Virology Seminar I: Case Studies

Monday, April 8, 2019 at 1:00 PM

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Assoc. Professor – Internal Medicine & Pediatrics

Systemic Viral Infections:
Mumps, Measles, Rubella
and Parvovirus B19

Susan Baker, Ph.D.

Comparison of Maximum and Current Morbidity in Vaccine-Preventable Viral Diseases

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This study shows that highlighting factual information about the dangers of communicable diseases can positively impact people's attitudes to vaccination. This method outperformed alternative interventions aimed at undercutting vaccination myths.

Mumps

- Acute viral illness
- Parotitis and orchitis described by Hippocrates in 5th century B.C.
- Viral etiology described by Johnson and Goodpasture in 1934
- Frequent cause of outbreaks among military personnel in prevaccine era
Mechanism of spread of mumps virus within the body

- Inoculation of respiratory tract
- Local replication
- Viremia
- Systemic infection

- Parotid gland
- Pancreas

\[ \text{Virus multiplies in ductal epithelial cells. Local inflammation causes marked swelling} \]

May be associated with onset of juvenile diabetes

Time Course of Mumps Infection

- Inoculation of respiratory tract
- Days 0, 2, 1, 2, 8, 3, 6, 4, 27, 1, 4

- Meningoencephalitis
- Orchitis
- Parotitis
- Virus-specific antibody present
- Recovery of virus from mouth or urine
- Recovery of virus from CSF

Disease Mechanisms of Mumps Virus

- Infects epithelial cells by respiratory tract
- Spreads systemically by viremia
- Systemic infection, especially of parotid gland, testes, and central nervous system
- Principle symptom is swelling of parotid glands because of inflammation
Cell-mediated immunity is essential for control of infection and responsible for a portion of the symptoms.

Antibody is not sufficient due to mumps’ ability to spread cell to cell.

Clinical Case Definition
- Acute onset of unilateral or bilateral swelling of parotid or salivary gland lasting ≥2 days without other apparent cause

Laboratory Criteria for Diagnosis
- Significant increase in mumps IgG antibody level between acute and convalescent samples, or positive serologic test for mumps IgM antibody

Mumps Vaccine

<table>
<thead>
<tr>
<th>Composition</th>
<th>Live-attenuated virus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>95%</td>
</tr>
<tr>
<td>Duration of Immunity</td>
<td>Lifelong</td>
</tr>
<tr>
<td>Schedule</td>
<td>1 dose, generally 1 boost</td>
</tr>
</tbody>
</table>

Administered with measles, rubella and varicella (MMRV)
Rationale for Constant Vigilance in Vaccination:

Mumps outbreak in England & Wales 2004-2005

Number of notified cases of mumps and proportion of cases that were laboratory confirmed by measure of mumps-specific IgM – England and Wales, 2004-2005

Testing temporarily halted for notified cases in persons born during 1981-1986

Number of notified cases of mumps by patient age – England and Wales, 2004-2005
So what happens when an English teenager gets a job as a camp counselor in the USA?

Interestingly, the camp health service and several doctors initially missed the mumps diagnosis (likely because they had never seen mumps…).

My calculation is 31 cases/513 people = 6% infected in a population with a 96% vaccine coverage rate.
Disease
Symptoms
• Mild respiratory infection
• Spread to cervical lymph nodes
• Viremia
• Fever and Rash

Target Organs
• Skin
• CNS (rarely)
**Clinical Consequences of Measles Virus Infection**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles</td>
<td>• characteristic maculopapular rash, coryza, cough and conjunctivitis, Kopli’s spots</td>
</tr>
<tr>
<td></td>
<td>• complications include otitis media, croup, bronchopneumonia, and encephalitis, the most severe complication (principal reason for vaccine)</td>
</tr>
</tbody>
</table>

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**Oral Temp (°F)**

<table>
<thead>
<tr>
<th>Day After Onset of Illness</th>
<th>Oral Temp (°F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>104</td>
</tr>
<tr>
<td>1</td>
<td>103</td>
</tr>
<tr>
<td>2</td>
<td>102</td>
</tr>
<tr>
<td>3</td>
<td>101</td>
</tr>
<tr>
<td>4</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>99</td>
</tr>
</tbody>
</table>

**Rash**

**Koplik’s Spots**

**Conjunctivitis**

**Coryza**

**Cough**

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**Day After Onset of Illness**

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Measles Infection

Measles: Complications

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percent Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any complication*</td>
<td>29</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8</td>
</tr>
<tr>
<td>Otitis media</td>
<td>7</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>6</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>0.1</td>
</tr>
<tr>
<td>Death</td>
<td>0.2</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>18</td>
</tr>
</tbody>
</table>

* Includes hospitalization; Based on 1985-1992 surveillance data

In the decade before 1963 when a vaccine became available, nearly all children got measles by the time they were 15 years of age.

