Session 8:  
Infectious Diseases Grand Rounds  

Learning Objectives  

1. Understand the issues relating to the changing epidemiology and treatment challenges of infections caused by *C. difficile*, *B. pertussis*, and *N. gonorrhoeae*.  
2. Implement the most recent changes in adult vaccine recommendations during routine visits.
Session 8

Infectious Diseases Grand Rounds

Faculty

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Dr Itskowitz earned his bachelor of arts degree from Cornell University, New York, and received his medical degree from the Medical College of Pennsylvania, where he was elected to the Alpha Omega Alpha honor medical society. He completed his residency and chief residency in internal medicine at Allegheny General Hospital. He currently practices internal medicine with Pittsburgh General Medicine Associates, Pennsylvania. His clinical interests include cardiovascular risk assessment, travel medicine, and perioperative medicine; he has lectured frequently on these topics.

Dr Itskowitz is a fellow of the American College of Physicians and a member of the Association of Program Directors in Internal Medicine. He is a diplomate of the American Board of Internal Medicine. Dr Itskowitz is the author of numerous journal articles and serves on the editorial board of *Emergency Medicine: Acute Medicine for the Primary Care Physician*. He also is a team physician for the Pittsburgh Pirates.

Faculty Financial Disclosure Statement

The presenting faculty reports the following:

Dr Itskowitz has no financial relationships to disclose.
Session 8:
10:15 AM – 11:15 AM

Infectious Diseases
Grand Rounds

Marc Itskowitz, MD, FACP

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Learning Objectives

- Understand the issues relating to the changing epidemiology and treatment challenges of infections caused by *C difficile*, *B pertussis*, and *N gonorrhoeae*.
- Implement the most recent changes in adult vaccine recommendations during routine visits.

Demographic Question

How many patients with a sexually transmitted disease or *C difficile* infection do you treat each week?

1. None
2. 1 - 5
3. 6 - 15
4. 16 - 25
5. Over 25

Outcomes Question #1

Which of the following is/are recommended for treating *uncomplicated* gonorrhea?

1. A 7-day regimen of PO cephalosporin
2. A single IM dose of ceftriaxone
3. A 7-day regimen of PO azithromycin
4. A single IM dose of ceftriaxone plus a single PO dose of azithromycin
5. Both 1 and 2 are recommended

Demographic Question

How many adults do you immunize each week?

1. None
2. 1 - 5
3. 6 - 15
4. 16 - 25
5. 26 - 40
6. Over 40
Outcomes Question #2

The most sensitive method for outpatient diagnosis of Clostridium difficile infection (CDI) in a symptomatic outpatient is:

1. Stool culture
2. Stool enzyme immunoassay (EIA) test
3. Stool polymerase chain reaction (PCR) test
4. Antibody serology test

Outcomes Question #3

A single Tdap dose is only recommended in pregnant women:

1. Who have never received a pertussis vaccine
2. During first pregnancy regardless of pertussis vaccine history
3. During each pregnancy, regardless of pertussis vaccine history
4. Never, since Tdap is contraindicated in pregnancy

Sexually Transmitted Infections

Case 1: Ms. Hamilton

A 25-year-old woman presents with vaginal discharge. She is sexually active with 2 male partners and uses oral contraception for birth control. On exam you find a shallow ulcer with heaped edges on her labia and a whitish vaginal discharge with a friable cervix.

