Measles Makes a Comeback
Epidemiology and Laboratory Testing

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Illinois Department of Public Health

2/10/2015
Measles Epidemiology

- Year round endemic transmission of measles ended in the United States in 2000 ("measles elimination")
  - Elimination does not mean gone forever!

- Measles remains widespread globally: 20 million cases and 150,000 deaths/year

- Importations continue. They
  - test our immunity, diagnostic skills, infection control protocols, and vaccination policies
  - can lead to serious illnesses, and outbreaks
Get Vaccinated: Prevent and Stop Measles Outbreaks

When measles happens anywhere in the world...

It can travel here and spread

Since measles is still common in many countries, unvaccinated travelers will continue to bring the disease into the U.S., and it can spread to other people.

Make sure you and your family members are up-to-date on your measles-mumps-rubella (MMR) vaccine, including before traveling internationally. Ask your doctor if everyone has received all recommended doses of MMR for best protection against measles.

www.cdc.gov/features/measles/
Note: Infants who get one dose of MMR vaccine before their first birthday should get two more doses (one dose at 12 through 15 months of age and another dose at least 28 days later).

Teenagers and adults who do not have evidence of immunity against measles should get two doses of MMR vaccine separated by at least 28 days.

* Acceptable presumptive evidence of immunity against measles includes at least one of the following: written documentation of adequate vaccination, laboratory evidence of immunity, laboratory confirmation of measles, or birth in the United States before 1957.
Number of Reported Measles Cases with onset date from Jun 2014 to Nov 2014 (6M period)

Data source: surveillance DEF file
Data in HQ as of 19 January 2015
Measles cases in the United States, 1944-2007

- Vaccine licensed
- Second dose recommended
- Second dose recommended
Measles, United States, 1996-Present

(Importations indicated by red bar, available since 2001)

*2014 case count preliminary as of June 20
Measles, United States, 2001-2014*
Age Specific Incidence

- ~65% unvaccinated
- ~15% vaccinated
- ~20% unknown

Most recent cases in adults, but incidence rates are lower
*2014 data reported as of October 31, 2014
Source: National Notifiable Diseases Surveillance System (NNDSS) and direct report to CDC
Measles in 2014—United States

- 644 cases from 27 states and 23 outbreaks
- 60 importations: Philippines (25), India (9)
  - 54 (91%) in US residents
- 78 cases (12%) hospitalized
- Cases in US residents (N=635)
  - 77% unvaccinated
  - 15% unknown vaccination status (mostly adults)
  - 8% vaccinated
  - Among unvaccinated
    - 79% personal belief exemptions
    - 3% travelers age 6 months to 4 years
    - 8% too young to be vaccinated
    - 10% unknown

Number of Cases

Year


0 0 1 32 0 0 3 0 5 0 10
Measles, Suburban Cook County --2015

<table>
<thead>
<tr>
<th>Age</th>
<th>Cases</th>
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<tbody>
<tr>
<td>25-50 y</td>
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<tr>
<td>6 mo-12 mo</td>
<td>6</td>
</tr>
<tr>
<td>12 mo-2 year</td>
<td>1</td>
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<tr>
<td>&lt; 6 months</td>
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<tr>
<td><strong>Total</strong></td>
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**Number of Cases vs Rash Onset Date**

<table>
<thead>
<tr>
<th>Date</th>
<th>Number of Cases</th>
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<tbody>
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<td>1</td>
</tr>
<tr>
<td>1/17/2015</td>
<td>1</td>
</tr>
<tr>
<td>1/18/2015</td>
<td>1</td>
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<tr>
<td>1/19/2015</td>
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**Rash Onset Date**

**Date**

- 1/16/2015
- 1/17/2015
- 1/18/2015
- 1/19/2015
- 1/20/2015
- 1/21/2015
- 1/22/2015
- 1/23/2015
- 1/24/2015
- 1/25/2015
- 1/26/2015
- 1/27/2015
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- 2/6/2015
- 2/7/2015
- 2/8/2015
- 2/9/2015
- 2/10/2015
- 2/11/2015
- 2/12/2015
- 2/13/2015
- 2/14/2015
- 2/15/2015
- 2/16/2015
Measles outbreak response has a high economic burden in the U.S.

