Infectious Disease Hodge Podge!

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Disclosures

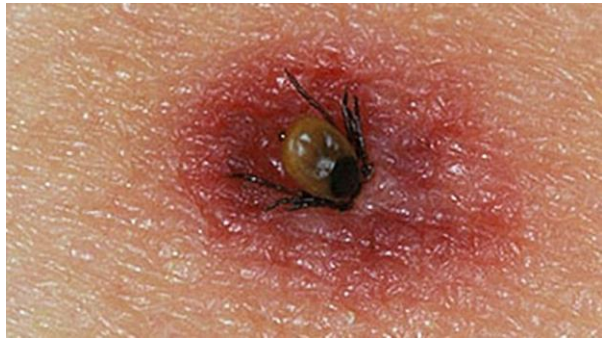
- None

Objectives

- Top 5 things you should know about these 4 things:
  - Lyme disease diagnosis and management
  - What's new this year with the flu?
  - TB testing and diagnosis of LTBI
  - Outbreaks after environmental disasters

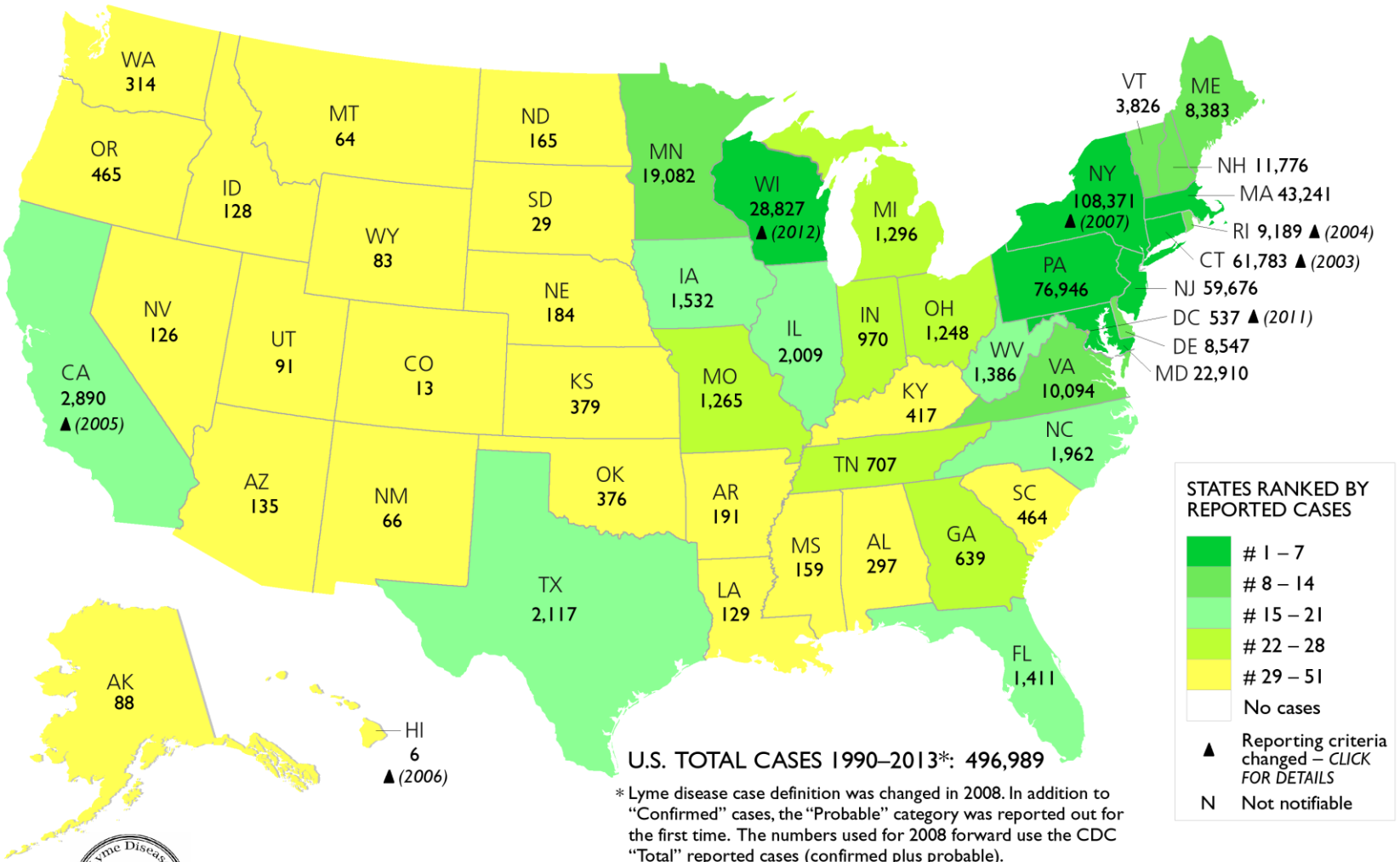
1.) How come it seems most of my patients never recall a tick bite?

