a historical review of the Measles virus, vaccine and outbreaks
Amy Prudhomme, DO pgy3
Objectives

- discuss history and clinical course of the Measles virus
- be able to recognize Measles exanthem
- discuss recent outbreaks and safety profile of vaccine in light of ever-growing culture of vaccine refusal
History of Measles

- First described by a Persian doctor, Rhazes, in the 9th century in efforts to distinguish it from smallpox.
- 1657: Measles first appears in Boston.
- 1861: Measles plays a role in the American Civil War.
  - Union army alone-67,000 cases and 4,000+ deaths from measles.
History of Measles

- 1912- Measles became a reportable disease in the US
  - in the first decade ~6,000 measles-related deaths were reported each year
- 1916- Measles antibodies identified by French researchers Charles Nicolle, MD and Ernest Consell, MD
  - serum from infected patient’s blood could be used to protect others from the disease
History of Measles

- by the 1950s, nearly all children got measles by the time they were 15 years old.
- estimated that 3-4 million people were infected each year
  - 400-500 deaths, 48,000 hospitalizations, 4,000 cases of encephalitis reported per year
Description of Virus

- Measles virus = Rubeola
- single-stranded enveloped RNA virus
- family Paramyxoviridae
- genus Morbillivirus
- only 1 serotype exists
- humans are the only vector of disease
Transmission

- one of the most contagious infectious diseases
- 9 out of 10 susceptible individuals exposed to measles will contract the disease
- transmitted by direct contact or respiratory droplets.
- virus can remain in the air or on a surface for up to two hours after an infected person leaves the area
- inactivated by heat, light, acidity
Infection Control

- importance of all healthcare workers to be immune
  - documentation of 2 vaccines or + IgG
- airborne precautions immediately
  - mask patient
  - healthcare workers- N95 mask
- isolation needed
  - suspected infected patients not allowed to wait in waiting rooms or common areas
- do not use exam room/ hospital room for >1 hour after patient leaves
Stages of Infection

- Incubation
- Prodrome
- Exanthem
- Recovery and Immunity
Incubation

- entry via respiratory tract, conjunctiva or mucosa
- replicates and spreads to lymphatic tissue
- incubation 7-21 days
- usually asymptomatic
- contagious 5 days before appearance of rash to 4 days post appearance
Prodrome

- 3 C’s-
  - cough
coryza
conjunctivitis
- fever
- malaise
- anorexia
- usually lasts 2-3 days
Conjunctivitis
Koplik spots

- small white elevations on an erythematous base
- "grains of salt on a red background"
- usually on day 2 or 3
- 48 hours before exanthem appears
- pathognomonic
- last for 12-72 hours
Koplik Spots
Exanthem

- day 3-5 of illness
- erythematous blanching macules
- papular
- coalescing
- starts on face
- cephalocaudal
Exanthem

- centrifugal
- degree of convalescence seems to correlate with severity of illness
Exanthem

- spares palms and soles
- accompanied by spike in fever
- more pronounced respiratory symptoms, pharyngitis, conjunctivitis
Exanthem

- clinical symptoms begin to improve within 48 hours
- exanthem lasts 6-7 days
- after 3-4 days turns brown
- desquamates
Recovery and Immunity

- cough can persist for up to 1-2 weeks
- fever up to 3rd to 4th day of rash
- immunity - lifelong
  - reinfection rare
- transient immunosuppression
  - suppression of T cell response
Diagnosis

- IgM antibody testing
  - gold standard in high-prevalence locations (WHO)
  - detectable ~3 and up to 30 days after exanthem appearance
- RNA PCR via nasopharyngeal swab - as soon as exanthem appears
- Viral culture - blood, respiratory secretions, conjunctival swab or urine
Histopathology