You should test for:

1. Syphilis
2. Gonorrhea
3. Chlamydia
4. HIV
5. HSV
6. All of the above

STI Trends – Syphilis

Syphilis - Overview

Sexually acquired infection; Treponema pallidum

3 stages

1. Local - Genital ulcer that is painless (3 week incubation)
2. Disseminated – rash (nonpruritic, involves palms and soles); malaise, lymphadenopathy, (3-6 weeks after ulcer)
3. Late – gumma, aortitis (occurs in 30% of untreated pts. 1-20 years after infection)

Latent (asymptomatic) periods occur between the clinical stages

Neurosyphilis: meningeal symptoms, patients can also be asymptomatic; occurs more frequently in early disease, and with HIV co-infection
To screen for syphilis, you should first obtain:

1. Blood for an RPR titer
2. A swab of the ulcer for culture
3. A swab of the ulcer for PCR
4. Blood for a *treponemal pallidum* EIA test
5. Any of the above
6. 1 or 4

**Question**

**Syphilis - Diagnosis**

- *Treponema pallidum* cannot be cultured
- Serology is most common diagnostic test
  - Nontreponemal serology (RPR; VDRL)
    - Not specific to the organism; used for screening
    - Results as a titer, can be used to follow therapy
  - Treponemal serology (FTA-ABS; MHA-TP; TP-PA; TP-EIA)
    - Confirms the RPR
    - Positive or negative result (no titer); stays positive even after treatment
- Darkfield microscopy and DFA performed directly from lesions
  - Not routinely available
  - Negative result does not rule out syphilis

**Syphilis - New Diagnostic Testing**

- Usually RPR test followed by TP test confirmation
- Reverse testing order (TP EIA followed by RPR) has been advocated
  - Cost savings; Fast
  - Problems with discordant results (EIA +/RPR-)
  - If discordant, do additional test (TP-PA) or get a consult
- If both RPR and TP test + → + syphilis
- RPR can be false positive or negative
  - Pair with treponemal test
  - If negative with high clinical suspicion (painless chancre), repeat in 1-2 weeks and consider a direct test

**Syphilis - Treatment**

Depends on stage of disease

- Early (infection within 1 year) vs. Late (>1 year)
  - Primary, Secondary, or Early Latent disease
    - Benzathine PCN G 2.4 million units IM x 1
  - Late disease or not known
    - Benzathine PCN G 2.4 million units IM x 1 per week x 3 weeks
    - Neurosyphilis: IV PCN G 18-24 million units/day x 10-14 days
    - OR procaine PCN 2.4 million units IM QD plus probenicid 500 mg QID PO x 10-14 days

PCN-allergic patients

- Doxycycline preferred; can use azithromycin/CTX as alternative options if early disease
- Desensitize to penicillin if pregnant or patient has neurosyphilis

Monitor RPR titers for 4x decline over next 6-12 months

**Gonorrhea (Neisseria gonorrhoeae)**

- Asymptomatic in 50% women, 10% men
  - Cervicitis, epididymitis, urethritis, or proctitis; also PID
- If untreated → infertility, Trisk ectopic pregnancy & HIV
- Co-pathogen with Chlamydia in up to 45% cases

**Diagnosis**

- Preferred method is nucleic acid amplification (NAATS)
  - Can perform on urine or on swab
  - NAAT for GC and chlamydia are done together; and may warrant screen for syphilis and HIV
- In men, can do a gram stain of urethral discharge
- Culture if treatment failure (for susceptibility) or if extra-genital disease

You also suspect that Ms. Hamilton might have genital gonorrhea
Question

The recommended gonorrhea treatment for Ms. Hamilton is:

1. A combined regimen of IM ceftriaxone and oral azithromycin
2. A single IM dose of ceftriaxone
3. A single IM dose of penicillin
4. A combined regimen of IM ceftriaxone followed by 7 days of oral cefixime
5. A 7-day regimen of azithromycin

Gonorrhea – Treatment Update

- "Oral cephalosporins no longer a recommended treatment for gonococcal Infections”
  – Published as 2012 update to CDC guideline
- Now need 2 drugs for therapy of uncomplicated infection
  – Ceftriaxone 250 mg IM x 1 PLUS azithromycin 1 gm PO x 1
  – Also treats chlamydia
  – Can use doxycycline in place of azithromycin if intolerant, or if proctitis or epididymitis infection
- If PCN allergic
  – Azithromycin 2 gm x 1

