Vaccine Preventable Disease Spots – A Rash of Measles

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VPDs - Why do we care?

- Prior to vaccine developments in the 1960s, viral diseases such as measles, rubella, and polio were standard childhood illnesses
- May cause severe or fatal disease
- Highly transmissible; infection prevention and control can be challenging
# Available Viral Vaccines

<table>
<thead>
<tr>
<th>Viral Disease</th>
<th>Reportable to Public Health*</th>
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<tbody>
<tr>
<td>Polio</td>
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<tr>
<td>Measles</td>
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<tr>
<td>Mumps</td>
<td>Yes</td>
</tr>
<tr>
<td>Rubella</td>
<td>Yes</td>
</tr>
<tr>
<td>Varicella (Chickenpox/Shingles)</td>
<td>Hospitalizations, deaths and outbreaks</td>
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<tr>
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<tr>
<td>Hepatitis B</td>
<td>Acute/chronic/perinatal</td>
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<td>Novel human strains</td>
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<td>Rotavirus</td>
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* California Code of Regulations, Title 17 Sections 2500, 2502 & 2505
VPDs Today

• The viruses in the MMR vaccine
• The disease presentations
• The vaccines
• Diagnosis
• Epidemiology
Measles, Mumps, Rubella – The Viruses

- Enveloped viruses with ss RNA genomes & glycoproteins that function in attachment

<table>
<thead>
<tr>
<th>Virus</th>
<th>Family</th>
<th>Genome</th>
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<tbody>
<tr>
<td>Rubella</td>
<td>Togaviridae</td>
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<tr>
<td>Measles &amp; Mumps</td>
<td>Paramyxoviridae</td>
<td>Negative sense RNA</td>
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- Each has only 1 serotype
- Infect only humans
- Transmitted by airborne droplet & fomites
Measles Mumps Rubella (MMR) Vaccine

• Live attenuated viruses
  – Measles first licensed in 1963
  – Mumps vaccine licensed 1967
  – Rubella vaccine licensed 1969 (7 yrs after 1st cultured)
  – Modern MMR vaccine licensed in 1971

• Efficacy: Measles 95%, Mumps 88%, Rubella >90%

• Protection: Lifelong?

• ACIP recommends two doses
  – One dose at 12 to 15 months
  – Second dose at 4 to 6 years recommended in 1989

• MMR diseases each declared eliminated from US, early 2000s

• Must be used to be effective...
<table>
<thead>
<tr>
<th>Year</th>
<th>Measles Cases</th>
<th>Mumps Cases</th>
<th>Rubella Cases</th>
<th>CRS</th>
<th>Varicella School Outbreak</th>
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<td>8</td>
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</table>

Source: CDPH Immunization Branch
Measles Mumps Rubella Diagnostics

Figure 3. Immune responses in acute measles infection (after [7])

- Virus detectable in nasopharynx
- Virus detectable in blood

Serology: IgM & IgG

Real-time RT-PCR

Genotyping

Culture
# Measles, Mumps, Rubella - Specimens for Diagnostic Testing

<table>
<thead>
<tr>
<th>Assay</th>
<th>Sample</th>
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<tr>
<td>RT-PCR, culture</td>
<td>Respiratory swabs</td>
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<tr>
<td></td>
<td>Measles/Rubella: NP or throat swabs</td>
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<tr>
<td></td>
<td>Mumps: Buccal swabs</td>
</tr>
<tr>
<td>RT-PCR, culture</td>
<td>Urine (Measles only)</td>
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<tr>
<td>Genotyping</td>
<td>PCR/culture-positive samples</td>
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<tr>
<td>IFA/EIA for IgM/IgG</td>
<td>Serum</td>
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</tbody>
</table>

* Culture: No longer routine, but is done by request

**Timing:** Samples for PCR/culture/genotyping: 0-10 d of onset; Serum: ~3-14 days from onset
A Word about Serology

• Serology is used to determine presence/absence of Ab to assess
  – If a person is immune or susceptible to a pathogen
  – If a person’s illness is due to a particular pathogen

