Objectives

- Brief history of the Red Book
  - Covers established/new infectious diseases
- 4.5 cases illustrative of established vs new
  1. Influenza – most common vaccine preventable infection in USA in 21st century
  2. Still "Whack-a-mole" with measles
  3. C difficile – Mostly Adults, now more Peds?
  - Emerging pathogens in KC
  4. Human parechovirus-3 (HPeV3)
  5. Enterovirus (EV) D68 (mini)

History of the Red Book

- 1930-American Academy of Pediatrics founded
- 1936-established AAP Committee on Immunization Procedures
- 1938-the first report of COIP published in pamphlet form

Diseases: Red Book 1938

<table>
<thead>
<tr>
<th>Disease</th>
<th>Antibacterial Rx</th>
<th>Vaccine</th>
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<tbody>
<tr>
<td>The common cold</td>
<td></td>
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<tr>
<td>Diphtheria</td>
<td>Antitoxin</td>
<td>Toxoid</td>
</tr>
<tr>
<td>Epidemic encephalitis</td>
<td>Convalescent serum</td>
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<tr>
<td>Erysipelas</td>
<td>Sulfanilamide</td>
<td>For recurrent disease</td>
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<tr>
<td>Epidemic meningitis</td>
<td>Sulfanilamide</td>
<td></td>
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<tr>
<td>Epidemic parotitis</td>
<td>Convalescent serum</td>
<td></td>
</tr>
<tr>
<td>Pertussis</td>
<td>Diphtheria pertussis antigen</td>
<td>3 unproven</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Sulfanilamide</td>
<td></td>
</tr>
<tr>
<td>Polio</td>
<td>Convalescent serum</td>
<td></td>
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<tr>
<td>Rabies</td>
<td></td>
<td>Post-exposure killed virus</td>
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<tr>
<td>Measles</td>
<td>Convalescent serum</td>
<td></td>
</tr>
<tr>
<td>Scarlet fever</td>
<td>Antitoxin</td>
<td>Toxin</td>
</tr>
<tr>
<td>Staph aureus</td>
<td>Antitoxin</td>
<td>Toxoid</td>
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<tr>
<td>Tetanus</td>
<td>Toxoid</td>
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<tr>
<td>Tuberculosis</td>
<td>BCG</td>
<td></td>
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<tr>
<td>Typhoid fever</td>
<td></td>
<td>Vaccine</td>
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<tr>
<td>Varicella</td>
<td>Convalescent serum</td>
<td>Vesicle content</td>
</tr>
<tr>
<td>Varicella</td>
<td></td>
<td>Calf vaccine</td>
</tr>
</tbody>
</table>

Through the Years

- Published every 1-5 years between 1938 and 1986 and every 3 years since then
- 10 prior editors over 30 years
- 1970s-liasons from CDC and FDA added
- 1982-associate editors added
- Inclusion of reference to AAP statements, CDC guidelines, ACIP recommendations and IDSA, AHA guidelines (GRADE)
- COID responsible for assembly and publication
2015 Edition Primary Reviewers

- 179 content experts
- 196 CDC reviewers
- 51 FDA reviewers
- 24 COID members
- 1 PhD microbiologist-Raj Selvarangan
- 30 internal AAP reviews

Grand Total-474 chapter reviewers

Red Book 2015

- Launched in May
- All chapters updated plus new chapters (eg, Ebola)
- Format stayed the same
  - 6 sections (active/passive immunization, care of children special circumstances, summaries, antimicrobial agents, antibiotic prophylaxis, appendices
  - Pathogen summaries
    • Clinical manifestations, etiology, diagnostic testing, treatment, isolation, control measures

Case 1

- 10 yo: T 101.6°F, RR 32, ill appearing
  - Cough X 5 days, “weak in the eyes”
  - Scattered rales, dull to percussion R base
  - Normal CBC, Rapid flu negative
  - Blood cx pending
  - CXR: Bilateral air space disease, RLL patchy consolidation
- Suspicion: CAP
  - Admitted for IVF, Abx and O2 initiated

Influenza Rapid Antigen Test

- Variable sensitivity/specificity
  - Compared with viral culture or RT-PCR.
  - Sensitivities ~50-70%
  - Specificities ~90-95%
- Highest sensitivity when collected early in course, best at ≤4-5 days in adults
- Young children excrete in higher titers and longer – so can be useful up to 8-10 days

Rapid Antigen Test-Influenza

- Positive and negative predictive values vary
  - Depends on current prevalence of influenza
- False-positive
  - More likely when prevalence is low
  - Occurs at beginning and end of season
- False-negative
  - More likely when prevalence is high
  - At height of the influenza season
- Every hospitalized child with influenza should receive oseltamivir

CDC FluView

Influenza: Season of 2014-15
Pregnancy Vulnerability

- IL-6 showed higher expression in pregnant women who died.
- IFN-β and TGF-β expression were lower in those pregnant women who died.