- giant cells with intracytoplasmic inclusions
- epithelial swabs
- urine

Measles pneumonia

Medium power view of a lung biopsy from a patient with measles pneumonia shows a nodular pattern with acute and chronic inflammation and areas of necrosis and fibrosis. Multinucleated giant cells with inclusions (arrows) are also shown (hematoxylin-eosin, 500X).
Additional Findings

- Laboratory
  - leukopenia
  - thrombocytopenia
- Chest Xray
  - interstitial pneumonitis
Reported Measles Cases
October 2014 - May 2015
Complications

- according to the CDC 30% of measles cases have one or more complication
- at risk population for complications
  - children younger than 5 years and adults 20 years and older
  - children in developing countries
    - <12 months of age
    - malnourished- Vitamin A deficiency
  - immunocompromised patients
  - pregnant women
Complications

- most common
  - diarrhea and otitis media 5-10%
- respiratory
  - pneumonia is the most common cause of death from measles
- occur most frequently in patients at ends of age spectrum
Complications

- neurologic
  - acute encephalitis - second most common cause of death from measles (1 per 1000 cases)
  - acute disseminated encephalomyelitis (ADEM) within 2 weeks of exanthem
  - subacute sclerosing panencephalitis (SSPE) fatal progressive degenerative CNS disease
    - pathogenesis - possible persistent infection
    - rare 5-10 per million cases
    - average 7 years post measles
Stages of SSPE

- Subacute Sclerosing Panencephalitis
  1) personality changes
  2) dementia and myoclonic jerks
  3) deterioration to flaccidity or rigidity and autonomic dysfunction
  4) vegetative state
Complications

- Eye manifestations-
  - keratitis, common cause of blindness in African children
  - corneal ulceration
- Gastrointestinal
  - gingivostomatitis
  - diarrhea
  - appendicitis
  - hepatitis
- Cardiac- myocarditis, pericarditis
Clinical Variants

- immunocompromised patient
- HIV, T-cell deficiency
- severe, prolonged course
- typical rash may be absent
Clinical Variants

- pregnant women-
  - increased risk for complications
  - low birthweight,
  - spontaneous abortion,
  - intrauterine fetal demise,
  - maternal death
Clinical Variants

- atypical measles
  - individuals who received the killed virus vaccine 1963-1968
  - encounter wild-type virus
  - fever and headache, cough, rash (peripheral to central)
  - difficult to diagnose
Treatment

- Supportive care
- Vitamin A
Vitamin A

- WHO recommends Vitamin A for children with measles who may be Vitamin A deficient.
- A Cochrane review meta-analysis was conducted with 8 randomized control trials and over 2500 patients.
- Concluded that two megadoses of Vitamin A 200,000IU x2 days reduced overall mortality and pneumonia specific mortality of measles in children <2 years old.
Back to the Timeline....
1954- Dr. John F. Enders and Dr. Thomas C. Peebles of Boston Children’s Hospital collected samples of infected children at a local private school in efforts to create a vaccine

13 yo David Edmonston was one of these children

- successful isolation of the virus from his blood

1958- tested vaccine on mentally handicapped children - developed antibodies but also symptoms

1963- Edmonston-B strain of measles virus, live vaccine was licensed for distribution in the US

- killed vaccine also licensed
Development of Vaccine

- 1968- the reformulated, more attenuated Edmonston-Enders strain continues to be the only vaccine used in the US still today
Goal of Measles Elimination

- 1978 CDC declared a goal of eliminating measles by 1982
  - not accomplished
- 1981 - 80% less cases than in 1980
- 1989-1991 Resurgence of Measles in the US occurred
  - 55,622 cases reported, 123 deaths
  - 90% of fatal cases were in persons who were not vaccinated
Resurgence

- unique demographics in regard to age and race
- 45% of cases were reported to be <5 years old
- incidence in infants <12 months twice as high as other age groups
- highest incidence in minority groups
  - hispanic and african american 4-7x higher than for non-hispanic white children
  - less likely to be age-appropriately vaccinated
- outbreak areas- vaccination rate as low as 50% by second birthday
2 dose vaccine schedule