• Immunity screens
  – Typically done by EIA or IFA. Is this appropriate? What does a positive EIA/IFA result tell you?
  – Indicates presence or absence of Ab, but not whether Ab is protective
  – Best assays: Functional neutralization tests (e.g., PRNT, FAMA), Avidity

• False positive IgM:
  – long-lasting IgM (e.g. WNV)
  – Polyclonal activation (e.g. EBV)

• False negative IgM: infected, previously vaccinated persons (e.g. measles, mumps, etc)

• Typically PHL receives only 1 serum sample per patient
Genotyping

- **Measles**: 23 genotypes (N gene)
- **Mumps**: 12 genotypes (SH gene)
- **Rubella**: 2 clades (E1 gene)
- Distinguish wild-type from vaccine strain
- Establish genetic relatedness between strains
  - Build phylogenetic trees
- Aids epidemiologic tracing of infection source

Measles reference strains
The Role of Epidemiologists

• Conduct disease investigations
  – Case contact investigations
  – Disease source

• Recommend appropriate prophylaxis

• Analyze surveillance data

• Monitor for state-wide outbreaks

• Share case and outbreak information with local public health jurisdictions and the CDC
MEASLES
Measles Clinical Features

• **Prodrome** – onset 8 to 12 days after exposure (range=7-21 days)
  – Fever to 101º F or higher
  – Cough, coryza, conjunctivitis
  – Koplik spots (rash on mucous membranes)

• **Rash**
  – 2-4 days after prodrome, 14 days after exposure
  – Maculopapular
  – Begins on face and head, becomes confluent
  – Persists 5-6 days
Transmission

• Highly contagious: $R_0 = 15-17$
• Cases are infectious from 4 days prior to 4 days after rash onset
• Transmission: droplet/aerosol/fomites
  – Aerosolized virus viable 30+ minutes
  – On fomites is viable < 2hr
  – Transmission can occur for up to 2 hours after an infectious person has left an exposure setting
→ All factors that make measles epi investigations time-intensive, time-sensitive, and expensive
Measles Annual Stats in the Prevaccine Era – United States, 1950s

• ~ 500,000 reported cases
  – 3-4 million cases including unreported?
• Severe complications
  – 4,000 encephalitis cases
  – 150,000 respiratory complications (pneumonia)
  – SSPE: rare progressive, fatal, late neurological complication from persistent wild-type measles
• 48,000 hospitalizations
• 450 deaths
Vaccine Licensed 1963

Measles – United States, 1950-2005

- Vaccine Licensed 1963
- 2nd dose 1989
- Endemic transmission interrupted
- Measles declared eliminated
## Cases and Outbreaks, 2005 to 2013

<table>
<thead>
<tr>
<th>Year</th>
<th>Confirmed Measles</th>
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</thead>
<tbody>
<tr>
<td>2005</td>
<td>4</td>
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<tr>
<td>2006</td>
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<tr>
<td>2007</td>
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<td>2011</td>
<td>31</td>
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<tr>
<td>2012</td>
<td>8</td>
</tr>
<tr>
<td>2013</td>
<td>18</td>
</tr>
</tbody>
</table>

- Cases in both adults and children
- Most cases imported or linked to importations
CSTE Measles Case Definition

- PCR positive OR
- IgM positive OR
- Significant rise in IgG OR
- Linked to a confirmed case
Measles Serology: EIA or IFA

• IgG
  – Testing for diagnosis requires acute/convalescent pair
  – A positive “immunity screen” only indicates presence of IgG antibody to measles, not whether person will be protected from infection
    • Requested during contact investigations

• IgM
  – Can be used to confirm a suspect case
  – False (+) IgM may occur w/ parvo B19, heterophile Ab, Rh factor
  – False (-) may occur in previously vaccinated individuals

→ PCR is preferred over IgM for acute case diagnosis
Molecular Detection

- **Test of choice: Real-time RT-PCR**
  - NP or throat swabs in VTM or urine collected 1-10d after rash onset
  - 3 gene targets: N, F & H genes