It is estimated 3 to 4 million people in the United States were infected each year. Also each year, among reported cases, an estimated 400 to 500 people died, 48,000 were hospitalized, and 1,000 suffered encephalitis (swelling of the brain) from measles.

www.cdc.gov/measles/about/history.html
Reported Measles Cases, by Year
*United States, 1950-1997*

Measles Resurgence 1989-1991
*United States (Chicago!)*

<table>
<thead>
<tr>
<th>Cases</th>
<th>&gt; 55,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group affected</td>
<td>Children &lt;5 yrs (45%)</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>&gt;11,000</td>
</tr>
<tr>
<td>Deaths*</td>
<td>136</td>
</tr>
<tr>
<td>Direct medical costs</td>
<td>&gt;$150 million</td>
</tr>
</tbody>
</table>

- Measles was declared eliminated (absence of continuous disease transmission for greater than 12 months) from the United States in 2000.
- This was thanks to a highly effective vaccination program in the United States, as well as better measles control in the Americas region.

www.cdc.gov/measles/about/history.html
Rationale for Constant Vigilance in Vaccination:

Sources of measles outbreaks include adopted children brought into the USA and international visitors to Disneyland!

Number of Measles cases reported by year 2010-2019** (as of March 7, 2019)

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>64</td>
</tr>
<tr>
<td>2011</td>
<td>55</td>
</tr>
<tr>
<td>2012</td>
<td>187</td>
</tr>
<tr>
<td>2013</td>
<td>188</td>
</tr>
<tr>
<td>2014</td>
<td>667</td>
</tr>
<tr>
<td>2015</td>
<td>120</td>
</tr>
<tr>
<td>2016</td>
<td>372</td>
</tr>
<tr>
<td>2017</td>
<td>228</td>
</tr>
</tbody>
</table>

Measles Vaccines: Overview

- Measles isolated 1964 by Enders (Edmonston)
- Live-attenuated measles vaccines were developed in the 1960s
- Since 1968 combined with live-attenuate mumps and rubella: MMR
- All MV vaccines are in genotype A
  - Edmonston-derived: Moraten, Schwarz, EZ, AIK-C
  - Non-Edmonston: CAM-70, Shanghai-191, Changchun-47
  - Genetic basis for attenuation is unknown
  - Vaccination protects against all genotypes
Strategy for sustainable measles mortality reduction

1. Strong routine immunization of ≥90%
2. Provide second opportunity for measles immunization
   - One time only “catch-up” campaign (< 15)
   - “Follow-up” campaigns every 3-4 years (< 5)
   - Campaigns linked to other priority health interventions (Vit A, polio, TT, bednets, etc.)
3. Surveillance
4. Improved case management
   (Vitamin A - antibiotics)

Global Measles & Rubella Laboratory Network - 2006
N = 678

Regions according to measles control goals, 2004
Measles virus research:

We need an improved measles virus vaccine that can be administered inexpensively (respiratory route?)

Device: Current options

- Nasal spray systems
- Ultrasonic nebulizers
- Jet nebulizers

Watch for future developments of measles vaccines!
Rubella (German Measles)

Symptoms

• URTI
• Maculopapular rash

The Course of Postnatal Rubella Virus Infection

- Vomiting
- Rash
- Arthritis/Arthralgia
- Respiratory Virus Sheding
- Serum Antibody and Respiratory Tract Secretory Antibody
- Clinical Illness

Exposure Days After Exposure:

0 7 14 21 28 35 42 6 mo 1 yr
Rubella: Laboratory Diagnosis

- Isolation of rubella virus from clinical specimen (e.g., nasopharynx, urine)
- Significant rise in rubella IgG by any standard serologic assay (e.g., enzyme immunoassay)
- Positive serologic test for rubella IgM antibody