Infectious Diarrhea

Case 2: Mr. Conti

- Mr. Conti is a 60-year-old male with COPD and diabetes
- He was in the hospital for a COPD exacerbation 2 weeks ago and he presents for his post-hospitalization follow-up. His COPD is stable.
- He was told he had “C diff” while in the hospital and finished his course of oral metronidazole last week
- He reports that he has no more diarrhea
Mr. Conti – Next Steps

You should:

1. Send a follow-up *C. difficile* test on his stool to make sure it is resolved
2. Reassure him that he won’t get that infection now that he’s discharged
3. Treat him with another 14-day course of metronidazole just in case he has residual spores
4. Tell him that *C. difficile* can recur and he should report any recurrence of diarrhea
5. 1 and 4

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**Clostridium Difficile Infection (CDI)**

- >200% increase in CDI diagnoses
- 9th leading cause of GI related mortality

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**Clostridium Difficile Infection**

- Although *C. difficile* is common in the environment, only 1 - 4% of adults are carriers.
- Normal colonic microflora confers colonization resistance against CDI.
- CDI results from overgrowth of CD with toxin production
- Traditional risk factors:
  - Age >65 years and/or underlying illness (weakened immune system)
  - Recent antibiotic exposure (up to 3 months prior), resulting in disturbed colonic microflora (dysbiosis)
  - Recent hospitalization or other health care exposure; can occur in community as well

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**C Difficile – Diagnosis**

- In patients with new diarrhea, *C. difficile* infection should be in the differential diagnosis
  - Increased risk if antibiotic or health care exposure
- *C. difficile* spores can be carried in the gut
  - Asymptomatic patients should not be tested and do not warrant therapy
  - Test stool only in actively symptomatic patients
  - PCR is best test (highly sensitive)
  - EIA less sensitive; if high clinical suspicion, start empiric therapy even if this test is negative and send a PCR

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**Antimicrobials for CDI**

<table>
<thead>
<tr>
<th></th>
<th>Metronidazole</th>
<th>Vancomycin</th>
<th>fidaxomicin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approved by FDA for CDI</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Comparative Cost</td>
<td>$</td>
<td>$5</td>
<td>$5$5$</td>
</tr>
<tr>
<td>Form used for CDI</td>
<td>Oral IV for severe or complicated disease</td>
<td>Oral, Intragastric or enema</td>
<td>Oral</td>
</tr>
<tr>
<td>Duration (d)</td>
<td>10-14</td>
<td>10-14</td>
<td>10-14</td>
</tr>
<tr>
<td>Notes</td>
<td>Preferred for mild to moderate disease</td>
<td>Preferred (and proven more effective) for severe disease; also indicated when metronidazole cannot be used or is not effective</td>
<td>Equal efficacy to vancomycin but may have lower recurrence rates; nausea (11%), vomiting (7%) most common adverse effects</td>
</tr>
</tbody>
</table>

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Mr. Conti: One Month Later

He returns with new onset diarrhea for the past week. It is watery, non-bloody, associated with some crampy abdominal pain. He is afebrile; abdomen is soft, not-tender and not distended.

You should:

1. Send a *C difficile* PCR test on his stool
2. Start empiric therapy with metronidazole while awaiting for the test results
3. Start therapy with vancomycin
4. Prepare him for a stool transplant
5. 1 and 3
Recurrent CDI

- Up to 30% of patients with CDI have recurrence within 3 months
  - Increased risk if antibiotic or proton pump inhibitors
- If relapse of diarrhea in patient with recent CDI, test for CDI recurrence
- Empiric treatment if fever, distended abdomen, high WBC and high clinical suspicion

Recurrent CDI Treatment Options

First recurrence

- Mild to moderate C difficile infection (CDI)
  - Oral metronidazole, 500 mg 3 times a day for 14 d
- Mild to moderate CDI (no response to oral metronidazole previously)
- Severe CDI
  - Oral vancomycin, 125 mg 4 times a day for 14 d