- **Genotyping**
  - 450 bp of N gene
  - Sequence compared against WHO reference strains
  - Phylogeny determined using WHO Global Measles Sequence Database
Measles 2014
January 2014

- In early January, CDPH epidemiologists were informed of a suspect measles case in a Southern California resident who had recent contact with international travelers.
- Within days, another suspect case was reported from a different county, this time in a person who had traveled to the Philippines.
- One week later, another case was reported, this one a traveler from India, followed by a case with no history of either travel or contact with international travelers.
- As the weeks turned to months, suspect cases continued to be reported.
- During the first 6 months of 2014, over 250 cases of suspect measles were reported to CDPH from around the state.
2014 Measles Testing

- Testing was performed on over 230 suspect cases
- PCR was performed on respiratory swabs and/or urine
  - Results were available either the same day or the day after specimen receipt
- IgM and IgG testing also were prioritized to identify new cases or provide evidence of prior exposure to measles
- Genotyping was performed on all PCR positive specimens
2014 Measles Testing

61 confirmed measles cases, Jan- June 2014:

- **47** cases PCR positive in urine and/or respiratory specimen
- **8** cases were IgM positive at outside labs
- **6** confirmed by epi-links to confirmed cases (no testing done)
California counties reporting measles cases (n=61)
January 1st - June 23rd, 2014

The majority of cases occurred in Southern California, with over 1/3rd of cases in Orange County and 1/6th in LAC.
Country | #Suspected | #Confirmed
---|---|---
Philippines | >44,000 | >16,000; 91 deaths
China | >91,000 | >42,000
Vietnam | >10,000 | 3,688
Measles 2014: Exposure source

• The majority of 2014 measles cases were travel-associated or contacts of known cases.
• Most of the imported cases were US residents who visited the Philippines, where a large measles outbreak has been occurring since October 2013.
Measles 2014: Genotypes

- Genotyping helped identify links between cases and define clusters
- Genotypes identified
  - **63% were B3**, including many with proven travel link to the Philippines
  - **11 were D8**, including travelers to India, Vietnam, Singapore, W. Europe
  - **2 were H1**, with travel to China and Thailand
DON'T VACCINATE MY KIDS!

Our support is spreading.

Spreading for sure!
2014 Measles: Vaccination Status

- 43% were unvaccinated
  - Most were due to Personal Belief Exemptions
  - Some were too young (<1 yr of age)
- 20% were vaccinated, including some with 2+ doses
2014 Measles Investigations

• Multiple clusters/outbreaks
  – Numerous secondary cases
• Healthcare settings
  – Other patients
  – Healthcare personnel
• Airplane
• School/daycare

→ Measles investigations are resource intensive
Measles in the US through June 16th, 2014

• Large increase in cases nationally
  – 488 cases
  – Highest yearly total since elimination
  – 49% of imports report travel to the Philippines
  – Most are genotype B3

• States with most cases:
  – OH (341), CA (61) and NY (31)

• 69% unvaccinated
  – 85% unvaccinated due to personal beliefs

Source: CDC/MMWR
“Measles” in recent MMR recipients?

- Rash and/or mild illness not uncommon; clinically severe measles is rare
- 10 recent vaccine recipients, ages 1-7 years, w/in 3 wks of vaccination
  - 9 PCR positive for Measles, + Rubella
  - No secondary cases (LAV vaccine!)
- Distinguish from wild-type measles by genotyping
  - US MMR measles strain in use is genotype A
  - No wild-type strain A known to be in circulation
  - 6/9 were type A; 3 unable to type (high Ct values)
Measles?

- A 30 year old male presented to ED in March with a 2 day history of rash on face, chest and back, conjunctivitis and fever.
  - Arrived from India 5 d prior. Measles was suspected.

