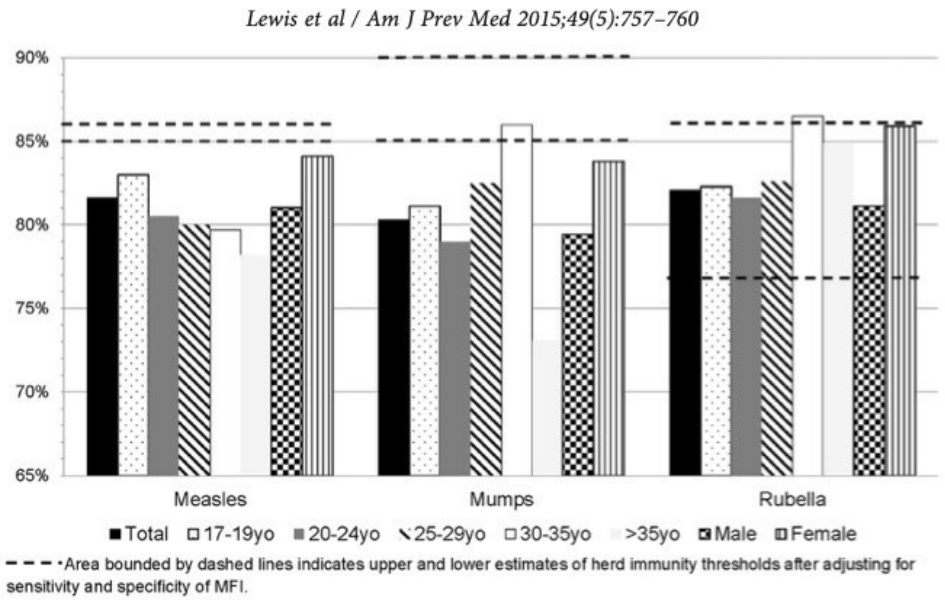
Images courtesy of Dale Smith, Ph.D.

Measles, Mumps and Rubella Titers

Measles, Mumps, and Rubella Titers in Air Force Recruits

Below Herd Immunity Thresholds?

Paul E. Lewis, MD, MPH,[1] Daniel G. Burnett, MD, MPH,[1] Amy A. Costello, MD, MPH,[2] Cara H. Olsen, PhD,[1] Juste N. Tchandja, PhD, MPH,[3] Bryant J. Webber, MD, MPH[3]



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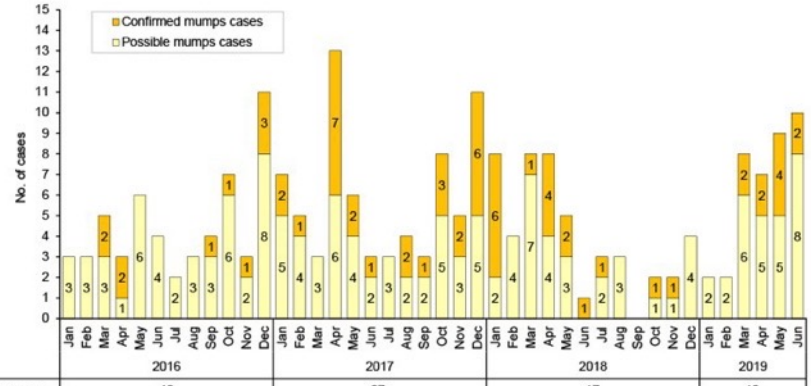
Measles, Mumps, Rubella and Varicella

> MSMR. 2019 Oct;26(10):2-12.

Measles, mumps, rubella, and varicella among service members and other beneficiaries of the Military Health System, 1 January 2016–30 June 2019

Valerie F Williams, Shauna Stahlman, Michael Fan

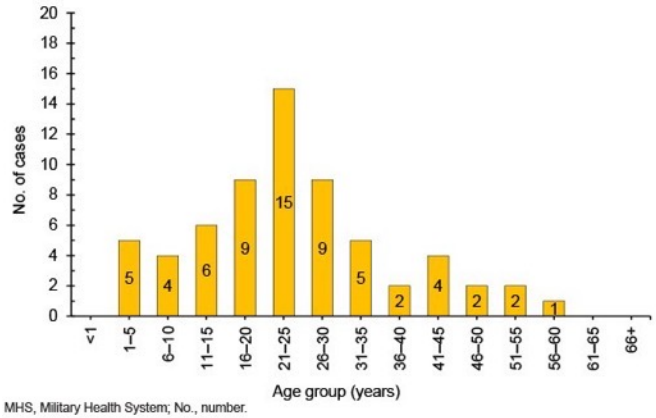
FIGURE 3. Confirmed and possible cases of mumps among MHS beneficiaries, by year and month, 1 January 2016–30 June 2019



	2016	2017	2018	2019
Confirmed	10	27	17	10
Possible	44	44	31	28

MHS, Military Health System; No., number.

FIGURE 4. Age distribution of confirmed cases of mumps among all MHS beneficiaries, 1 January 2016–30 June 2019



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Rubella

- Rubella virus is a Togavirus with humans as the only natural host
- It is inactivated by many chemicals, UV light, heat
- It is spread via aerosolized droplets
- Infectivity is normally 3 to 8 days after exposure for 11-14 days
- Infectious 5 days before and 6 days after the onset of rash

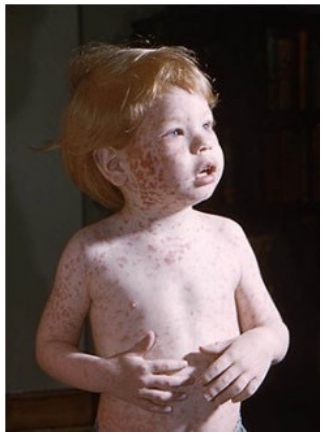
EPIDEMIOLOGY

- Endemic regions experience late winter to spring outbreaks
  - 2-4 year cycles
- Most experienced rubella in childhood (3-9 years of age)
- Attack rates in closed communities like colleges and military will approach 75-90%
- Most cases now are acquired by foreign travel and foreign born
- No longer endemic in the U.S. after 2003

Rubella – Clinical Manifestations

Acquired Rubella

- Rash and lymphadenopathy
- Rash begins on the face and spreads cephalocaudally over 24 hours – fades in same pattern over 2-3 days
- Lymphadenopathy may precede the rash by 1 week
  - Suboccipital
  - Post-auricular