- 1989- outbreak prompted the AAP, AAFP, and advisory committee on immunization practices to recommend a second dose of MMR vaccine in the preschool age population
  - result= rapid decline of measles cases
- 1997- 2 year old vaccination rate was 91%
Measles Elimination

- 2000-United States declared Measles elimination
  - absence of continuous disease transmission for 12 months in a specific geographic region
  - different from eradication (zero prevalence)
  - no longer endemic (constantly present)
  - largely due to vaccine compliance (1)
Goal Elimination
Measles Vaccine

- attenuated Edmonston-Enders strain
- measles+mumps+rubella= MMR
  - +varicella= MMRV “ProQuad”
- chick embryo fibroblast tissue culture in powder form
- reconstituted in sterile, preservative-free water
- human albumin, neomycin, sorbitol, gelatin
MMR Vaccine

- live virus
  - 95% of patients will develop antibodies with first dose at 12 months of age
  - vaccine failure rate with single vaccine 2-5%
  - 2 dose efficacy 99%
  - duration of immunity - lifelong
  - foreign travel < 1 year of age
2015 Recommended Immunizations for Children from Birth Through 6 Years Old

| Age  | HepB | HepB | RV | RV | RV | HepB | DTaP | DTaP | Hib | Hib | Hib | Hib | PCV | PCV | PCV | IPV | IPV | Influenza (Yearly)* | MMR | MMR | Varicella | Varicella | HepA^5 |
|------|------|------|----|----|----|------|------|------|-----|-----|-----|-----|-----|-----|-----|-----|---------------------|-----|-----|-----------|-----------|-------|
| Birth|      |      |    |    |    |      |      |      |     |     |     |     |     |     |     |     |                     |     |     |           |           |       |
| 1 month | HepB |      |    |    |    | HepB |      |      |     |     |     |     |     |     |     |     |                     |     |     |           |           |       |
| 2 months |      | HepB |    |    |    |      |      |      |     |     |     |     |     |     |     |     |                     |     |     |           |           |       |
| 4 months |      |      |    |    |    |      |      |      |     |     |     |     |     |     |     |     |                     |     |     |           |           |       |
| 6 months |      |      |    |    |    |      |      |      |     |     |     |     |     |     |     |     |                     |     |     |           |           |       |
| 12 months |      |      |    |    |    |      |      |      |     |     |     |     |     |     |     |     |                     |     |     |           |           |       |
| 15 months |      |      |    |    |    |      |      |      |     |     |     |     |     |     |     |     |                     |     |     |           |           |       |
| 18 months |      |      |    |    |    |      |      |      |     |     |     |     |     |     |     |     |                     |     |     |           |           |       |
| 19–23 months |      |      |    |    |    |      |      |      |     |     |     |     |     |     |     |     |                     |     |     |           |           |       |
| 2–3 years |      |      |    |    |    |      |      |      |     |     |     |     |     |     |     |     |                     |     |     |           |           |       |
| 4–6 years |      |      |    |    |    |      |      |      |     |     |     |     |     |     |     |     |                     |     |     |           |           |       |

*Shaded boxes indicate the vaccine can be given during the shown age range.
## Adverse Side Effects

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>fever</td>
<td>5-15%</td>
</tr>
<tr>
<td>rash</td>
<td>5%</td>
</tr>
<tr>
<td>joint symptoms</td>
<td>25%</td>
</tr>
<tr>
<td>thrombocytopenia</td>
<td>&lt;1/30,000 doses</td>
</tr>
<tr>
<td>parotitis</td>
<td>rare</td>
</tr>
<tr>
<td>deafness</td>
<td>rare</td>
</tr>
<tr>
<td>encephalopathy</td>
<td>&lt;1/1,000,000 doses</td>
</tr>
</tbody>
</table>
MMR + V vs MMRV