Second recurrence

- Oral vancomycin tapered over 6 wk
  - 125 mg 4 times daily for 14 d
  - 125 mg 2 times daily for 7 d
  - 125 mg once daily for 7 d
  - 125 mg once every other day for 8 d
  - 125 mg once every 3 d for 15 d

Future recurrences

- Oral vancomycin, 125 mg 4 times a day for 14 d, followed by rifaximin, 400 mg twice daily for 14 d
- Consider fecal microbiota transplantation
- Consider intravenous immunoglobulin, 400 mg/kg, repeated up to 3 times at 3-wk intervals
- Consider combination therapy with oral vancomycin and oral rifaximin

Fecal Microbiota Transplantation (FMT)

- Oral vancomycin tapered over 6 wk
  - 125 mg 4 times daily for 14 d
  - 125 mg 2 times daily for 7 d
  - 125 mg once daily for 7 d
  - 125 mg once every other day for 8 d
  - 125 mg once every 3 d for 15 d

CDI Prevention and Precautions

- For Clinicians
  - Hand Hygiene! Clean hands with soap and water (preferred) or alcohol based rub before and after caring for every patient *
  - Contact precautions (gowns/gloves); Environmental Disinfection (bleach)
  - Limit antibiotics
- For Patients
  - HH (for yourself and your provider)
  - Only use antibiotics when prescribed
- For Households
  - HH (yourself and your family)
  - Keep high touch surfaces clean

* Alcohol does not effectively kill CD spores

Pertussis Update
Case 3: Mr. Smith

40-year-old man presents with prolonged cough. It began 3 weeks ago and comes on suddenly, sometimes followed by emesis. No fever, chills. Exam is normal and CXR is clear. He states he received the usual childhood vaccines.

Which of the following suggests that a pertussis diagnosis is unlikely?

1. Lack of inspiratory whoop
2. Lack of fever
3. Clear CXR
4. History of vaccination
5. All of the above

Pertussis Epidemiology

- Highly contagious acute respiratory illness (“whooping cough”) caused by *Bordetella pertussis*
- Endemic in the US; the majority of cases in adolescents and adults
  - Waning immunity is key factor
- Recent resurgence with epidemic numbers in Washington state

Pertussis – Signs and Symptoms

- Three phase illness
- Catharral - malaise, rhinorrhea, mild cough, conjunctival irritation, lacrimation
  - Non-specific; lasts up to 3 weeks
- Paroxysmal phase; 1-6 weeks
  - On expiration: vigorous cough in spasms
  - On inspiration: whooping sound
- Convalescent phase; up to 3 weeks
  - Cough lessens in severity
  - In adolescents and adults, these symptoms may be less pronounced

Mr. Smith

You want to test Mr. Smith for pertussis. What is the most specific test?

1. Anterior nasal PCR
2. Culture of throat for Bordetella
3. Serum antibody for Bordetella
4. Culture of posterior nasopharynx for Bordetella
5. None of the above

Pertussis – Diagnosis

- Early diagnosis is key; decrease spread, mitigate symptoms with antibiotics
- Clinical definition: cough lasting > 2 weeks with one or the following features:
  - Paroxysmal cough
  - Inspiratory whoop
  - Posttussive emesis
- Clinical criteria enough for diagnosis: Probable or confirmed (if linked to lab diagnosed case)

Pertussis Specimen

Posterior nasopharyngeal specimen is needed – this is uncomfortable and will induce cough/sneeze….

... the sampler should wear a goggles, mask and gloves!!