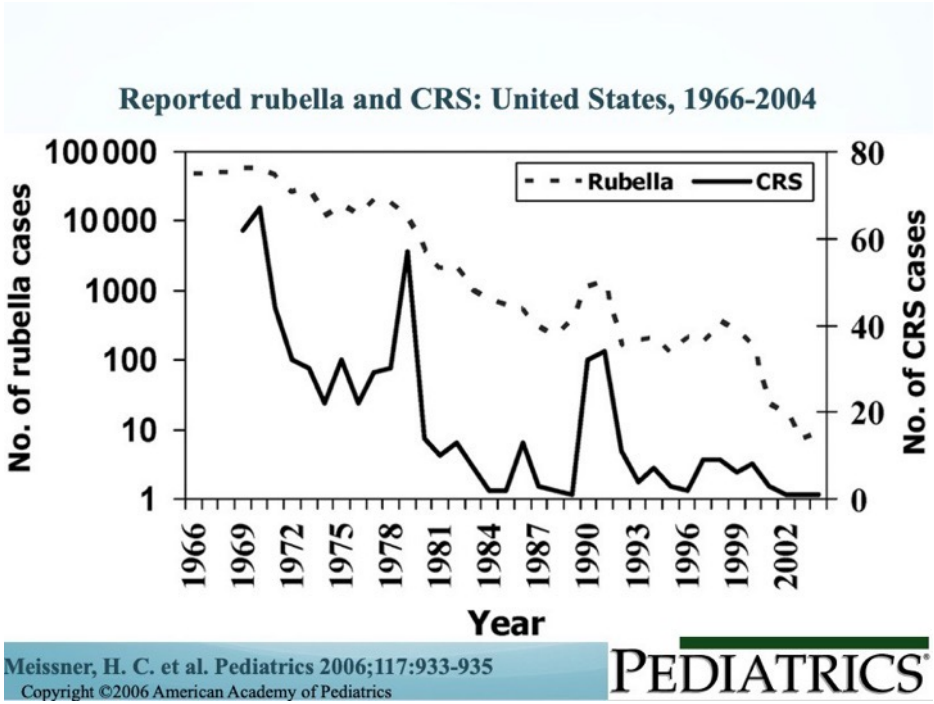


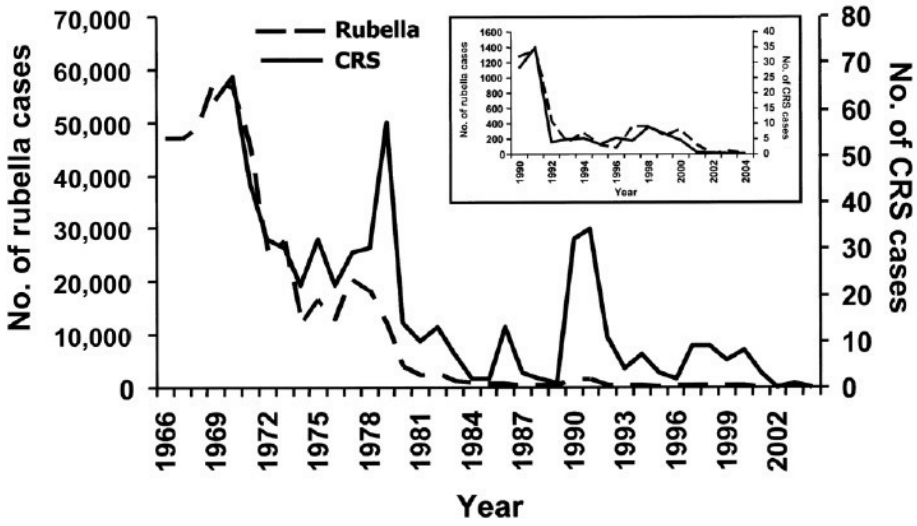
From Rubella (German Measles, Three-Day Measles), Signs and Symptoms, CDC.gov

Congenital Rubella

- Ophthalmologic
  - *Cataracts*, retinopathy, glaucoma
- Cardiac
  - *PDA*, peripheral pulmonary artery stenosis
- Auditory
  - *Sensorineural hearing impairment*
- Neurologic
  - Behavioral d/o, meningoencephalitis, MR
- Other
  - *Growth retardation*
  - Hepatosplenomegaly
  - Thrombocytopenia
  - *Purpuric skin lesions*

Impact of Immunization on Rubella and Congenital Rubella Syndrome





Meissner, H. C. (2006). Elimination of rubella from the United states: A milestone on the road to global elimination. *PEDIATRICS, 117*(3), 933-935. doi:10.1542/peds.2005-1760

Rubella Hotspots Still Exist

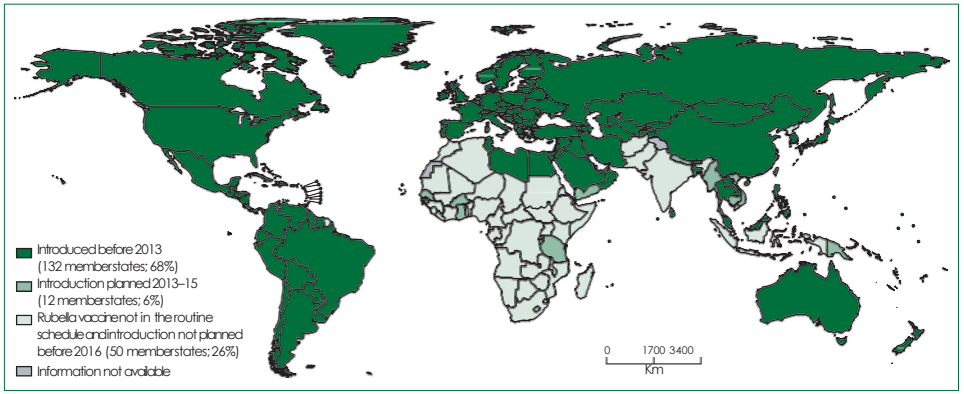


Figure 2: **Distribution of countries using rubella-containing vaccine in their routine immunisation schedule in 2012, and countries planning introduction during 2013–15**

Information is subject to change based on country decisions on when to introduce rubella-containing vaccine in the 194 WHO Member States. Data taken from WHO database, Department of Immunization, Vaccines and Biologicals, unpublished.

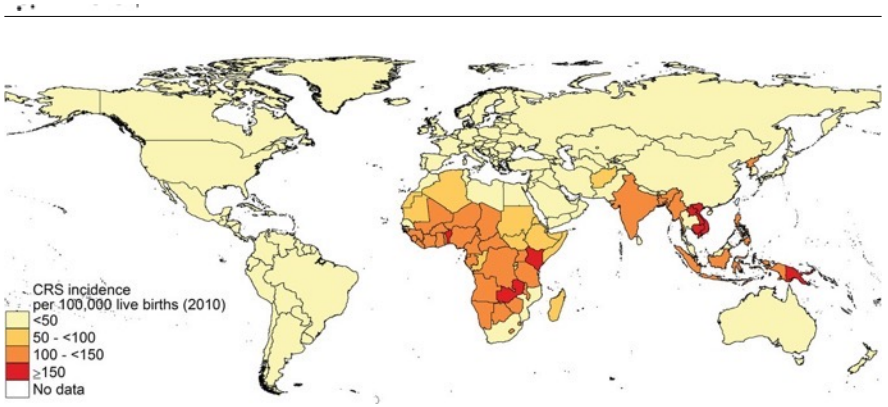


Fig 4. Estimates of the median incidence of CRS per 100,000 live births by country in 2010.

Rubella and Congenital Rubella Syndrome. (n.d.). Retrieved March 14, 2021, from https://www.who.int/

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Congenital Rubella Outbreak in Vietnam

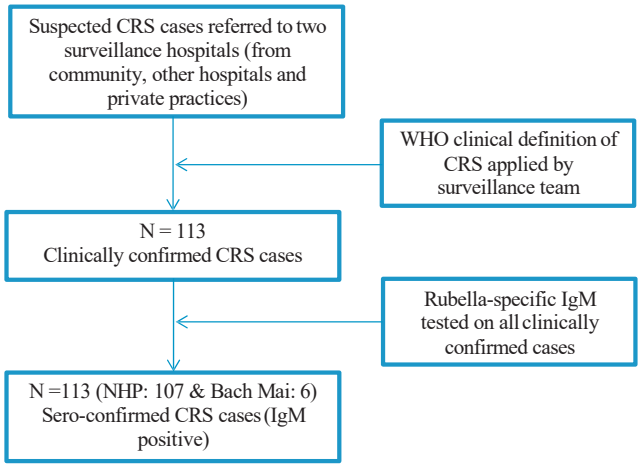


Fig. 1. Outline of CRS surveillance in Hanoi, Vietnam.

Table 1
Clinical signs and symptoms of CRS.

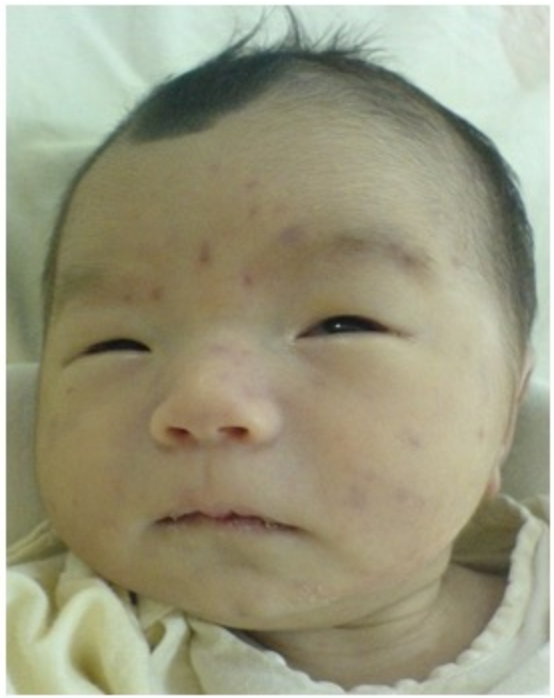
Clinical manifestations	Frequency (N = 113)	Percentage
Congenital anomalies		
CRS multiorgan defect[a]	44	38.9
Congenital heart malformation[b]	72	63.7
Deafness at birth	35	31.0
Hearing loss at 1st month	37	32.7
Cataract	29	25.7
Other eye abnormalities[c]	24	21.2
Microcephaly[d]	41	36.3
Developmental delay	3	2.6
Signs at birth		
Thrombocytopenia[e] (<100.000/mm^3)	96	85.0
Neonatal hemorrhage (purpura)	84	74.3
Splenomegaly	72	63.7
Hepatomegaly	71	62.8
Anemia	69	61.1
Blueberry muffin rash	69	61.1
Hepatitis (liver enzymes > 2 UNL)	54	47.8

[a] 16 cases with three major CRS defects (deafness, eye abnormality and congenital heart malformation, 14 cases with deafness and congenital heart malformation and another 14 cases with eye abnormality and congenital heart malformation).
[b] Congenital heart malformation included: 52 patent ductus arteriosus (PDA), 8 PDA with pulmonary stenosis (PS), 6 PDA with atrial septal defect (ASD), 3 PS and 2 PDA with ventricular septal defect (VSD).
[c] Other eye abnormalities included: 21 microphthalmia, 2 lacrimal canal obstruction and 1 glucoma.
[d] Ahead circumference at birth <2 SD for fetal age.
[e] Thrombocytopenia lasted for more than 15 days in 71 cases.