H1N1 pnd 2009
Less Severe after 2010

- Post-pandemic years, H1N1 disease:
  - Lower median age
  - Less likely to have underlying condition
  - Lower likelihood of intubation and ARDS
  - Decreased mortality

- DOI: http://dx.doi.org/10.1016/j.jcv.2015.07.308

Influenza Vaccine for 2015–16

- IIV-3 (new H3N2 and B)
  - A/California/7/2009 (H1N1)-like virus
  - A/Switzerland/9715293/2013 (H3N2)
  - B/Phuket/3073/2013-like (Yamagata lineage)
- IIV-4 and LAIV-4
  - IIV-3 strains
  - B/Brisbane/60/2008-like (Victoria lineage)
  - Same 2nd B as 2013–14 and 2014–15

Doses of Flu Vaccine 0.5 through 8 YO

- The two doses need not have been received during the same season or consecutive seasons.
- Doses should be administered 4–6 weeks apart.

Case 2 - The rash

- A 4 month old Micronesian is admitted for suspected Kawasaki Disease.
- Fever for 4 days and rash, red eyes, very irritable
- Inflammatory markers are elevated

Differential Diagnosis

Important “don’t want to miss” considerations

- Kawasaki Disease
- Tick borne infection, leptospirosis
  - Seasonality, exposures
  - Measles
    - Key: immunization history, exposure, travel
  - Staphylococcal or GAS toxin syndromes
  - Drug hypersensitivity reactions
    - Classic: TMP/SMX, carbamazepine
**Irritable infant with fever, rash and red eyes**

Image courtesy Jennifer Goldman, MD

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**The 2014 Kansas City Outbreak**

- **Imported disease - Genotype B3**
  - 3rd largest 2014 US outbreak behind OH and CA
  - Largest per population base
- **May 6 - First case in Clay County, Missouri**
- **May 13 & 15 - 2 more cases, first infant case**
  - May 20….new case in a choir member
  - Additional cases followed a restaurant exposure
- **Data from first 22 cases:**
  - 2 wks old to 37 years old (median age 5 years)
  - None immunized

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**Another Imported Case**

- Measles at the “The Happiest Place on Earth”
- Dec 2014 – Apr 2015
- 136 cases related to visit to Disneyland and surrounding theme parks
- B3 genotype (predominant Philippines strain)
- 60% adults

70% not immunized, 20% hospitalized, two other imported cases added to exposures

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**What To Do If You Suspect Measles**

- Know the signs/symptoms/incubation period
- Isolate suspected cases
  - Highly contagious for 4 days pre- and post rash
  - Airborne precautions
  - Do not refer/send to healthcare facility without first calling
- Notify HD immediately and/or ID consultant on call
- Testing
  - Throat swab and urine for measles PCR
  - Blood sample for measles specific IgM serology
- Understand exposed unimmunized persons need PEP

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**Measles Symptom Timeline**

Compatible clinical symptoms plus
1. Unimmunized against measles
2. Contact with unimmunized or international traveler
3. Travel to current outbreak area
4. Travel to US tourist destinations popular with international travelers
  - For example national amusement/theme parks
5. International travel - measles may occur anywhere
  - But…..CDC specific health alerts for Philippines and Vietnam
  - Other countries with measles as of June 2015
    - Angola, Bosnia, Ethiopia, Germany, Kyrgyzstan
What Do Two-Dose Cases Look Like?

3 C’s not present, rash not classic distribution

1. Fever 101, conjunctivitis, no cough, but did report coryza
   Rash started on face, then to chest and shoulders. Did not affect to extremities. Had traveled to China, had no known exposure

2. Subjective fever, conjunctivitis, cough, no coryza
   Rash started on face, moved to chest, arms then stomach (lasted 4 days)
   Exposed to measles in an UC waiting room

3. Fever 101, no conjunctivitis, cough or coryza
   Rash started on face, then to body, arms, legs (lasted 3 days)
   Exposed to measles in household

4. Subjective fever, conjunctivitis, no cough or coryza
   Rash spread head downward, duration unknown
   Exposed on a flight to CA measles case

Exposure history critical for Dx

Other Aspects of Rash in Immunized Patients

- Itchy rash?
  - May be itchy from day 4-7, but not itchy immediately

- Rash on palms and soles?
  - Measles rashes may be on palms and soles but not as prominent as on face and chest

- What is the rash distribution and spread look like?
  - Even if disease is modified the order of appearance (face and head) and direction of spread is the same
  - Timing of fever in relation to rash not defined

Case 3-Diarrhea in a 10 year old

- Starts amoxicillin for sinusitis after a URI symptoms persist for 10 days
- Day 4 on antibiotic
  - Abdominal pain and watery diarrhea
- Day 6
  - Diarrhea worse, cramping – Abx stopped
- Day 11
  - Stools become bloody