See CDC video: [http://www.cdc.gov/pertussis/clinical/diagnostic-testing/specimen-collection.html#swab-testing](http://www.cdc.gov/pertussis/clinical/diagnostic-testing/specimen-collection.html#swab-testing)
**Pertussis Diagnosis**

- Nasopharygeal culture is gold standard
  - highly specific; sensitivity decreases after 2 weeks
- If cough lasting 2 - 4 weeks: do both culture and PCR
  - PCR should only be done up to 4 weeks from cough onset
  - Need a dacron swab (not cotton)
- After 4 weeks, do serology

http://www.cdc.gov/pertussis/clinical/diagnostic-testing/diagnosis-confirmation.html

**Pertussis Treatment**

- Antibiotics decrease symptoms and reduce spread
- Most effective before the paroxysmal phase
  - Diagnosis may be unclear at this stage
  - Treat before test results back if infant or known outbreak
  - Treat up to 3 weeks from onset of cough
- Azithromycin x 5 days
  - TMP/SMX x 14 days if can’t take azithromycin (nonpregnant)
- Can return to work/school after 5 days of antimicrobial therapy
- Post-exposure prophylaxis for close contacts
  - Pregnant, infant, immunocompromised
- Report to public health
  - Prevent pertussis with Tdap vaccine!

**Update on Adult Immunizations**

**ACIP Recommendation for Tdap 2012**

- Adults
  - All adults 19 years and older, including those 65 years and older, should get a dose of Tdap (tetanus, diphtheria, and pertussis) vaccine
    - Adults ≥ 65 years who have not previously received Tdap, and who have or who anticipate having close contact with a child younger than age 12 months, should receive a single dose of Tdap
    - Adults ≥ 65 years who have not previously received Tdap may be given a single dose of Tdap
    - There is no minimum interval needed between receiving tetanus toxoid, reduced-dose diphtheria toxoid (Td) and Tdap vaccines when given to protect infants or other vulnerable individuals


**ACIP Tdap Recommendations 2012**

- Pregnancy
  - Tdap should be administered to all pregnant women.
    - A dose of Tdap should be given during each pregnancy irrespective of the patient’s prior history of receiving Tdap
    - To optimal timing for Tdap administration is between 27 and 36 weeks gestation
    - For women not previously vaccinated with Tdap, if Tdap is not administered during pregnancy, Tdap should be administered immediately postpartum.

The ACIP recommendation is at odds with the FDA, which has only approved Tdap for one-time use, rather than multiple uses

Measles - United States, 1950-2007

Measles on the Rise


Cases 55,622

Age group affected Children <5yrs

Hospitalizations >11,000

Deaths 123

Direct medical costs >$150 Million

More measles

The United States seems to be on track to have more measles cases than any year in more than a decade.

2011: 361 cases

2010: 299 cases

2009: 52 cases

2008: 12 cases

ACIP Provisional MMR Recommendations December 2012

• Adequate presumptive evidence of immunity to measles
  – documentation of age-appropriate vaccination with a live measles virus-containing vaccine:
    • Preschool-aged children: 1 dose
    • School-aged children (grades K-12): 2 doses
    • Adults not at high risk: 1 dose, or
  – Laboratory evidence of immunity, or laboratory confirmation of disease, or
  – Born before 1957

• The first dose of MMR vaccine should be administered on or after age 12 months; the second dose of measles- or mumps-containing vaccine should be administered no earlier than 28 days after the first dose.

MMR = Measles Mumps Rubella

ACIP Recommendation for HPV Vaccination in Males

• Routine use of quadrivalent HPV vaccine (HPV4; in boys 11 or 12 years of age
• Also recommended for boys and men 13 to 21 years of age
• Only HPV4 recommended for men
• Administer second dose 1-2 months after first dose, and third dose 6 months after first dose
• Men who have sex with men (MSM) might benefit from vaccination to prevent condyloma and anal cancer

ACIP Recommendation for HPV Vaccination in Males

HPV Vaccines

Human Papillomavirus Vaccines

• HPV4
  – contains types 16 and 18 (high risk) and types 6 and 11 (low risk)
• HPV2
  – contains types 16 and 18 (high risk)
• Both vaccines are supplied as a liquid in a single dose vial or syringe
• Neither vaccine contains an antibiotic or a preservative