- Organism – Borrelia burgorferi
- Vector – Deer tick (Ixodes scapularis, Ixodes dammini, Ixodes pacifcus
- Ticks are very tiny, often never seen
- Generally ticks need to be attached for many hours/significantly engorged to transmit the bacteria



LYME DISEASE ASSOCIATION (LDA)

U.S. LYME DISEASE REPORTED CASES 1990–2013*



U.S. TOTAL CASES 1990–2013*: 496,989

STATES RANKED BY REPORTED CASES

- # 1 – 7
- # 8 – 14
- # 15 – 21
- # 22 – 28
- # 29 – 51
- No cases
- ▲ Reporting criteria changed – *CLICK FOR DETAILS*
- N Not notifiable

* Lyme disease case definition was changed in 2008. In addition to "Confirmed" cases, the "Probable" category was reported out for the first time. The numbers used for 2008 forward use the CDC "Total" reported cases (confirmed plus probable).

Note: CDC states only 10% of Lyme disease cases meeting the surveillance definition are reported – 10,000 cases are reported, 100,000 cases occurred (does not include all the cases falling outside the stringent surveillance case definition). In 2013, CDC announced that about 300,000 cases of Lyme actually occur annually.

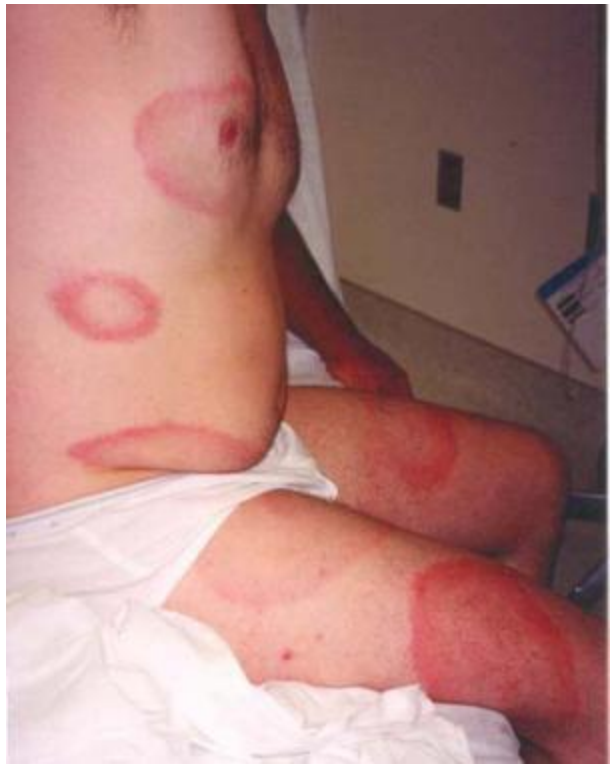
Source: Data compiled from CDC pub. data (MMWR)

www.LymeDiseaseAssociation.org

2.) Is there a new “staging” system for Lyme disease?

- Historically, illness is divided into 3 stages:
  - Stage I – flu like symptoms and typical skin rash (erythema migrans)
  - Stage 2 – weeks to months later – cranial nerve palsy, meningitis
  - Stage 3 – months to years later – arthritis
- Great deal of overlap and in reality we will see patients who have skin, CNS, and musculoskeletal complaints in early or late disease
- New classification divides disease into early and late manifestations based on local or disseminated infection

Stage 1 – Early, Localized Infection



- Infection is classically characterized by erythema migrans rash appearing ~1 week after tick bite (range 3-30 days)
- 10-20% of patients do not have typical lesions or lesions go unnoticed
- Most patients have a concurrent viral-like illness when rash is present
- Symptoms generally resolve in 3-4 weeks
- Completely asymptomatic disease can occur but is extremely uncommon

Stage 2 – Early, Disseminated Infection

- Up to 50-60% of patients with erythema migrans are bacteremic and within days to weeks will develop secondary (smaller) skin lesions
- Malaise, fatigue, fever, headache common
- 4-10% of patients have cardiac issues
  - Heart block, arrhythmia, myopericarditis
- 10-15% have neurologic manifestations
  - Aseptic meningitis, cranial nerve palsies (facial nerve, especially)
- Patients c/o “brain fog,” long-lasting fatigue

Stage 3 – Late, Persistent Infection

- Occurs months to years after initial infection
- Generally manifests with musculoskeletal and neurologic complaints
- If disease is recognized and treated early (IgM positive), less than 10% of patients will go on to have musculoskeletal manifestations
  - Classic involvement is monoarticular or oligoarticular arthritis of the knee or other large joints
  - Chronic arthritis may develop – likely an immunologic phenomenon and NOT persistent “infection”
- Rarely, nervous system involvement with encephalopathy, memory loss, mood disorders

3.) Why are there so many controversies in Lyme diagnosis?