<table>
<thead>
<tr>
<th>Year</th>
<th>Location</th>
<th>Number of cases (outbreaks)</th>
<th>Estimated public health cost*</th>
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<tbody>
<tr>
<td>2011</td>
<td>US</td>
<td>107 (16)</td>
<td>$2.7-5.3M</td>
</tr>
<tr>
<td>2011</td>
<td>Utah</td>
<td>13 (2)</td>
<td>&gt;$330,000</td>
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<tr>
<td>2008</td>
<td>California</td>
<td>12 (1)</td>
<td>$125,000</td>
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<tr>
<td>2008</td>
<td>Arizona</td>
<td>14 (1)</td>
<td>$800,000 (limited to cost for 2 hospitals to respond to 7 cases in their facilities)</td>
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<tr>
<td>2005</td>
<td>Indiana</td>
<td>34 (1)</td>
<td>$168,000</td>
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<tr>
<td>2004</td>
<td>Iowa</td>
<td>1</td>
<td>$142,000</td>
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Measles Chronology
1. Test: Individuals with fever and with classic measles signs/symptoms
   • Fever $> 101^\circ$ and disseminated maculopapular rash and coryza, conjunctivitis, or cough
   • If no rash on face/head/neck or if rash starts on trunk – measles not likely

2. Test: Individuals who have
   • a known measles exposure or were in a high risk setting during the likely exposure period (7-21 days prior to rash onset, and
   • have a fever and rash (temp and rash characteristics may vary)
   • regardless of vaccine history (or prior IgG seropositivity)
3. All other situations will require clinical judgment!

4. For testing of suspect cases without classic measles (e.g., fever <101, non-classic rash) and have no known exposure....this may depend on:

   • Epidemiology of measles in your community – are there cases with an unknown source?

   • Whether the suspect case potentially exposed others in sensitive settings (healthcare facility, childcare facility with infants), e.g., did the suspect visit an NICU while potentially infectious?

   • International travel, international travelers
5. Testing is discouraged if a patient’s clinical presentation is not consistent with measles and the patient has no known increased risk for exposure to measles.

6. Local Health Dept. may decide not to test every contact with measles signs/sx in some situations.

7. Testing of contacts with low grade fever with cough/coryza/conjunctivitis and no rash (ie during possible measles prodrome) may be recommended in some situations.
8. Other considerations

- Itchy rash? May be itchy from day 4-7 but not at onset
- Rash on palms and soles? Rash may be on palms and soles but not as prominent as on face and chest
- What is the rash distribution and spread? Even if disease is modified* the order of appearance (face and head) and direction of spread is the same
- Timing of sign and symptom onset/evolution
- Subjective fevers: case by case determination
- Atypical measles: rash often not “classic”
- Immunocompromised: low threshold for testing

* due to pre-existing, incomplete antibody response
What do recent two dose (modified) measles cases in California look like?

1. Fever to 101, no cough, conjunctivitis, but did report coryza. Rash started on face and went to chest and part of arms. Did not descend to extremities. Case had traveled to China, had no known exposure.

2. Reported subjective fever, cough, conjunctivitis, no coryza. Rash started on face and progressed to chest, arms then stomach; rash duration was 4 days. Case was exposed to measles in an urgent care waiting room.

3. Fever to 101, no cough, no coryza, no conjunctivitis. Rash started on face and descended to body, arms, legs. Rash duration was 3 days. Exposed to measles by household contact.

4. Subjective fever, conjunctivitis, no cough, no coryza. Rash spread from head and descended, rash duration unknown. Exposed to measles by a CA measles case on a flight.
Vaccine Reactions

- Rash that occurs days 5-12 post vaccination with MMR
- Patients can have symptoms comparable to those associated with wild type measles
- PCR on the patient’s throat swab will likely be positive for measles
- Additional testing (genotyping) is needed to discriminate between vaccine strain and wild type strain
  - Vaccine strain is genotype A
  - Additional testing is done at CDC (Atlanta)
- In some cases the level of virus is too low to successfully genotype
Vaccine Reactions, cont.