- CDC recommends first dose as MMR + V in the age group 12-15 mos
- second dose may be MMRV in older population
<table>
<thead>
<tr>
<th>Protection against measles, mumps, rubella and varicella</th>
<th>MMR and Varicella Vaccines (Administered at the same doctor visit)</th>
<th>MMRV Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protection against measles, mumps, rubella and varicella</td>
<td>Provides the same protection against the four diseases as the MMRV vaccine</td>
<td>Provides the same protection against the four diseases as the MMR and varicella vaccines</td>
</tr>
<tr>
<td>Number of shots</td>
<td>Two shots needed at the same doctor visit to provide protection against measles, mumps, rubella, and varicella</td>
<td>One shot needed to provide protection against measles, mumps, rubella, and varicella</td>
</tr>
<tr>
<td>Fever</td>
<td>Fewer children have fevers of 102°F or higher within 42 days of being vaccinated (about 15 out of every 100 children vaccinated; the highest risk for fever occurs during 5-12 days after vaccination)</td>
<td>More children have fevers of 102°F or higher within 42 days of being vaccinated (about 22 out of every 100 children vaccinated; the highest risk for fever occurs during 5-12 days after vaccination)</td>
</tr>
<tr>
<td>Febrile seizures (Seizures caused by fever)</td>
<td>Fewer children have febrile seizures during the 5-12 days after vaccination (about 4 out of every 10,000 children vaccinated)</td>
<td>More children have febrile seizures during the 5-12 days after vaccination (about 8 out of every 10,000 children vaccinated)</td>
</tr>
</tbody>
</table>
any other adverse reactions?

Safety of Measles-Containing Vaccines in 1-Year-Old Children

Pediatrics February 2015

123,200 MMRV  584,987 MMR+V

compared 7 main outcomes

- anaphylaxis, ITP, ataxia, arthritis, meningitis/encephalitis, acute demyelinating encephalomyelitis, Kawasaki disease

other than previously identified increased risk of fever and febrile seizure, no other new safety concerns were identified

outcomes unlikely to occur after either vaccine
Who should Not get the Vaccine?

- persons who experienced anaphylaxis following prior administration of MMR vaccine
- pregnant women
- severely immunosuppressed individuals
  - high dose corticosteroids (20mg/day for 14 days)
- recent blood products
Back to the Timeline....
2014

668 cases of measles from 27 states reported by the CDC

Greatest number of cases since measles was declared eliminated in 2000
Outbreak identified at Disneyland in Anaheim, CA

Jan 7 - officials warned the public that a Disneyland visitor may be linked to 7 confirmed cases of the measles in CA, 2 in Utah

5 Disneyland employees also contracted measles

Doctors suspect the index case visited the park December 15-20, 2014
Rapid Spread

- Over the next several weeks, the virus spread throughout CA
- Jan 9-Orange County: 5 more cases
- Jan 12- Longbeach County: 1 case
- Jan 13- San Bernardino County: 3 new cases
- Jan 16- San Diego: 7 new cases
- Jan 17- at least 51 cases of Measles diagnosed
  - all but 9 were connected to Disney theme parks
  - 45 were in California
Outbreak Ended

- April 17, 2015 the measles outbreak was declared over
- at least two 21 day incubation periods (42 days) have elapsed from the end of the infectious period of the last known outbreak-related measles case
by April 17, 2015 162 cases of Measles were reported in 19 states
Extent of Disease

Measles Cases and Outbreaks
January 1 to April 17, 2015*

162 Cases

4 Outbreaks


representing 90% of reported cases this year

U.S. Measles Cases by Year

*Provisional data reported to CDC’s National Center for Immunization and Respiratory Diseases
Extent of Disease

- 147 from 7 states were linked to the Disneyland outbreak.