CDC Threat Report

- 250,000 Americans suffer from C. difficile infection annually
- >85% of reported cases are adults
- Recent data conflicting on pediatric C diff disease vs. asymptomatic "carriage"

http://www.cdc.gov/drugresistance/threat-report-2013/
Introduction

*Clostridium difficile*
- Gram-positive anaerobic bacillus
- Can exist in vegetative or spore form
- Causes hospital and community-acquired diarrhea

Epidemiology

*C. difficile* colonization
- Become colonized in the 1st-3rd months of life
- Up to 73% of 6 month olds
- Colonization decreases in the 2nd and 3rd year of life
- Up to 3% can have asymptomatic carriage at 3 years of age (similar to adults)
- Can be colonized with toxigenic or non-toxigenic strains

Clinical Manifestations

<table>
<thead>
<tr>
<th>Table 1. Comparison of Community-Acquired and Hospital-Acquired <em>Clostridium difficile</em> Infection in Children, 1991–2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
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<tr>
<td>Median age, y (range)</td>
</tr>
<tr>
<td>Male sex</td>
</tr>
<tr>
<td>Antibiotic exposure</td>
</tr>
<tr>
<td>Gastric acid suppression use</td>
</tr>
<tr>
<td>Severe CDI</td>
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<tr>
<td>Severe complicated CDI</td>
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<tr>
<td>Recurrent CDI</td>
</tr>
</tbody>
</table>

Candidate for *C diff* Testing?

A. 6 month old with streaky blood in stool for 5 days
B. 2 year old with mucous and blood in stool for one day
C. 6 year old with abdominal pain and diarrhea for 4 days, formed stool today
D. 10 year old with IBD has diarrhea for 10 days while hospitalized for TPN
E. 12 year old completing metronidazole after *C diff* diagnosis as “test of cure”

Diagnostics—correct test in correct situation

- *C. difficile* could be cultured using selective media but this won’t identify if toxin present
- Testing is targeted to identifying the toxin
- 2 step testing
  1. ELISA for *C. difficile* glutamate dehydrogenase (GDH) antigen
  2. If GDH positive then test for toxin A and B antigens
     - PCR testing for toxin genes

Diagnostics—correct test in correct situation


CMH *Cdiff* Test Order Algorithm

*https://www.childrensmercy.org/Health_Care_Professionals/Medical_Resources/Clinical_Practice_Guidelines/Clostridium_Difficile/Cl*
Treatment
- Classify disease severity
  - Oral metronidazole
  - Oral vancomycin
  - Oral, PR vancomycin plus IV metronidazole
- FMT for refractory C. difficile
  - Administer stool via enema, colonoscopy, NG
  - DIY follows IDSA guidelines for choosing “donor”

Case 4 – R/O sepsis infant
- 2 week old presents in August:
  - History
    - Fever 101.2 F at home
    - Poor feeding, Very irritable
    - Transient truncal rash
  - PE
    - Abdominal distension, is irritable
  - Lab
    - Leukopenia with lymphopenia
    - Normal CSF exam

SBI IN YOUNG INFANTS
- Non-infectious etiologies - e.g. volvulus
- UTI most common and E coli predominates
- CNS infections
  - Viral agents (HSV, enteroviruses, others)
  - Bacterial pathogens
    - Group B streptococcus
    - Less common: E coli, other gram-negatives, Listeria monocytogenes
    - S pneumoniae and N meningitidis

Enteroviruses
- 10-15 million children infected yearly
- 100 different viruses
- Polioviruses and non-polio viruses
- Non-Polioviruses
  - Echoviruses
  - Coxsackie viruses A and B
  - Numbered enteroviruses

“Typical” Enteroviruses
- Summer-fall
- Typical clinical presentations
  - Nonspecific febrile illness
  - HFMD-classically Coxsackie A-16; atypical cases Coxackie A-6
  - Enterovirus meningitis-classically echoviruses
- Rare but distinct associations
  - Enterovirus 71-acute flaccid paralysis


Atypical HFMD

FIGURE 2. Percentage of enterovirus reports, by week of specimen collection — United States, 1985-2007
**Human parechoviruses (HPeV)**

- Single-stranded, non-enveloped RNA viruses Picornaviridae family
- Types 1 and 2 were initially designated echovirus 22 and 23 within the Enterovirus (EV) genus
- HPeV type 3 (HPeV-3), identified in 2004, and 16 HPeV types are now known
- 2-3 year cycle of late summer-fall outbreaks
  - Mostly like EV meningitis
  - But...meningoencephalitis and severe disease may occur in neonates
- Differential Dx includes HPeV vs enterovirus vs HSV
- Diagnosis confirmed by PCR detection in CSF