- Evidence based protocols call for serologic testing to be positive for antibodies to B. burgdorferi by ELISA (not IFA – less sensitive/specific)
  - All positive antibodies or equivocal antibiotics should reflex to Western Blot confirmatory testing
  - IgM antibody appears in 2-4 weeks, peaks at 6-8 weeks, and then declines to low/normal levels in 4-6mo
    - BEWARE of Lyme IgM+ in a patient with >6mo of symptoms
  - IgG antibody occurs after 6-8 weeks of illness and peaks at 4-6mo and may remain elevated indefinitely
- Up to 50% of patients can be antibody negative in early disease
  - Repeat testing after several weeks

LYME DISEASE,EIA W/RFL WB		*See Endnote 3*	TBR
LYME DISEASE SCREEN	**0.91 H**	0-0.9 INDEX VALUE	
LYME DISEASE AB(IGG,M),IB			
LYME DISEASE AB (IGG),IB		*See Endnote 4*	TBR
LYME DISEASE (IGG),WB	NEGATIVE	NEGATIVE	
18 KD (IGG) BAND	NONREACTIVE		
23 KD (IGG) BAND	NONREACTIVE		
28 KD (IGG) BAND	NONREACTIVE		
30 KD (IGG) BAND	NONREACTIVE		
39 KD (IGG) BAND	NONREACTIVE		
41 KD (IGG) BAND	**REACTIVE**		
45 KD (IGG) BAND	NONREACTIVE		
58 KD (IGG) BAND	NONREACTIVE		
66 KD (IGG) BAND	NONREACTIVE		
93 KD (IGG) BAND	NONREACTIVE		
LYME DISEASE (IGM),IB		*See Endnote 5*	TBR
LYME DISEASE INTERP (IGM)	NEGATIVE	NEGATIVE	
23 KD (IGM) BAND	**REACTIVE**		
39 KD (IGM) BAND	NONREACTIVE		
41 KD (IGM) BAND	NONREACTIVE		

4.) What is IGeneX testing and why don't we use it?

- Be wary of CASH pay labs
- IGeneX in California - $660 for Lyme testing with "complete coinfection panel"
  - Uses IFA testing which is less sensitive/specific
  - Lowers threshold for positivity – numerous false + tests result
- Practitioners (especially holistic, alternative medicine practitioners) will recommend IGeneX testing and further employ non-FDA approved, non-evidence based treatments for VERY long periods of time
  - Antibiotics, vitamin infusions, etc. – all at out-of-pocket cost to the patient

Tests performed at 795 San Antonio Rd, Palo Alto, CA, except portion of the PCR which is performed at 797 San Antonio Rd, Palo Alto, CA

TEST NAME	RESULT	UNITS
LYME IgM WESTERN BLOT	.....	

REVISED 3/16/11

IGeneX interpretation is based on internal validation studies. By IGeneX criteria, IgM WB is considered positive if two or more of the double starred bands below are present. The IgM WB is considered negative if less than 2 starred bands are present. A positive result suggests exposure to B burgdorferi. By CDC/NYS criteria, IgM WB is reported positive if 2 of the following bands are present:23-25,39,41kDa. The IgM WB is negative if less than 2 bands are present.

LIMITATION: Positive result for 31 and/or 34kDa may be present after Lyme vaccination in uninfected persons. Infection with HSV,EBV,HCV and/or syphillis (RPR+) may give false (+) results.

****PRESENCE OF ONLY ONE DOUBLE STARRED BAND OR INDETERMINATE DOUBLE STARRED BANDS IN A NEGATIVE REPORT MAY INDICATE CLINICAL SIGNIFICANCE.****
THEREFORE, WE RECOMMEND TESTING WITH ANOTHER METHOD AND/OR RETEST IN 4-6 WEEKS.

BAND INTENSITY: Negative (-): No band detected. Indeterminate (IND): Band present with intensity < calibration standard. Positive (1+ to 4+): Band present at an intensity > or = to calibration standard.