Van Bang, N., Anh, N. T., Van, V. T., Thai, T. T., Van Thuong, N., Khandaker, G., & Elliott, E. (2014). Surveillance of CONGENITAL RUBELLA syndrome (CRS) in tertiary care hospitals in Hanoi, Vietnam during A Rubella epidemic. *Vaccine, 32*(52), 7065-7069. doi:10.1016/j.vaccine.2014.10.087

4 month old from Vietnam

Patient Permission Obtained and provided courtesy of COL (Dr.) Ashley Maranich, M.D.



"Blueberry Muffin" Rash

Cataracts - bilateral

Varicella (Chickenpox)

- Chickenpox is caused by the Varicella Zoster Virus
  - A member of the herpes virus family
  - Remains latent in sensory nerve ganglia
  - May re-emerge at herpes zoster (shingles)
- It is spread via inhaled aerosolized droplets and requires airborne precautions
  - 90% of susceptible contacts will get disease
- Incubation period is 10 - 21 days
  - Prodrome of fever for 1-2 days before rash
  - This is the most infectious time period
- Clinical manifestations occur following 7-21 days of incubation

EPIDEMIOLOGY

- Prior to the varicella immunization, about 4 million cases annually in the U.S.
  - 10,500 - 13,000 were infected
  - 100-150 died each year

Impact of Immunization (% Decrease)

Vaccine	Incidence	Hospitalizations	Deaths	Infants
1 dose		93%		
2 dose	85%	38% (Additional)	94%	90%

- Breakthrough Varicella
  - Usually mild, afebrile, low fever
  - One dose – 25-30% will still have disease similar to unvaccinated

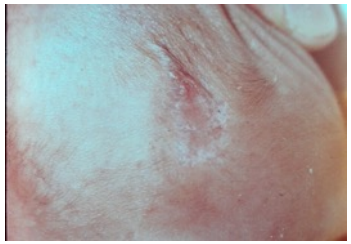
Varicella – Clinical Manifestations

Unvaccinated Varicella

- Generalized and Pruritic Rash
  - Macules→ Papules → Vesicle → Crust
- Rash begins on the torso and face and spreads over the body
- Temperatures of 102^{o}F and rash for 2-3 days

Breakthrough Varicella

- Breakthrough infection with wild-type in immunized people can occur
  - May occur in up to 42 days post exposure
- Tend to have less than 50 lesions
- Rash is likely to be maculopapular



Immunocompromised

- May develop visceral dissemination
  - Pneumonia, hepatitis, encephalitis, DIC
- Atypical rash with more lesions and > 7 days

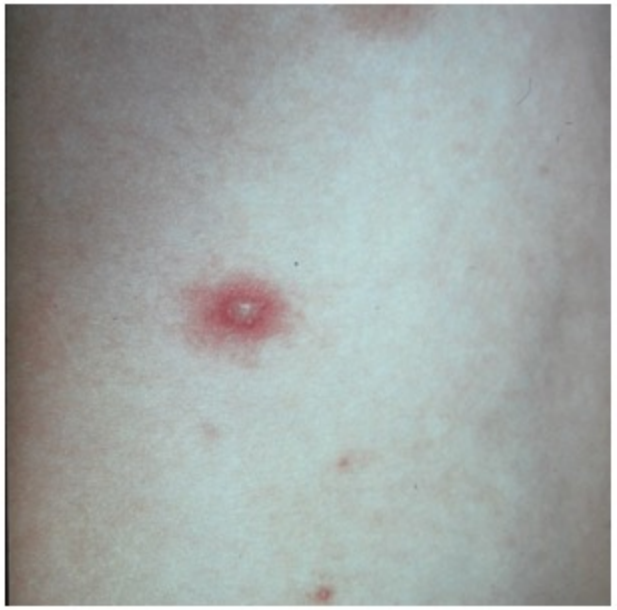
HIV or AIDS (Low CD_4 Counts)

- Atypical rash may come up for weeks/months
- May develop visceral dissemination
- Retinitis

Pregnant Women

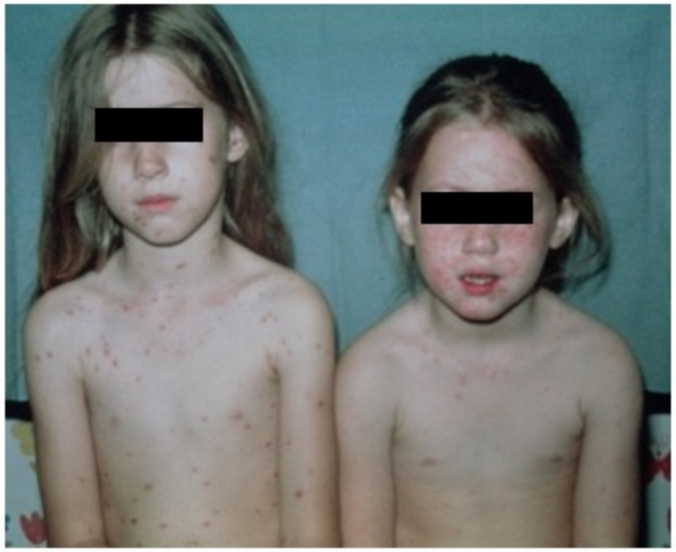
- At risk for pneumonia (Esp., 3rd Trimester)
- 1st and 2nd Trimester (0.4-2.0%) Congenital Varicella Syndrome
  - Scarring, Limb Abnormalities, Brain, Eyes, LBW
- Neonatal Varicella
  - 5 days before to 2 days after delivery
  - Up to 30% mortality

Varicella Rashes

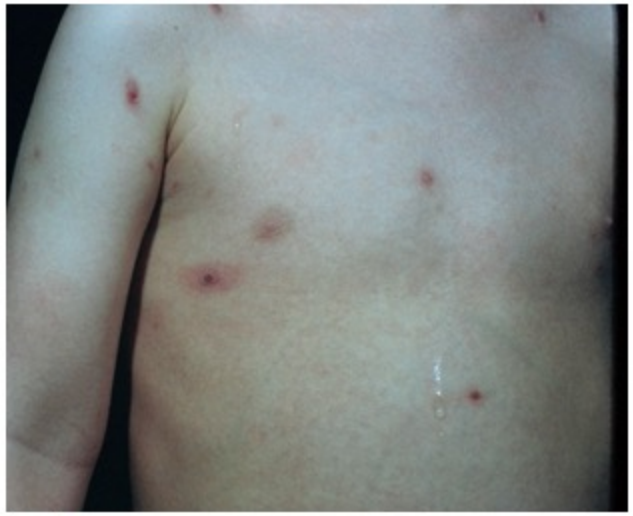


Dew Drop on Rose Petal

Varicella



Measles



Healing Scabs

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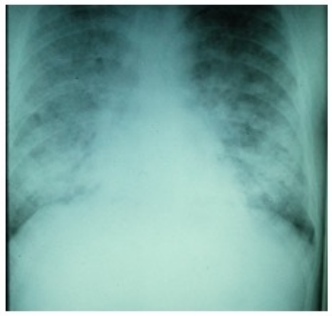
Varicella - Complications

Most Common

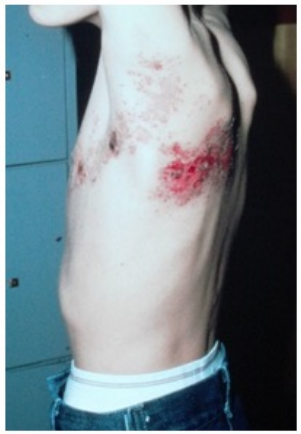
- Children – Bacterial infections of the skin and soft tissues

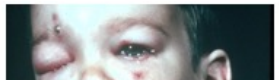
- Adults - Pneumonia



Severe Complications

- Septicemia
- Toxic Shock Syndrome
- Necrotizing Fasciitiis
- Osteomyelitis
- Bacterial Pneumonia
- Septic Arthritis





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Varicella – Who is Immune?