Congenital Rubella Syndrome

**Acute Infection**

1st 3 Months of Pregnancy

Infection of Fetus

- Severe Spontaneous Abortions Stillbirths
- Mild, Chronic Congenital Rubella Syndrome

Tissue and Skin

Neutralizing Antibody
Congenital Rubella Syndrome

- Deafness
- Cataracts
- Heart defects
- Microcephaly
- Mental retardation
- Bone alterations
- Liver and spleen damage

Congenital Rubella Syndrome

U.S. Epidemic 1964-1965

- 12.5 millions rubella cases
- 2,000 encephalitis cases
- 11,520 abortions (surgical/spontaneous)
- 2,100 neonatal deaths
- 20,000 CRS cases
  - Deaf - 11,600
  - Blind - 3,580
  - Mentally retarded - 1,800
Rubella Incidence – United States
1966-1993

* 1993 provisional data

Reported Rubella – United States
1980-1993

Rubella in Japan

NEJM, 2013

A 21-year-old woman presented to the emergency department after 1 day of fever, sore throat, arthritis, and rash. Diffuse erythema of the face that blanches on pressure was noted over the face, neck, trunk, and arms, along with posterior cervical lymphadenopathy. The next day, the fever and rash subsided, but she remained joint and ear pain. Serologic testing revealed a positive rubella IgM antibody titer, consistent with the diagnosis of rubella. The number of rubella cases in Japan, especially in Tokyo, has been increasing in the past year. Approximately 70% of reported cases of rubella involve middle-aged men, partly because boys were not vaccinated against rubella by the national immunization program until 1995. To prevent the congenital rubella syndrome, the vaccination of women of childbearing age and their partners is currently a priority.
Rationale for Constant Vigilance in Vaccination:

- **High coverageRates with MMR**
- **Low incidence of CRS**

This report presents new recommendations adopted in June 2009 by CDC's Advisory Committee on Immunization Practices (ACIP) regarding use of the combination measles, mumps, rubella, and varicella vaccine (MMRV). For the first dose of measles, mumps, rubella, and varicella vaccine at age 12-47 months, either measles, mumps, and rubella (MMR) vaccine and varicella vaccine or the combination MMRV vaccine may be used. Unless the parent or caregiver expresses a preference for MMRV vaccine, CDC recommends that MMR vaccine and varicella vaccine should be administered for the first dose for this age group. For the second dose at any age (15 months-12 years) and for the first dose at age >48 months, use of MMRV vaccine generally is preferred over separate injections of MMR and varicella vaccines.
Mechanism of spread of parvovirus within the body

Parvovirus B19

- Single-strand DNA virus with capsid
- Spread by respiratory and oral secretions
- Infects mitotically active erythroid precursor cells in the bone marrow and establishes lytic infection
- Initial symptoms are flu-like and viral shedding
- Virus can cross the placenta and infect the fetus!
- Later phase is related to immune response and circulating immune complexes of antibody and virus that do not fix complement – can result in erythematous maculopapular rash, arthralgia and arthritis
- Depletion of erythroid precursor cells can initiate aplastic crisis in persons with chronic anemia
- Specific antibody is important for resolution and prophylaxis

Clinical Consequences of Parvovirus B19 infection

- Mild, flulike illness with fever, headache, chills, myalgia, malaise
- Erythema infectiosum; also termed fifth disease/slapped cheek syndrome
- Aplastic crisis in persons with chronic anemia
- Arthropathy (polyarthritis: symptoms in many joints)
- Risk of fetal loss as a result of B19 virus crossing the placenta, causing anemia-related disease but not congenital anomalies
Detection of Parvovirus B19

- Erythema infectiosum is generally a clinical diagnosis
- For other presentations, virus specific IgM and/or viral DNA should be evaluated

Viruses discussed today

- Mumps – paramyxovirus: neg RNA, envelope
- Measles – paramyxovirus: neg RNA, envelope
- Rubella – togavirus: positive RNA, envelope
- Parvovirus B19 – parvovirus: ssDNA virus, no envelope

Practice using the 7 Question approach:
Go to Loyola.wired, click on the LUMEN link, Mechanisms of Human Disease, click on Educational Resources, Virus 7 Question Approach Quizzes link

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