U.S. Multi-state Measles Outbreak
December 28, 2014 - April 17, 2015

Cases*:
- 0
- 1-4
- 5-9
- 10-19
- 20+

From December 28 to April 17, 2015, 147 people from 7 states [AZ (7), CA (131), CO (1), NE (2), OR (1), UT (3), WA (2)] were reported to have measles and are considered to be part of a large outbreak linked to an amusement park in California*. 

*Provisional data according to CDC; National Center for Immunization and Respiratory Diseases
Outbreak linked to Vaccine Refusal

RESEARCH LETTER

Substandard Vaccination Compliance and the 2015 Measles Outbreak

- JAMA Pediatrics article March 2015
- Substandard vaccination rates
- Estimated vaccination rate was 50-86% in exposed population
- 95% is needed for herd immunity

\[ V = \frac{I}{V_E} = \frac{1 - (R_E/R_{0})}{V_E} \]
Vaccine Refusal

- growing cultural movement
- Louisa Clinic
  - 4 mo male and 3yo brother
  - vaccine “not safe”
- “Personal Exemption”
Effect of Age on the Risk of Fever and Seizures Following Immunization With Measles-Containing Vaccines in Children

Ali Rowhani-Rahbar, MD, MPH, PhD; Bruce Fireman, MA; Edwin Lewis, MPH; James Nordin, MD, MPH; Allison Naleway, PhD; Steven J. Jacobsen, MD, PhD; Lisa A. Jackson, MD, MPH; Alison Tse, ScD; Edward A. Belongia, MD; Simon J. Hambidge, MD, PhD; Eric Weintraub, MPH; Roger Baxter, MD; Nicola P. Klein, MD, PhD

[+ ] Author Affiliations

"There is no evidence whatsoever of the ability of vaccines to prevent any diseases. To the contrary, there is a great wealth of evidence that they cause serious side effects." -- Dr. Viera Scheibner

"My suspicion, which is shared by others in my profession, is that the nearly 10,000 SIDS deaths that occur in the United States each year are related to one or more of the vaccines that are routinely given children. The pertussis vaccine is the most likely villain, but it could also be one or more of the others." -- Dr. Mendelsohn, M.D.
megan’s story
Anti-vaxer converts

Family defects from anti-vaccination stance after 7 children contract whooping cough

“I want them to know that we tried our best to protect our kids when we were afraid of vaccination and we are doing our best now, for everyone’s sake, by getting them up to date,” Hill concluded. “We can’t take it back … but we can learn from this and help others the same way we have been helped.”
Pro-vaccine Media

Elmo And The Surgeon General Ponder Why Some People Don’t Get Vaccinated
Over the last two decades, extensive research has asked whether there is any link between childhood vaccinations and autism. The results of this research are clear: Vaccines do not cause autism. We urge that all children be fully vaccinated.

Rob Ring  
Chief Science Officer, Autism Speaks
Conclusion

- better understand history and clinical course of the Measles virus
- able to recognize Measles exanthem
- discuss recent outbreaks and safety profile of vaccine with future patients
references

- [http://www.cdph.ca.gov/HealthInfo/discond/Pages/Measles.aspx](http://www.cdph.ca.gov/HealthInfo/discond/Pages/Measles.aspx)
- [http://www.historyofvaccines.org/content/timelines/measles](http://www.historyofvaccines.org/content/timelines/measles)
- Oldstone, M. Viruses, Plagues and History 146-147 (2009)
- photos courtesy of [www.vaccineinformation.org](http://www.vaccineinformation.org)
- Vitamin A for Treating Measles in Children Hui Ming Yang, Meng Mao, Chaomin Wan Editorial Group: [Cochrane Acute Respiratory Infections Group](http://www.cdph.ca.gov/HealthInfo/discond/Pages/Measles.aspx) Published Online: 19 OCT 2005 DOI: 10.1002/14651858.CD001479.pub3
- CDC, Measles. Pink Book
- WHO.int/mediacentre/factsheets
Thank You

- Dr. Begue and Dr. Lefevre