- Documentation of Age-Appropriate Vaccination
  - Preschool – 1 dose
  - School age and above – 2 doses
- Laboratory evidence of immunity or disease
  - Commercial labs will detect disease induced immunity but may not detect vaccine induced
- Birth in the United States before 1980
  - Does not count for healthcare personnel
  - Pregnant women
  - Immunocompromised people
- Diagnosis or verification of a history of varicella or herpes zoster
  - Epidemiologic link to another typical varicella case or lab confirmed case
  - Evidence of laboratory confirmation in acute disease
  - If verification is not up to this standard then a vaccine is recommended

Varicella – Management of High-Risk

Who is high risk?

- Immunocompromised
  - Leukemia or Lymphoma
  - Meds to suppress the immune system
  - Cellular immunity
- Newborns whose mothers have varicella 5 days before and 2 days after
- Premature babies
  - ≥ 28 weeks and have no evidence of immunity
  - < 28 weeks or weigh less than 1,000 grams
- Pregnant women with no evidence of immunity

Treatment – High Risk Persons

- Varicella-Zoster Immune Globulin (VariZIG)
  - Lack Immunity to varicella
  - Exposure is likely to result in infection
  - High-Risk for severe varicella
- Oral Acyclovir Treatment (Valacyclovir)
  - Healthy people < 12 years of age
  - Chronic skin or pulmonary disorders
  - On long-term ASA
  - Receiving short, intermittent or inhaled corticosteroids
- IV Acyclovir –
  - Severe disease (Pneumonia, encephalitis, thrombocytopenia, hepatitis)
  - Immunocompromised

MMR – MMRV – Why two doses?

	1st Dose	2nd Dose
Measles	93%	97%
Mumps	78%	88%
Rubella	97%	
Varicella*	82%/100%	98%/100%

* Varicella vaccine: Any form of varicella/severe varicella

- Measles
  - 2nd shot is to protect against vaccine failure
  - Immunity for lifetime
- Mumps
  - Immunity decreases over time
  - Consider a 3rd dose if close contact with mumps patient
- Rubella – one dose, lifetime immunity
- Varicella
  - 1st dose 97% protective in 1st year
  - 1st dose 86% protective in 2nd year
    - Stable until year 8

MMR and MMRV Safety

- Febrile Seizures
  - 4/10,000 children have febrile seizures in 7-10 days when MMR and varicella given separately with first dose
  - Rate increases by 2-fold for children receiving MMRV
  - Children less than 7 years of age, rate is 1 in 3,000-4,000
- Immune Thrombocytopenic Purpura (ITP)
  - Increased risk for 6 weeks after MMR
  - Rate 1 in 40,000 vaccinated children
- Joint Pain
  - Associated with the rubella portion
  - More common in adults receiving the vaccine
  - Women >> Men
    - 1 in 4 post-pubertal women
    - Begins 1-3 weeks post-immunization and lasts 2 days
- Measles Inclusion Body Encephalitis
  - Much more common with wild-type measles (1 in 1,000)
  - Tends to occur within 1 year after infection
  - Three published cases following the MMR

Diphtheria, Pertussis and Tetanus

DTap, Tdap, Td Immunizations

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Diphtheria

Pre-Immunization

- First described by Hippocrates in 5th Century B.C.
- 1921
  - 206,000 cases/15,520 deaths
- Death rates range from 20% for those age < 5 years and > 40 years to 5-10% between ages 5-40 years

Post-immunization

- Diphtheria rates dropped rapidly
- U.S. – no cases 2004-2008
- Independent States of the Former Soviet Union
  - Decrease in public health led to huge surge of cases
  - 150,000 cases/> 5000 deaths

- Caused by the bacterium *Corynebacterium diphtheriae*
  - After attaching to respiratory epithelium, it secretes a toxin with two subunits
  - A subunit inhibits protein synthesis in the cell
    - Cells die and induce a robust inflammatory response
    - Develops an exudate that becomes fibrinous – pseudomembrane
    - Toxin produced can travel throughout the body
      - Myocarditis
      - Peripheral neuropathy – myelin
      - Kidney disease

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Varicella - Complications

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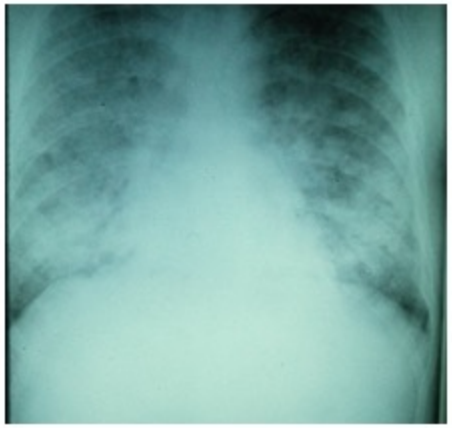

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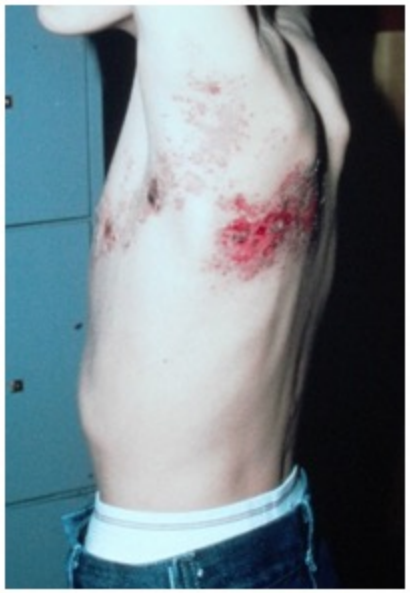

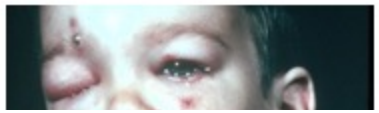

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Diphtheria

- Treatment (Antitoxin and Antibiotics)
  - Antitoxin – need to treat early
    - Available thru the CDC

Laryngeal/Pharyngeal (< 48 hours)	20,000 – 40,000 U
Nasopharyngeal	40,000 – 60,000 U
Severe Pharyngeal/Laryngeal	80,000 – 120,000 U[!]

  - Antibiotics
    - 14 day course of Penicillin or erythromycin
    - IV if cannot take oral medication
    - Should have follow up cultures after 2 weeks
      - 10 days of erythromycin if still positive
  - Immunization should also occur in convalesence

- Prevention
  - Active immunization with Diphtheria toxoid (DT or adult Td)
    - Pediatric formulations have 3-4 times more toxoid
    - Combined into DTP or DTaP
    - Primary Series is 5 doses followed by boosters of Td every 10 years
    - First booster is Tdap at age 11-12 yrs
  - Immunization is directed vs. the phage-mediated toxin
    - Often response is incomplete
    - Need 70-80% immunization level to prevent epidemic spread*
    - Texas Outbreak#
      - No immunization – 30-fold increase in symptomatic
      - Incomplete – 11.5 fold increase

! Mixed symptoms or > 48 hours

*Am J Public Health 1985; 75: 1393-1397

Vaccine 1994; 12:1167-1172

The Great Race of Mercy

- A diphtheria outbreak occurred in Nome, AK in 1925
- It was noted after the last supply ship for the fall had left
- The only mechanism to get antitoxin to the city was by dogsled
- They faced temperatures -70^{o}F
- The last sled team was led by Balto who has become immortalized for his role in the trip

U.S. Bureau of Land Management - U.S. Bureau of Land Management
Map of the historical Iditarod Trail and the current Iditarod National Historic Trail in Alaska, USA