HPV Vaccines

13-Valent Pneumococcal Conjugate Vaccine for Adults

• 2010: FDA approves 13-valent pneumococcal conjugate (PCV13) vaccine and recommended by ACIP for children aged 6 weeks through 71 months
• December 2011: FDA approved PCV13 for prevention of pneumonia and invasive disease caused by PCV13 serotypes among adults aged ≥50 years
  – In adults, PCV13 elicited antibody titers that were comparable to, or higher than, responses elicited by PPSV23
• October 2012: ACIP recommends PCV13 for immunocompromised adults aged ≥19 year, who have not previously received PCV13 or PPSV23
  – 1 dose of PCV13 followed by 1 dose of PPSV23 at least 8 weeks later

13-Valent Pneumococcal Conjugate Vaccine for Adults

MMWJ June 1, 2012 / 61(21);394-395.
### 2013 Adult Immunization Schedule

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>22-26 yrs</th>
<th>27-49 yrs</th>
<th>50-59 yrs</th>
<th>≥ 65 yrs</th>
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<tbody>
<tr>
<td>Influenza</td>
<td>1 dose annually</td>
<td>1 dose annually</td>
<td>1 dose annually</td>
<td>1 dose annually</td>
</tr>
<tr>
<td>Tetanus, diphtheria, pertussis (Tdap)</td>
<td>Substitute 1 time dose of Tdap for Td booster; then boost with Td every 10 yrs.</td>
<td>Substitute 1 time dose of Tdap for Td booster; then boost with Td every 10 yrs.</td>
<td>Substitute 1 time dose of Tdap for Td booster; then boost with Td every 10 yrs.</td>
<td>Substitute 1 time dose of Tdap for Td booster; then boost with Td every 10 yrs.</td>
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<tr>
<td>H. influenza</td>
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<td>1 dose</td>
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<tr>
<td>Human Papillomavirus (HPV) Female</td>
<td>3 doses</td>
<td>3 doses</td>
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<td>1 dose</td>
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<tr>
<td>Human Papillomavirus (HPV) Male</td>
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<td>3 doses</td>
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<td>Varicella</td>
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<tr>
<td>Zoster</td>
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<tr>
<td>Measles, mumps, rubella (MMR)</td>
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<td>1 or 2 doses</td>
<td>1 or 2 doses</td>
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<td>Pneumococcal polysaccharide (PPSV23)</td>
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<td>Pneumococcal 13-valent conjugate (PCV13)</td>
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<td>Meningococcal</td>
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<tr>
<td>Hepatitis A</td>
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<td>Hepatitis B</td>
<td>1 dose</td>
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Consult CDC schedule document for important footnotes
http://www.cdc.gov/mmwr/preview/mmwrhtml/su6201a3.htm

### ACP Immunization Tools

American College of Physicians Immunization Portal

**Immunization Guideline**
- Practice Improvement
- Practical Advice
- Vaccines and Their Indications
- Special Populations

**ACP Immunization Advisor** app for smartphones and tablets
Go to http://immunization.acponline.org/app/

### Outcomes Question #1

Which of the following is/are recommended for treating *uncomplicated* gonorrhea?

1. A 7-day regimen of PO cephalosporin
2. A single IM dose of ceftriaxone
3. A 7-day regimen of PO azithromycin
4. A single IM dose of ceftriaxone plus a single PO dose of azithromycin
5. Both 1 and 2 are recommended

### Outcomes Question #2

The most sensitive method for outpatient diagnosis of Clostridium difficile infection (CDI) in a symptomatic outpatient is:

1. Stool culture
2. Stool enzyme immunoassay (EIA) test
3. Stool polymerase chain reaction (PCR) test
4. Antibody serology test

### Outcomes Question #3

A single Tdap dose is only recommended in pregnant women:

1. Who have never received a pertussis vaccine
2. During first pregnancy regardless of pertussis vaccine history
3. During each pregnancy, regardless of pertussis vaccine history
4. Never, since Tdap is contraindicated in pregnancy

### Questions

?