- No known transmission from a vaccine recipient experiencing rash, no reason to isolate the patient
  - Different approach could be recommended if patient is immunocompromised

- The dilemma is that some cases are clinically indistinguishable from wild type disease and will be PCR and IgM positive so only genotyping will provide a definitive answer (assuming it is successful)

- Approach to case differs depending on current situation - in an outbreak setting, the conservative approach is to start the investigation prior to receipt of laboratory results

- The epidemiology of measles in the community will also be a consideration
Measles Chronology

| Rash onset Exposure | DAY 8 | DAY 9 | DAY 10 | DAY 11 | DAY 12 | DAY 13 | DAY 14 | DAY 15 | DAY 16 | DAY 17 | DAY 18 | DAY 19 | DAY 20 | DAY 21 | DAY 22 | DAY 23 | DAY 24 | DAY 25 | DAY 26 | DAY 27 | DAY 28 | DAY 29 | DAY 30 | DAY 31 | DAY 32 | DAY 33 | DAY 34 | DAY 35 |
|---------------------|------|------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| Fever (°C)          |      |      |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |
| 39.5°               |      |      |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |
| 39.0°               |      |      |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |
| 38.5°               |      |      |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |
| 38.0°               |      |      |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |
| 37.5°               |      |      |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |
| 37.0°               |      |      |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |
| 36.5°               |      |      |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |

CLINICAL SYMPTOMS
- COUGH
- CORYZA
- CONJUNCTIVITIS
- KOPLICK SPOTS
- RASH

LABORATORY INVESTIGATIONS
- SEROLOGY
  - IgM
  - IgG
- VIRAL CULTURE
  - NOSE/THROAT, NPA
  - LYMPHOCYTES
  - URINE
- RT-PCR
  - SERUM
  - LYMPHOCYTES
  - NOSE/THROAT, NPA
  - URINE

RASH ONSET
Specimens for Laboratory Diagnosis

- **PCR—Respiratory specimen**
  - Successful detection of measles virus depends on timing of specimen collection, quality of specimen collected, and proper care of specimen
  - Throat swab or NP swab or NP aspirate
  - Urine – Not an acceptable specimen for PCR testing at IDP
  - PCR sensitivity likely varies over time and by vaccination status. For best sensitivity collect specimen within 7 days of rash onset (optimally within 4 days)

- **Blood – for antibody testing (not performed by IDPH)**
  - Does not need to be collected for every suspected case; e.g. order antibody testing when a suspected case is identified late, and the timing is not right for PCR testing
  - False positive and false negative IgM results can occur
Specimens for Laboratory Diagnosis

- **PCR**
  - Performed at IDPH Lab in Springfield and Chicago
  - Throat swab or NP swab or NP aspirate
    - Place swab in viral transport media
    - Specimen should be shipped on a cold pack, immediately if possible
    - Determine if specimen can arrive at IDPH the same day or the next day
  - OK to refrigerate at 4 degrees C for up to 72 hours
  - Otherwise freeze at -70 degrees C and ship on dry ice
  - Avoid repeated freeze/thaw cycles
Antibody Testing (not done at IDPH)

- **IgM antibody**
  - Indicates acute infection (false positives can occur)
  - May be undetectable during 1\(^{st}\) 3 days of rash
  - Present for about 30 days: may be useful if too late to do PCR

- **IgG antibody**
  - In the absence of IgM antibody, indicates prior infection or immunity
  - Four fold rise in titers or conversion from negative to positive indicate acute infection

In recently vaccinated persons (6-45 days prior to rash onset), neither IgM nor IgG titers can distinguish recent disease from response to vaccination.
Call your LHD immediately—1) If you suspect measles 2) If measles testing is being ordered (IgM) or requested (PCR)

1. Key information
   - Patient Name
   - Signs/symptoms/rash onset and progression with dates
   - Priority status (how urgent is PCR testing?)
   - Have specimens been collected and when do you want to ship the specimens?
   - Courier and tracking information

2. If requesting PCR at IDPH, complete the specimen submittal form and include in package with the specimens. The form is at http://www.idph.state.il.us/about/laboratories/CDform082002a.pdf
Submitting Specimens for PCR Testing

3. Package properly, with a cold pack, as Category B (diagnostic) specimens

http://www.idph.state.il.us/about/laboratories/manual/Instructions/Bio_Cat-B.pdf

4. Specimens should each be shipped in their own plastic bag with an absorbent pad

5. Weekend deliveries can be a challenge

- Obtain IDPH approval and make sure “airtight” arrangements are in place when specimens are to arrive on a weekend
Weekend Measles PCR Testing at IDPH

- Weekend testing at IDPH is considered on a case by case basis depending on the importance of testing results for public health or clinical actions.