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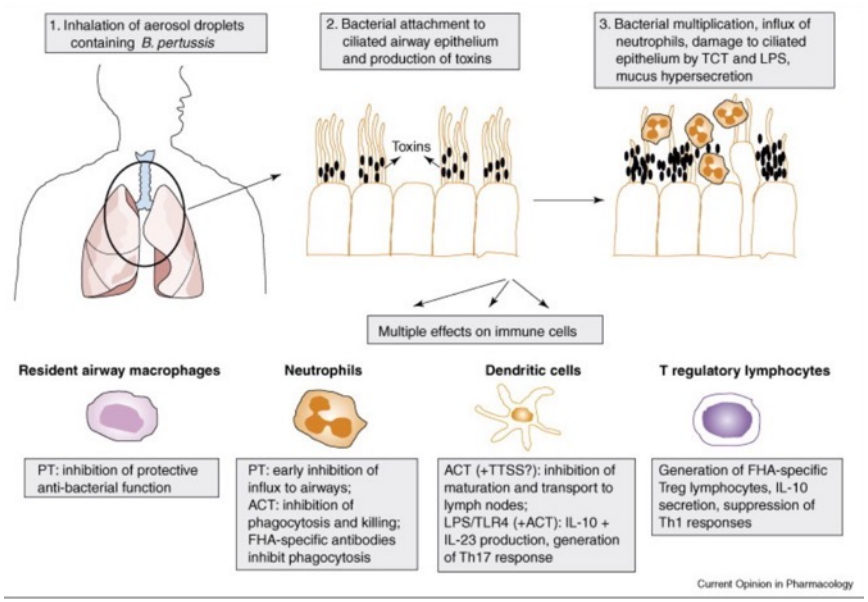
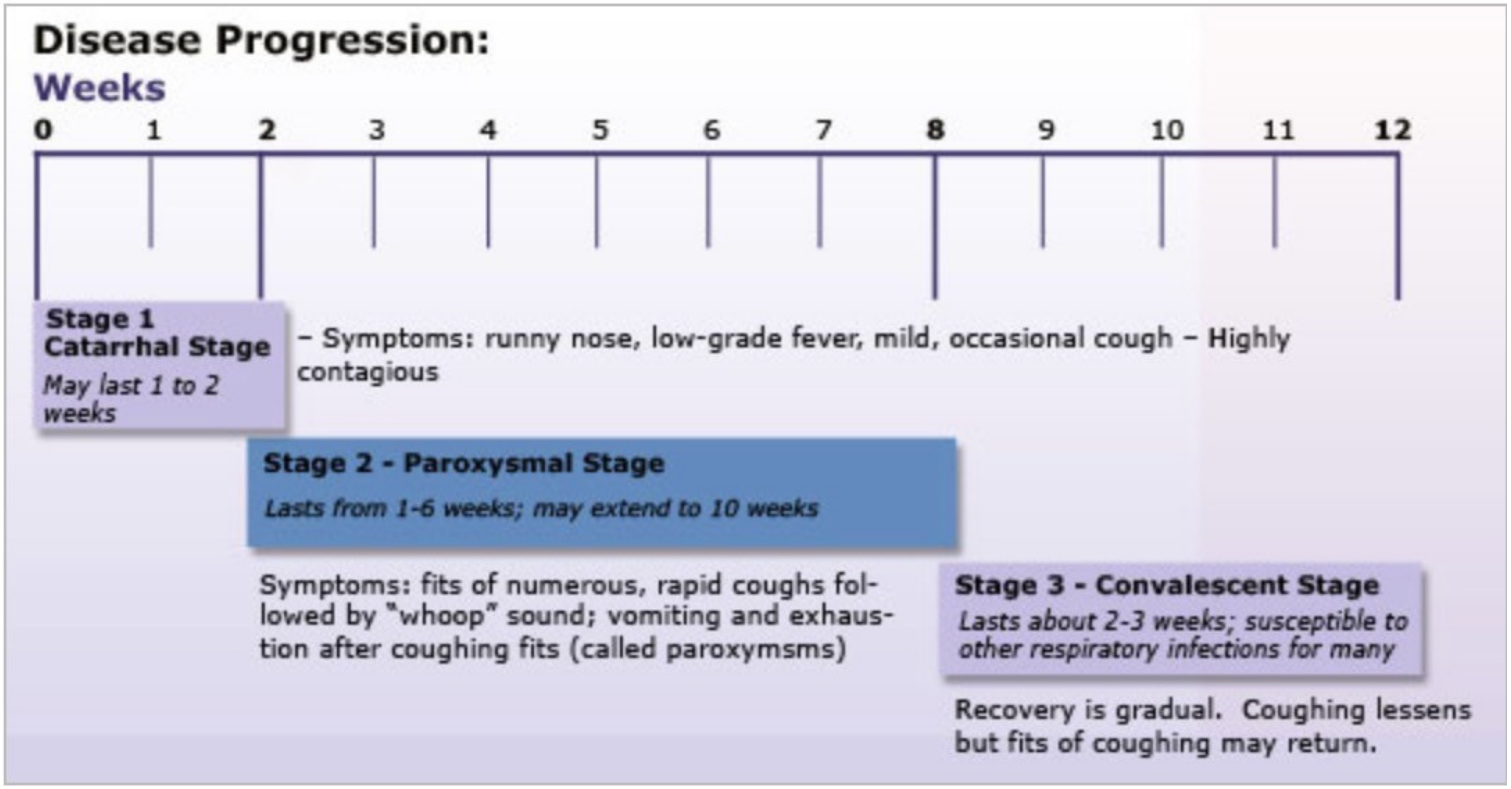
Pertussis – Whooping Cough

- Caused by *B. pertussis*
  - Fastidious, gram-negative bacteria
  - Only infects humans
  - Multiple virulence factors lead to infection and symptomatic disease
    - Pertussis toxin
    - Filamentous hemagglutinin
    - Agglutinins
    - Adenylate cyclase
    - Pertactin
    - Tracheal cytotoxin



CARBONETTI, N. (2007). Immunomodulation in the pathogenesis of *Bordetella pertussis* infection and disease. *Current Opinion in Pharmacology, 7*(3), 272-278. doi:10.1016/j.coph.2006.12.004 Current Opinion in Pharmacology, 2007, 7:272-278.

Pertussis – Clinical Disease



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Antibiotics in Pertussis

Treatment

- Treatment should occur as early as possible – needs to occur during the paroxysmal phase
  - 3 weeks of cough onset if older than 1 y/o
  - 6 weeks of cough onset if younger than 1 y/o
- Drugs of Choice
  - Azithromycin*#
  - Clarithromycin*
  - Erythromycin*

Post-Exposure Prophylaxis

- All household contacts of a pertussis case
- All high-risk people within 21 days of exposure to a pertussis case
  - Infants and women in the 3rd trimester of pregnancy
  - People with pre-existing health conditions which may be exacerbated
  - People living with infants or those with pre-existing conditions
  - People in high-risk settings
    - NICU, Childcare settings, Labor/Delivery

*Concern for hypertrophic pyloric stenosis in infants

Consider other agents with patients with prolonged QT syndrome

Pertussis Diagnostic Criteria

Clinical Criteria

- Cough Illness lasting > 2 weeks with at least one of the following:
  - Paroxysms of Coughing
  - Inspiratory Whoop
  - Post-tussive vomiting
  - Apnea

Laboratory Criteria

- Isolation of *B. pertussis* from a clinical specimen
- Positive PCR for *B. pertussis*

Epidemiologic Linkage

- Contact with a laboratory-confirmed case of pertussis

Case Classifications

Probable

- In the absence of a more likely diagnosis, illness meets clinical criteria

OR

- Illness with cough of any duration with at least one
  - Paroxysms of Coughing
  - Inspiratory Whoop
  - Post-tussive vomiting
  - Apnea

AND

- Contact with a laboratory confirmed case

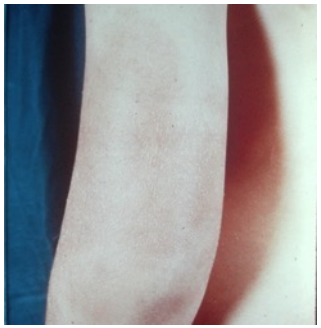
Confirmed

- Acute cough illness of any duration
  - Isolation of pertussis from a clinical specimen
  - PCR positive for *B. pertussis*

Pertussis Immunization – whole-cell (wP)

Historical

- First immunizations were developed in 1930's by Leila Denmark
- Developed a whole-cell killed B. pertussis bacteria
- This was very immunogenic
- Side effects were prevalent – increased with the addition of doses
  - Fevers
  - Arm swelling



Controversy

- 1970's and 80's
  - Great decrease in incidence of pertussis
  - There were a few very severe diseases associated with encephalopathy
- DPT producers began to stop due to lawsuits
- *DPT: Vaccine Roulette – WRC-TV4*
  - Increased lawsuits
  - National Childhood Vaccine Injury Act