- In June, a young female adult presented to the ED with 5d history of sore throat and malaise and 1 day rash descending from her face.
  - Arrived from Afghanistan 2 days prior to admission
  - Admitted to an isolation room with suspected measles
RUBELLA

- At VRDL, throat/nasal swabs and urine were tested by rRT-PCR on an ABI 7500Dx
  - Measles negative
  - Rubella positive

- These 2 adults were the first cases of rubella in California since 2012. No additional cases or cases of CRS were identified.
Rubella, AKA “German measles”

- Mild disease: Low fever, inflamed lymph nodes, mild cough, polyarthralgias
- Pink rash of discrete spots. May desquamate.
- Transmitted by airborne droplet/fomites
  - From 7d before to 7d after rash onset
- Clinical presentation can be similar to measles
  - Suspect cases tested for both rubella and measles.
Congenital Rubella Syndrome (CRS)

- If pregnant woman is infected in 1st 11 wks of pregnancy, >90% infants will develop CRS
- Miscarriage, stillbirth, congenital anomalies
  - Cataracts, heart defects, hearing loss
- Neonates shed a lot of virus and are IgM (+)
  - Remain infectious for up to 1 yr
- Primary reason a vaccine was developed
Rubella Epidemiology

- Few cases are reported annually in the US and California:
  - 0 to 2 in California from 2009-2013; 3-10 nationally.
- World-wide, thousands of cases still occur
  - 2013: Poland (>38K), China (>17K), Japan (>14K), Uganda, India and elsewhere (WHO data)

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**Figure 1.** Number of reported rubella cases and proportion of males by epidemiological week of diagnosis, Tokyo, Japan, Week 1, 2012–Week 16, 2013

- **Laboratory-confirmed cases (n = 1760)**
- **Clinical cases (n = 622)**
- **Proportion of males (%)**

<table>
<thead>
<tr>
<th>Week and year</th>
<th>Number of cases</th>
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The Mumps

- Headache
- Swollen Glands
- Fever
- Chills
- Fatigue

The Chumps

- No Vaccines
Mumps
Epidemic Parotitis

- Fever, headache, lethargy
- Painful unilateral or bilateral swelling of salivary (parotid) glands
- Epidemic peaks: 2-5 years in late winter/spring
- Transmitted by airborne droplet/fomites
Mumps – Epidemiology

• Rare complications (typically post-pubertal):
  – Orchitis: ~30% (inflammation of testes; impairs fertility in 13%)
  – Oophoritis: 0.5-7% (inflammation of ovaries)
  – Meningitis: 15%
  – Deafness: 4% – usually temporary

• Pre-vaccine (1967)
  – >100 cases/100,000 population
  – Leading cause of viral meningitis
  – The most common cause of unilateral deafness in children

• 2010 – Mumps declared eliminated from US
U.S. Mumps 2014: 965 cases as of Aug 15

- Outbreaks in 4 colleges & unvaccinated populations
  - Imported cases and outbreaks in close-quarter settings
  - Typical year has 100-300 cases
- Still endemic in many countries
  - Outbreaks in Japan, Spain, Egypt from poor vax coverage
Is Measles Still a Threat?

- Increase in measles cases in California and nationally with many cases linked to Philippines and other international outbreaks
- Increase in local transmission in California and US compared with prior years
- Majority of measles cases are among those who are unvaccinated
Why are these diseases still here?

- Eliminated in the US but cause outbreaks or are endemic in many other countries
  - Poor infrastructure
  - Different vaccine coverage decisions
- Choosing not to vaccinate
  - Belief that the diseases are no longer a threat
  - Personal belief exemptions
  - Mis-information about vaccine risks
VPD Testing: Why so much effort?

• Clinical differentiation of rash illnesses caused by measles and rubella is difficult
  – Fewer cases equates to less accurate clinical diagnosis
  – Measles is highly contagious; rubella may have deleterious consequences for pregnancy
  – Concurrent testing advantageous

• Genotyping is key to understanding transmission routes

• Prompt and accurate diagnosis is critical for disease control efforts
Acknowledgements

VRDL

IZB

MeaslesNet Labs

County Public Health Partners