- In general, urgent testing is prioritized when public health risk is high and epidemiologic support for the diagnosis of measles has not been identified.

- If there are epidemiologic factors suggest measles is likely, public health action should typically proceed without waiting for confirmation of the diagnosis.
PCR Testing

- Information regarding the IDPH Measles PCR assay, including collection and shipping requirements can be found in our online manual of services located at

  http://www.idph.state.il.us/about/laboratories/manual/Manual_of_Services_OHP_LABS.pdf
Results

• Specimens are tested within one day of arrival
• Results will be reported back to the submitter
• IDPH and LHD epidemiologists also receive official results
Summary

- Measles is due to failure to vaccinate
- Measles elimination is a global problem
- Measles happens in the U.S., including Illinois
- Maintenance of elimination is challenging and resource intensive
  - Maintaining vaccine coverage—increasing vaccine exemption
  - Health care worker diagnostic skills
  - Intensive case/contact investigations
  - Advanced laboratory techniques
Acknowledgments

- Jane Seward, CDC
- IDPH Communicable Disease Staff
- IDPH Laboratory Staff
- Local Health Department Staff
- Doctors, Nurses, other health care workers
- Hospitals
- Laboratories
Supplementary slides
Antibody Testing

Unimmunized person

- Specimen collected < 72 hours after rash onset
  - Test for IgM
    - IgM positive = measles “confirmed”*
    - IgM negative = cannot rule out measles
      • Collect another specimen > 72 hours after rash onset
  - Specimen collected ≥ 72 hours after rash onset
    - Test for IgM and IgG
      • IgM positive/IgG positive or negative = measles confirmed*
      • Measles IgM negative/IgG negative = measles ruled out

*false positives can occur
Antibody Testing

Person with unknown immunization history or Person with documented history of one or more doses of measles-containing vaccine

- Specimen collected < 72 hours after rash onset
  - Test for IgM and IgG
    - IgM positive/IgG positive or negative = measles confirmed*
    - IgM negative/IgG negative = cannot rule out measles
      - Collect another specimen 72 hours or more after rash onset
      - Did not respond to vaccination or was never vaccinated
    - IgM negative/IgG positive = measles ruled out
      - Demonstrates previous immunity to measles due to either prior vaccine or previous disease

*false positives can occur
Antibody Testing

- Person with unknown immunization history or Person with documented history of one or more doses of measles-containing vaccine

- Specimen collected ≥ 72 hours after rash onset

  - Test for IgM and IgG
    - IgM positive/IgG positive or negative = measles confirmed*
    - IgM negative/IgG negative = measles ruled out
      - Recommend immunization
    - IgM negative/IgG positive = measles ruled out
      - Demonstrates previous immunity to measles due to either prior vaccine or previous disease

*false positives can occur
Antibody Testing

• False positive Measles IgM results are reported to occur due to rheumatoid factor and other rash illnesses

• Suspect when
  ▪ Surveillance reveals no source or spread of cases
  ▪ When case does not meet clinical case definition
  ▪ When IgG result is positive within 3 days of rash onset in an unvaccinated person

• PCR testing at IDPH and/or antibody testing at CDC can inform decision making if false positive test is suspected
CDC Case Definition - Confirmed

- An acute febrile rash illness\(^{\dagger}\) with:
  - isolation of measles virus\(^{\ddagger}\) from a clinical specimen; or
  - detection of measles virus-specific nucleic acid from a clinical specimen using by polymerase chain reaction; or
  - IgG seroconversion\(^{\ddagger}\) or a significant rise in measles immunoglobulin G antibody\(^{\ddagger}\) using any evaluated and validated method; or
  - a positive serologic test for measles immunoglobulin M antibody\(^{\ddagger}\)§; or
  - direct epidemiologic linkage to a case confirmed by one of the methods above.