Pertussis Immunization – acellular (aP)

History

- Sato develop the acellular vaccine to counteract Japanese disapproval with wP
  - Pertussis toxin (PT) and filamentous hemagglutinin (FHA)
- To increase efficacy, pertactin (pt) and type 2 and 3 fimbriae (fim) were added
- A switch was made as these vaccines were acutely efficacious with less side effects

Present formulations

- Dtap
  - Daptacel®, Pentacel®, Quadracel® (PT – 10ug, FHA – 5 ug, pt – 3 ug, fim – 5ug)
    - Pentacel® has half the PT and FHA
  - Infanrix ®, Kinrix®, Pediarix® (PT - 25 ug, FHA – 25 ug, pt – 8)
- Tdap
  - Adacel® (PT – 2.5ug, FHA – 5 ug, pt – 3 ug, fim – 5 ug)
  - Boostrix® (PT - 8 ug, FHA – 8 ug, pt – 2.5)

Impact of Change in Pertussis Vaccine

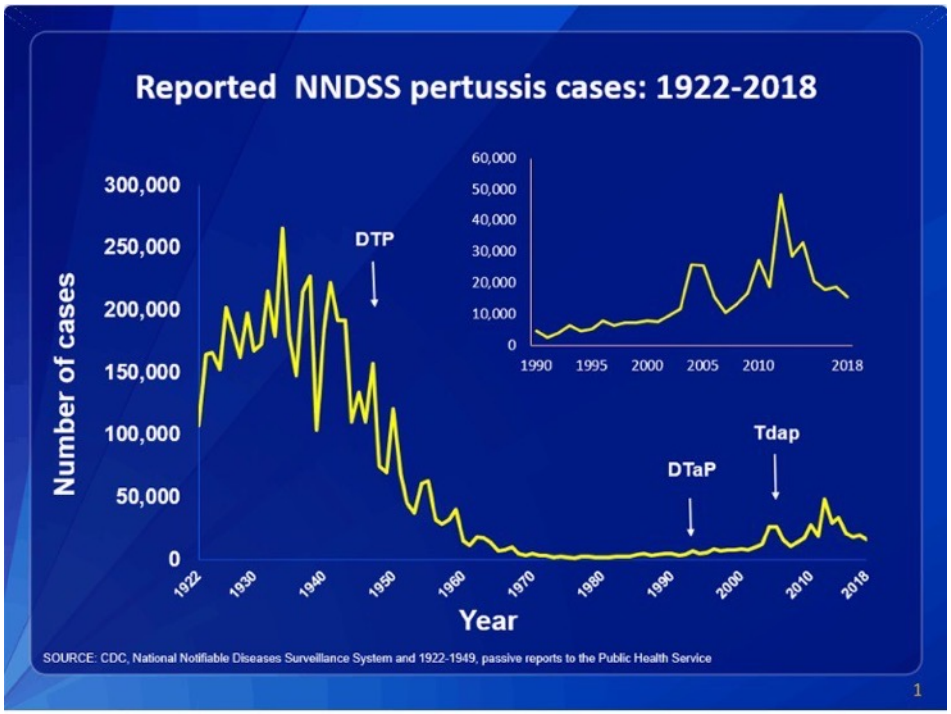
Increased incidence of Pertussis

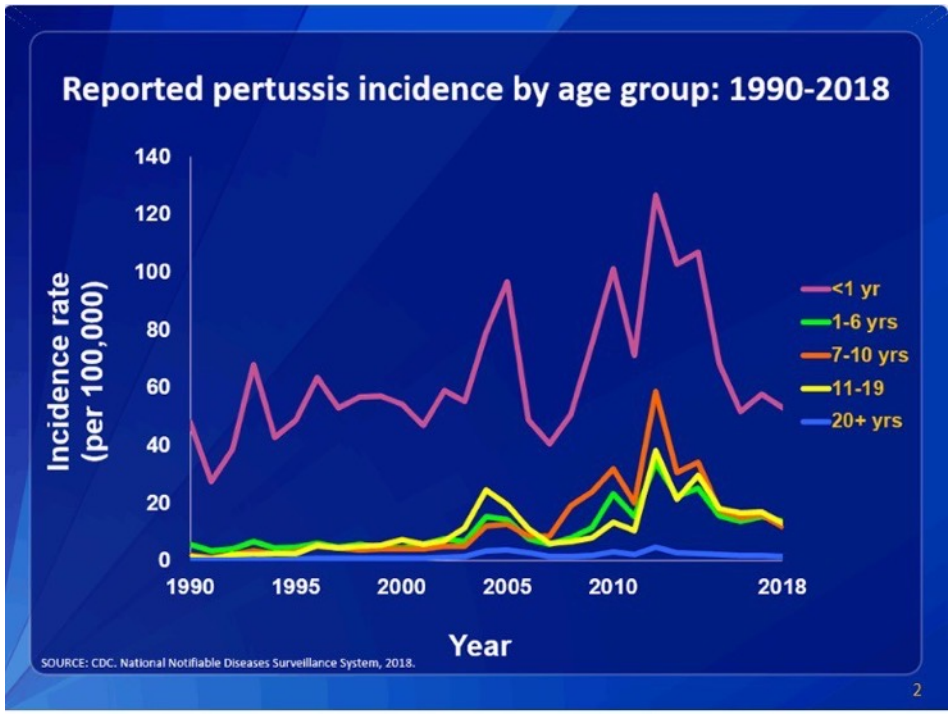
- Increased awareness (young adults)
- Improved diagnostic testing
  - Molecular techniques
- Improved reporting and surveillance
- Increased circulation of the bacteria
- Waning Immunity
  - aP vaccines are not as durable

Efficacy of aP Vaccines

- DtaP (completion of 5 doses)
  - 1 year – 98%
  - 5 year – 71%
- Tdap - Adolescents
  - 1 year – 73%
  - 4 year – 34%
- Tdap – Pregnant Women
  - Decreased pertussis cases by 78% in 2 month olds
  - Decreased hospitalizations by 90% in 2 month olds

Epidemiology of Pertussis in the U.S.





Pertussis. (2019, December 17). Retrieved March 14, 2021, from https://www.cdc.gov/pertussis/surv-reporting.html#surv

2019 Provisional Pertussis Surveillance Report

Reported Pertussis Cases and Percent Hospitalization by Age Group

Age	No. of Cases (% of total)	Age Inc /100,000	% Hospitalized by age**
< 6 mos	1202 (7.7)	62.5	40.7
6-11 mos	638 (4.1)	33.2	9.8
1-6 yrs	3282 (21.0)	13.7	3.1
7-10 yrs	1988 (12.7)	12.2	1.1
11-19 yrs	4758 (30.4)	12.6	1.5
20+ yrs	3736 (23.9)	1.5	8.2
Unknown Age	58 (0.4)	N/A	N/A
Total	**15,662 (100)**	**4.8***	**6.7**

Reported DTaP Vaccine Status of Children with Pertussis, Ages 6 months through 6 years

Age	Vaccine History Unknown	Unvaccinated	Undervaccinated (1-2 doses)	Completed Primary DTaP Series (3+ doses)	Total
	No. (%)	No. (%)	No. (%)	No. (%)	No.
6-11 mo	311 (48.8)	48 (7.5)	85 (13.3)	194 (30.4)	638
1-4 yrs	1206 (49.2)	234 (9.5)	89 (3.6)	923 (37.6)	2452
5-6 yrs	360 (43.4)	63 (7.6)	29 (3.5)	378 (45.5)	830
Total*	**1877 (47.9)**	**345 (8.8)**	**203 (5.2)**	**1495 (38.1)**	**3920**

Reported Pertussis Deaths

Age	Deaths*
Cases, aged < 1 yr	3
Cases, aged ≥ 1 yr	6
Total	**9†**

Pertussis. (2019, December 17). Retrieved March 14, 2021, from https://www.cdc.gov/pertussis/surv-reporting.html#surv

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Tetanus

- Caused by the bacterium – *Clostridium tetani*
  - It is spore forming – normally located in soil, dust, manure
  - Infection occurs through inoculation via contaminated objects or breaks in the skin
    - Wounds contaminated by dirt, feces, saliva
    - Puncture wounds via nails/needles
    - Burns
    - Crush trauma
- Incubation Period
  - 3-21 days, average of 14
  - Shorter incubation with more contaminated wounds
- Spores will germinate in anerobic environments and produce toxins
- Tetanus toxin will cause release of neurotransmitters
  - Seizures
  - Autonomic instability

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Tetanus, cont.