**Case 5-What else?**

- August 2014: an outbreak of asthma like illness in children requiring PICU care
  - 3 signals: physician alert, microbiology records, PLUS “us too”
  - Prompted request for CDC typing
  - The emergence of EV68 in KC and the rest of the states

**FilmArray™ for Molecular ID Respiratory Pathogens**

- Has the ability to potentially identify 19 respiratory pathogens
- “FilmArray RP utilizes a combination of PCRs that can detect rhinovirus or that may more broadly detect rhinovirus/enterovirus without distinguishing between the two”
  - Biased toward recognition of rhinovirus


**Figure 1 Weekly entero/rhino detections 2013 compared to 2014; week 33**

- 5-7/week
- 30/week for prior 2 wks

Courtesy Dr. Rangaraj Selvarangan
**2014 EV D-68 Outbreak**

- Largest outbreak of EV D68 severe respiratory illness across the US
  - In KC, we confirmed 333 cases with 61 to the PICU
- Spectrum of infection uncertain
  - Severe bronchospasm with respiratory failure
  - ? Extent of mild disease
- Severely ill EV D-68 positive children were older (5-10 YO), more likely to have history of asthma/wheeze, high rate respiratory failure
- Don’t miss “the forest for the trees” – especially in high risk hosts
  - 36% of strains submitted to CDC confirmed
  - 60% confirmed from CMH PICU patients
- Unusual EV68 manifestations?
  - Association with polio like cases still under investigation

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**Red Book Timeline**

<table>
<thead>
<tr>
<th>Date Range</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aug 18 to Oct 5, 2013</td>
<td>Finalize AEs and primary reviewers</td>
</tr>
<tr>
<td>Aug 26 to Feb 14, 2014</td>
<td>Primary reviewers review chapters</td>
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<tr>
<td>Feb 14, 2014 to Feb 4, 2014</td>
<td>AEs to incorporate primary reviewer edits</td>
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<tr>
<td>Mar 4 to June 5, 2013</td>
<td>CDC, FDA, and Internal Reviewers review chapters</td>
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<tr>
<td>Aug 5 to Oct 7, 2013</td>
<td>AEs to incorporate CDC, FDA, and Internal Reviewer edits</td>
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<tr>
<td>Mar 1 to Feb 2, 2014</td>
<td>CSS, liaison primary and secondary reviews</td>
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<tr>
<td>Feb 7 to March 14, 2014</td>
<td>AEs review primary and secondary CSS and liaison reviewers’ edits</td>
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<tr>
<td>March 18 to March 24, 2014</td>
<td>Marathon Meeting</td>
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<tr>
<td>March 20 to April 3, 2014</td>
<td>AEs to incorporate Marathon Meeting edits</td>
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<tr>
<td>April 4 to Aug 11, 2014</td>
<td>Copying editing (Shaw) and final editing (Kimberlin)</td>
</tr>
<tr>
<td>Aug 17, 2014 to Feb 16, 2015</td>
<td>Review (Kimberlin), and proofreading (Peg Maloney)</td>
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<tr>
<td>Mar 2 to Mar 15, 2015</td>
<td>Indexing (outside company, coordinated through Marathon Meeting)</td>
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<td>Feb 10 to Mar 30, 2015</td>
<td>Shaw and Kimberlin cross-check edits</td>
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<td>March 1, 2015 to April 7, 2015</td>
<td>Typesetting (Peg Mulcahy)</td>
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<tr>
<td>Aug 11, 2014 to Feb 16, 2015</td>
<td>Board review (from Word documents), Editor (Kimberlin), and proofreading (Peg Maloney)</td>
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10 Editors of the Red Book over 30 years

- John Toomey first 8 editions
- Jerry Klein in 1982-appointed the first associate editors
- George Peter and Larry Pickering 10 editions between 1986 and 2012
- David Kimberlin, editor 2015 edition

COID Members + Liaisons


Current Liaisons to COID

- Committee on Practice
- Ambulatory Medicine
- Section on Infectious Diseases
- American Academy of Family Physicians
- American Thoracic Society
- Canadian Pediatric Society
- Pediatric Infectious Diseases Society
- Society for Healthcare Epidemiology of America (SHEA)
- CDC
- FDA
- National Institutes of Health
- National Vaccine Program Office

Enterovirus D-68 Confirmation

- Samples to CDC August 19
- Confirmation of EV D-68 in clinical samples August 26
- EV D-68 identified in 1962 in respiratory samples from CA cases (Schieble, et al, Am J Epidemiol 1967)
- Rare reports next 36 years
- Since 2008, small clusters
- MMWR 2011-disease could be missed b/o misidentification as a rhinovirus

Disease Extent and Severity

Mid-August, 2014

Children's Mercy-Kansas City

- Clinical signal
- Microbiologic signal
  - Asked for confirmation from CDC
- Hospital burden particularly in PICU