\(^{\dagger}\) Temp does not need to reach 101 and rash does not need to last \(\geq 3\) days

\(^{\ddagger}\) Not explained by MMR vaccination during the previous 6-45 days. (Genotyping can distinguish wild type

\(^{\ddagger}\)§ Not otherwise ruled out by other confirmatory testing or more specific measles testing in a public health laboratory

*Note: Genotype identification is required to distinguish wild type from vaccine strain if vaccinated within 18 days of rash onset.*
MEASLES VACCINATION RATES FOR PRESCHOOLERS

Nationally, about 91 percent of 19- to 35-month-olds have been vaccinated for measles, according to data gathered from the Centers for Disease Control and Prevention. But in 17 states, fewer than 90 percent of young children have been immunized for the disease, which puts those states at a higher risk for widespread infection.

SOURCE: Trust for America’s Health
Tribune analysis: More Illinois schools reach key measles vaccine threshold (2/2015)

![School measles vaccination rates graph](image)

**School measles vaccination rates**

By school year, as a percentage of schools

Percentage of schools reporting measles vaccination rates worse than 95%

- 2008-2009: 11.5%
- 2009-2010: 9.2%

Rates worse than 90%

- 2008-2009: 5.1%
- 2009-2010: 2.8%

**SOURCE:** Illinois State Board of Education

@ChiTribGraphics
Estimated percentage of children enrolled in kindergarten who have been exempted from receiving one or more vaccines* — United States, 2012–13 school year
Weighted number and percentage* of children enrolled in kindergarten with a reported exemption to vaccination, by state/area and type of exemption — United States, 2012–13 school year

<table>
<thead>
<tr>
<th>State/Area</th>
<th>Medical exemptions†</th>
<th>Nonmedical exemptions†</th>
<th>Total exemptions†</th>
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<tr>
<td></td>
<td>No.</td>
<td>(%)</td>
<td>Religious no.</td>
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<tr>
<td>California</td>
<td>923</td>
<td>(0.2)</td>
<td>—**</td>
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<tr>
<td>Florida</td>
<td>905</td>
<td>(0.4)</td>
<td>3,281</td>
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<td>Georgia</td>
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<tr>
<td>Pennsylvania</td>
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http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6230a3.htm
Measles Webinar
Disease and Prevention

Kenneth Boyer, MD
Women’s Board Chair of Pediatrics
Rush University Medical Center

2/11/2015
Measles in My Career

- Pre 1963 in U.S. (every child got it)
  - 4,000,000 cases/year
  - 40,000 hospitalizations/year (1/100)
  - 4,000 encephalitis cases/yr (1/1,000)
  - 400 deaths/year (1/10,000)

- Vaccine(s) introduced in 1965
- Endemic transmission ended in 1998
Classic “Wild-Type” Measles

- Febrile illness with rash
  - Incubation 10 days
  - Prodromal “cough, coryza, conjunctivitis”
  - Koplick’s spots
  - Macular rash spread face-trunk-extremities
  - Fever usually >103, lyses by crisis
  - Longer febrile course implies complications
Other Manifestations

- Modified measles
  - Maternal antibody
  - Prior immunization
- Atypical measles
  - Prior killed vaccine
- Vaccine measles
- Hecht’s giant-cell pneumonia
  - T-cell immunodeficiency
- SSPE
Complications

- Bacterial superinfections
- Viral pneumonia
- Croup
- Diarrhea/dehydration-esp infants
- Pregnancy fatal loss
- TB exacerbation
Measles Look-Alikes

- Roseola (fever disappears)
- Enterovirus (summer)
- Rubella (much milder)
- Scarlet (confluent)
- Adenoviruses (usually w/o rash)
- Kawasaki (more prolonged)
- Drug reaction (exposure)
Treatment

- Supportive
- Vitamin A
- No evidence-based antivirals
- Steroids harmful
- Immunoglobulins not beneficial
Prevention

- Vaccine (Moraten strain in MMR and MMRV)
  - Standard schedule (12-15 mos, 4-6 years)
  - Catch-up
  - Epidemic control (start age 6 months)
  - Exposed susceptible (< 72 hours)

- Immunoglobulin
  - IMIG (0.25 mL/kg-modifying)
  - IMIG (0.5 mL/kg-preventive)
  - IVIG (400 mg/kg)