Epidemiology

- Who gets tetanus?
  - Unimmunized individuals
  - Those who have not received 10-year boosters
- 2009-2017
  - 264 cases reported in the U.S.
  - 60% between 20 and 64 years of age
  - 25% older than 65 years of age*

Risk Factors for Tetanus in the U.S.

- Diabetes
  - 13% of all cases and 25% of all deaths
- IV drug use
  - 7% of all cases
- Natural Disasters

* Group at highest risk of disease

Tetanus, cont.

Clinical Manifestations

- Lockjaw – Trismus
  - Caused by muscular contractions of the masseter and neck muscles
- Abdominal Rigidity
  - Often the first sign
- Generalized seizures
  - Induced by sensory stimuli
- Neonatal Tetanus – infected umbilical stump

Type	Lockjaw Present	Seizures Present	Localized Muscle Spasms	Facial Nerve Palsies	Mortality
Generalized	Yes	Yes			10-20%
Localized			Yes		
Cephalic				Yes	

Localized and Cephalic may rarely progress to Generalized

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Tetanus, cont.

Prevention

- Wound Assessment
  - Dirty
    - Soil, feces, saliva (human or animal)
  - Penetrating wounds
    - More likely to be contaminated
  - Wounds with devitalized tissue
    - Frostbite, crush injuries, avulsion injuries
- Clean all wounds to remove dirt, foreign material and necrotic material

Prevention

- Evaluate to see if they have completed a primary series (3)
- If yes
  - If last dose is < 5 years, they are protected
  - If last dose is > 5 years, give a booster
- If no, and a contaminated wound, you would give Tetanus Immunoglobulin (TIG)
  - Can bind and remove unbound toxin
  - 250 IU IM x 1
  - HIV patients and those with significant immunosuppression should also receive TIG

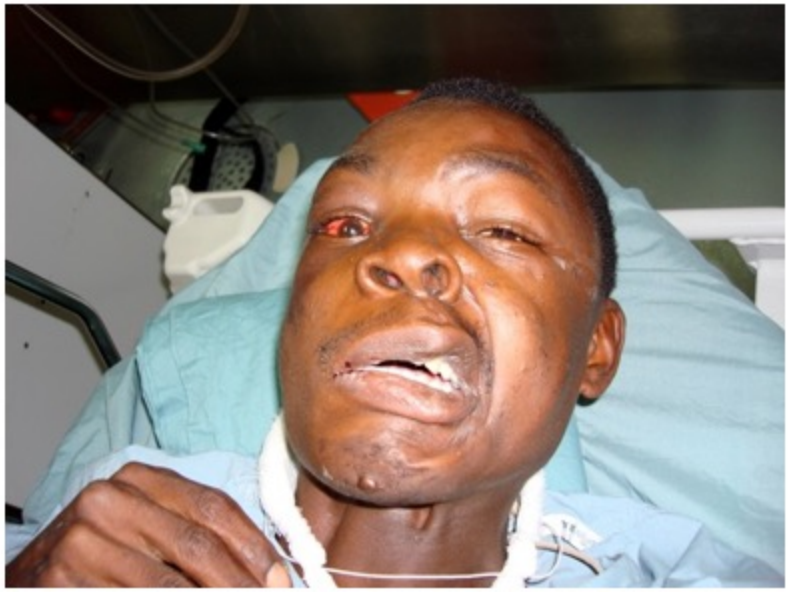
Tetanus – Why is this important?

- Operation Unified Response Haiti following the January 12, 2010 earthquake
- USNS COMFORT accepted first patients Jan 19
- Earthquakes produce a large number of wounded
- Haiti underimmunized to tetanus (~50%)
- In total, 6 tetanus patients were admitted over a ~50 day period of operations

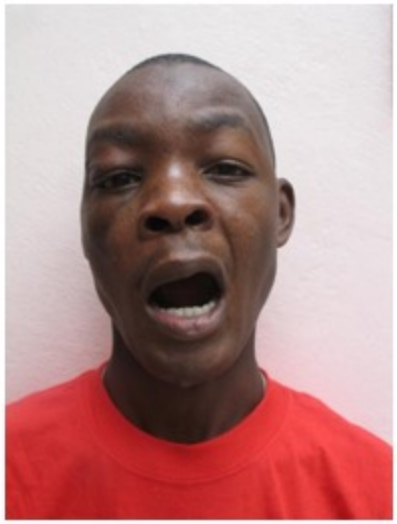
Courtesy of CAPT (Dr.) Todd Gleeson, M.D., M.P.H.

Tetanus – why is this important?

Patient with acute tetanus – Jockjaw



Patient follow-up at three weeks after D/C



Patient permission was obtained and provided courtesy of CAPT (Dr.) Todd Gleeson, M.D., M.P.H.

Poliovirus and Poliomyelitis

Oral Polio Vaccine (OPV), Inactivated Polio Vaccine (IPV)

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Poliomyelitis

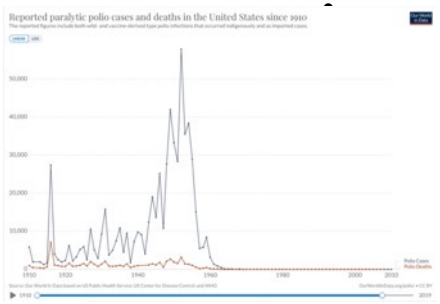
- Caused by *Poliovirus*
  - Member of the Enterovirus family
  - Three types of Poliovirus (1,2,3)
    - Wild poliovirus type 2 – eradicated in 2015 (WHO)
    - Wild type poliovirus type 3 – has not been detected since 2012
  - Humans are the only reservoir
- Polio remains only endemic in three countries (Never interrupted transmission)
  - Nigeria
  - Pakistan
  - Afghanistan
- Pathophysiology
  - Transmitted via the fecal-oral route
  - Transmission most likely due to contaminated drinking water
- Incubation Period – up to 10 days
- 75% of patients exhibit no symptoms
- 24% of patients develop abortive poliomyelitis
  - Fever
  - Cold-like symptoms
- 1-5% develop aseptic meningitis
  - Associated with stiff limbs for 10 days
- $\leq$ 2% lead to paralytic poliomyelitis

Paralytic poliomyelitis

- It is a biphasic illness
  - Resolution of viral syndrome
  - High fever returns with muscle pain and loss of reflexes
- Progression is sudden and quick with loss of motor function in a limb occurring over hours
  - Peaks about day 5
- Hallmark is asymmetric paralysis
  - Proximal muscles > distal muscles
  - Lower ext. > upper ext.
- Bladder and bowel atony are common
- CNS and cranial nerves can be involved
  - Cranial Nerves in 5%-35% of cases
- Respiratory Failure
  - Leading cause of death
  - Causes
    - Respiratory muscle weakness
    - Brainstem involvement
    - Cranial Nerves 9, 10, 12 lead to paralysis of the pharynx, soft palate and vocal cords
- Outcomes
  - Paralysis
    - Maximal improvement in 6 months
    - 60% of patients have some residual deficit
    - Spinal Poliomyelitis has a mortality rate is 7%
      - Vs. 60% in pre-ventilator era

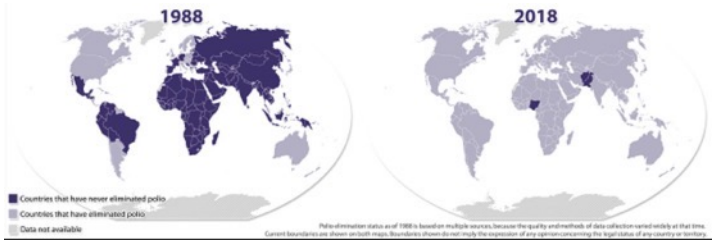
Poliomyelitis

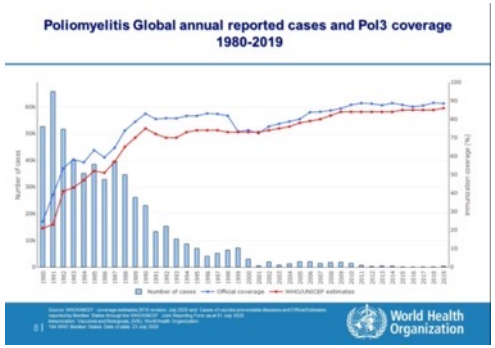
- Historical Perspective
  - Endemic
    - Few cases of Poliomyelitis
    - Overlap between maternal protection and early exposure
  - Epidemic
    - Occurred as hygiene improved
    - This overlap was spread out
      - U.S. epidemics showed ages ranging between 1 and 6 years of age
  - Vaccine Era



- Polio impact reduced first in more developed countries
- Eradicated from the Western Hemisphere in 1994

- Global Perspective
  - Wild-type poliovirus remains endemic in three countries
    - Afghanistan, Pakistan and Nigeria
  - Nearing eradication – possible due to no non-human reservoir

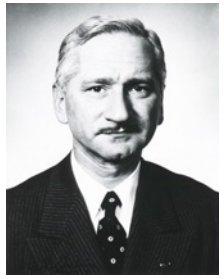




Poliomyelitis. (n.d.). Retrieved March 14, 2021, from https://www.who.int/

Poliomyelitis – The Vaccine Era

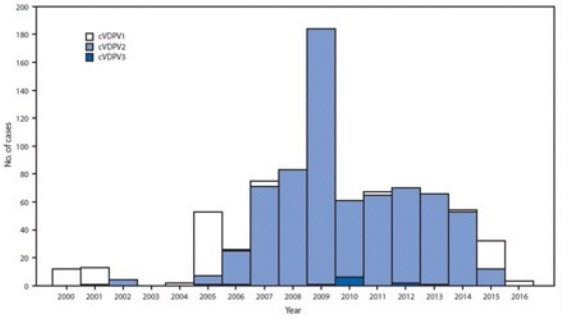
"Well, the people I would say. There is no patent. Could you patent the sun?", Jonas Salk, M.D., 1955



- Inactivated Polio Vaccine
  - Jonas Salk developed formaldehyde-inactivated polio vaccine
  - This vaccine was injectable
  - Initial study was on children who had previously had polio
    - Measured increased Ab levels
  - Conducted a randomized placebo-controlled trial
    - 1:1 – Aged 6 to 9 years of age
    - Coined "Polio Pioneers"
    - 90% effective at preventing paralytic polio
    - Tragic event in which 200 cases of paralytic polio and 11 deaths were attributed to a batch of vaccine that was not inactivated

- Oral Polio Vaccine
  - Prior to WWII, Sabin had worked on live Poliovirus cultures
  - Upon his return, he was at Cincinnati, conducted autopsies on all deaths within 400 miles
    - Determined that poliovirus began by first growing in the intestinal tract
  - Sabin tested many strains and found 3 that did not cause paralysis
  - Large-scale trial conducted in Soviet Union
  - Sabin's strains were delivered to Pfizer for mass production

Present Vaccines



- Vaccine Schedule
  - 2 months, 4 months, 6-18 months and 4 through 6 years
  - Recs are for IPV or trivalent OPV
  - Final dose > 4 years of age
- Oral Polio Vaccines (OPV)
  - Trivalent (tOPV) was the staple of use in the global eradication efforts
  - Bivalent (bOPV - 1,3) is the predominant vaccine in use
  - Monovalent immunizations exist
- Inactivated Polio Vaccine (IPV)
  - Protective against all virus types

- Vaccine-Derived (Associated) Paralytic Poliovirus
  - Vaccine Associated is when a spontaneous mutation occurs that leads to neurovirulence
    - 1 in 2.7 million cases
  - Derived – virus slowly transforms to be more virulent
    - Occurs in areas of low immunization coverage
    - Almost all were serotype 2
  - Led to changes in U.S. and use of bilavent vaccine globally

PERSPECTIVE | VIEWPOINT: COVID-19

Can existing live vaccines prevent COVID-19?

Konstantin Chumakov[1,2], Christine S. Benn[3], Peter Aaby[4], Shyamasundaran Kottilil[5], Robert Gallo[2,5]
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Science 12 Jun 2020:
Vol. 368, Issue 6496, pp. 1187-1188
DOI: 10.1126/science.abc4262

Science
Vol 368, Issue 6496
12 June 2020

The Journal of Clinical Investigation

CLINICAL MEDICINE

BCG vaccination history associates with decreased SARS-CoV-2 seroprevalence across a diverse cohort of health care workers

Magali Noval Rivas,[1,2] Joseph E. Ebinger,[3,4] Min Wu,[3,4] Nancy Sun,[3,4] Jonathan Braun,[5] Kimia Sobhani,[6] Jennifer E. Van Eyk,[3,7,8] Susan Cheng,[3,4,7] and Moshe Arditi[1,2,4]

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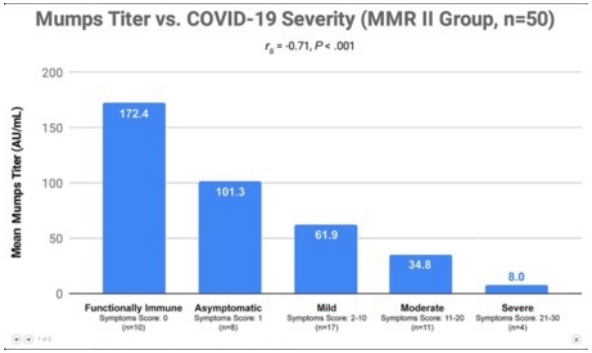
RESEARCH ARTICLE
Therapeutics and Prevention

Analysis of Measles-Mumps-Rubella (MMR) Titers of Recovered COVID-19 Patients

Jeffrey E. Gold,[a] William H. Baumgartl,[b] Ramazan A. Okyay,[c] Warren E. Licht,[d] Paul L. Fidel, Jr.,[e] Mairi C. Noverr,[f] Larry P. Tilley,[g] David J. Hurley,[h] Balázs Rada,[h] John W. Ashford[i]



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Immunization Contraindications and Precautions

Vaccine	Contraindications	Precautions
MMR	1. Severe reaction of anaphylaxis after previous dose 2. Pregnancy 3. Known severe immunodeficiency 4. Family history of altered immunocompetence	1. Receipt of antibody containing blood products (≤ 11 months) 2. History of thrombocytopenia or thrombocytopenic purpura 3. Need for tuberculin skin testing or interferon-gamma release assay (IGRA) testing 4. Moderate or severe acute illness with or without fever
DTaP	1. Severe reaction of anaphylaxis after previous dose 2.Encephalopathy within 7 days of a previous dose with no other source	1. Progressive neurologic disorder, including infantile spasms, uncontrolled epilepsy, progressive encephalopathy 2. Guillain-Barre Syndrome < 6 weeks after previous dose of tetanus-toxoid–containing vaccine 3. History of Arthus-type hypersensitivity reactions after a previous dose of diphtheria-toxoid–containing or tetanus-toxoid–containing vaccine 4. Moderate or severe acute illness with or without fever
IPV	1. Severe reaction of anaphylaxis after previous dose	1. Pregnancy 2. Moderate or severe acute illness with or without fever
Varicella	1. Severe reaction of anaphylaxis after previous dose 2. Pregnancy 3. Known severe immunodeficiency 4. Family history of altered immunocompetence	1. Receipt of antibody containing blood products (≤ 11 months) 2. Receipt of specific antiviral drugs (acyclovir, famciclovir, or valacyclovir) 24 hours before vaccination; avoid use for 14 days following immunization 3. Use of aspirin or aspirin containing products 4. Moderate or severe acute illness with or without fever

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Key Takeaways

- Childhood vaccines have decreased the morbidity and mortality of children globally.
- Clinicians must be cognizant of the clinical presentation of vaccine- preventable diseases (VPD) in order recognize them in outbreak settings.
  - Particularly important for DoD personnel who may deploy to any setting
  - Clinicians need to understand both local and global epidemiology of VPD
- Immunizations are safe but they do have important adverse events which need to be monitored.

Acknowledgments

- Historical photos have been provided by Dr. Dale Smith, Ph.D., Professor of Military Medicine and History, USUHS. Photos have been taken from the following websites which are public domain.
  - www.loc.gov/pictures/
  - www.nlm.nih.gov/hmd/ihm/index.html
  - www.wellcomecollection.org/collections

- Photos of Congenital Rubella are used with permission by Dr. Ashley Maranich, M.D., LTC (P), MC, USA, Assistant Dean for Clinical Sciences, USUHS.

- Photos of Tetanus are used with permission from Dr. Todd Gleeson, M.D., M.P.H., CAPT, MC, USN.
- Additional clinical photos have been obtained from personal files and those of the Department of Pediatrics at USUHS.

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