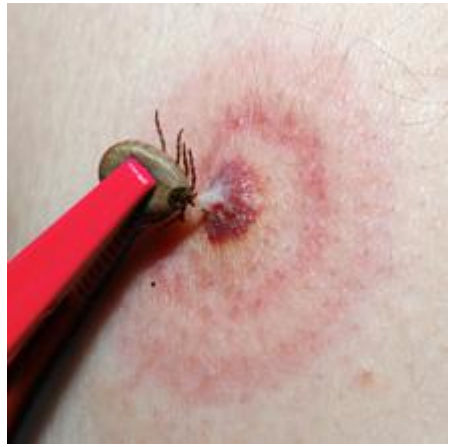
IGENEX IGM RESULT	POSITIVE
CDC/NYS RESULT	NEGATIVE
18 kDa.	-
**23-25 kDa.	-
28 kDa.	-
30 kDa.	-
**31 kDa.	+++
**34 kDa.	IND
**39 kDa.	-
**41 kDa.	+
45 kDa.	-
58 kDa.	-
66 kDa.	-
**83-93 kDa.	+

Diagnosis should not be based on laboratory tests alone. Results should be interpreted in conjunction with clinical symptoms and patient history.

False + Lyme Testing

- Rheumatoid arthritis
- Lupus
- Infectious mono/EBV viremia
- Cytomegalovirus/CMV viremia
- Endocarditis
- Syphilis
- Relapsing fever
- Leptospirosis
- Nonspecific enteroviral/other viral illnesses
- Gingeval disease (cross reactivity with oral treponemes)

5.) What is the treatment for Lyme disease? What about “chronic Lyme?”



- Scenario – a patient calls your office the evening after hiking in the woods and finds an engorged tick, still attached
- He uses tweezers or a tick key to remove the entire tick
- What do you prescribe?
- Doxycycline 200mg p.o. x 1 dose

Treatment cont'd. (IDSA Guidelines)

- Erythema migrans or Lyme IgM + WITH appropriate symptom duration
  - Doxycyline 100mg p.o. BID or amoxicillin 500mg p.o. TID or cefuroxime 500mg p.o. BID all for 2-3 weeks
- Facial palsy without meningitis – same as above
- Other CNS involvement – ceftriaxone 2gm IV q24h for 2-4 weeks
- Arthritis:
  - Doxycycline or amoxicillin or cefuroxime x 4 weeks
  - Ceftriaxone 2gm IV q24h x 2-4 weeks

Treatment cont’d.

- Treatment of “Chronic Lyme Disease” or “post-Lyme disease syndrome”
  - Treated symptomatically with supportive care only
  - Prolonged p.o. or IV antibiotics are not recommended and these treatment strategies are not evidence based
    - Reviewed and re-reviewed by the IDSA
  - Beware of predatory practitioners who employ long course therapies or infusions at high out-of-pocket cost to our patients

Just one example of what's out there…

- "Dr. Klinghardt's basic treatment strategies are summarized below. His full treatment protocol is too complex to include here, but if you want details, I recommend reading our 2009 article that focuses on those specific Lyme treatment strategies. You can also visit Dr. Klinghardt's website, where he posts his treatment protocols and recipes. There are five basic steps:
  - **Evaluation of all external factors.** External factors include electrosmog, EMF, microwave radiation from wireless technologies, and molds. (For more information on mold, go to Ritchie Shoemaker's website).
  - **Remediation and mitigation of external factors.** Once external factors have been assessed, they're remediated and mitigated. (Please refer to our previous article on mold remediation.) To mitigate microwave radiation, Dr. Klinghardt recommends shielding the outside of your home with a graphite paint called Y Shield. Inside**, he uses a special silver-coated cloth for your curtains. Patients are instructed to remove all cordless** telephones and turn off all the fuses at night, until they have recovered from Lyme disease.
  - **Addressing emotional issues.** Emotional components of the disease are addressed using Energy Psychology tools, including psychokinesiology (PK), which is similar to the Emotional Freedom Technique (EFT), but more refined and advanced.
  - **Addressing parasitic, bacterial and viral infections.** Dr. Klinghardt addresses the parasites first, followed by the bacteria and the viruses. The "Klinghardt antimicrobial cocktail," which includes wormwood (artemisinin), phospholipids, vitamin C, and various herbs, is an integral part of this treatment. He addresses viral infections with Viressence (by BioPure), which is a tincture of Native American herbs.
  - **Addressing other lifestyle factors.** Nutritional considerations and supplements are addressed."

1.) What flu vaccines are available for the 2016-2017 flu season?

- 2016-2017 Flu season offers trivalent and quadrivalent vaccines
  - CDC expresses no preference for any particular vaccine product
  - LAIV (Flu-Mist) for 2-17yo not offered this year
    - Waning VE noted 2013-2016, ~3% last year for H1N1pdm09

- Strains covered for 2016:
- A/California/7/2009 (H1N1)-like virus
- A/Hong Kong/4801/2014 (H3N2)-like virus
- B/Brisbane/60/2008-like virus
- ***B/Phuket/3073/2013-like virus***

2.) When should our patients get the flu vaccine?

Yes, It Is Possible To Get Your Flu Shot Too Soon

September 15, 2016 · 5:00 AM ET

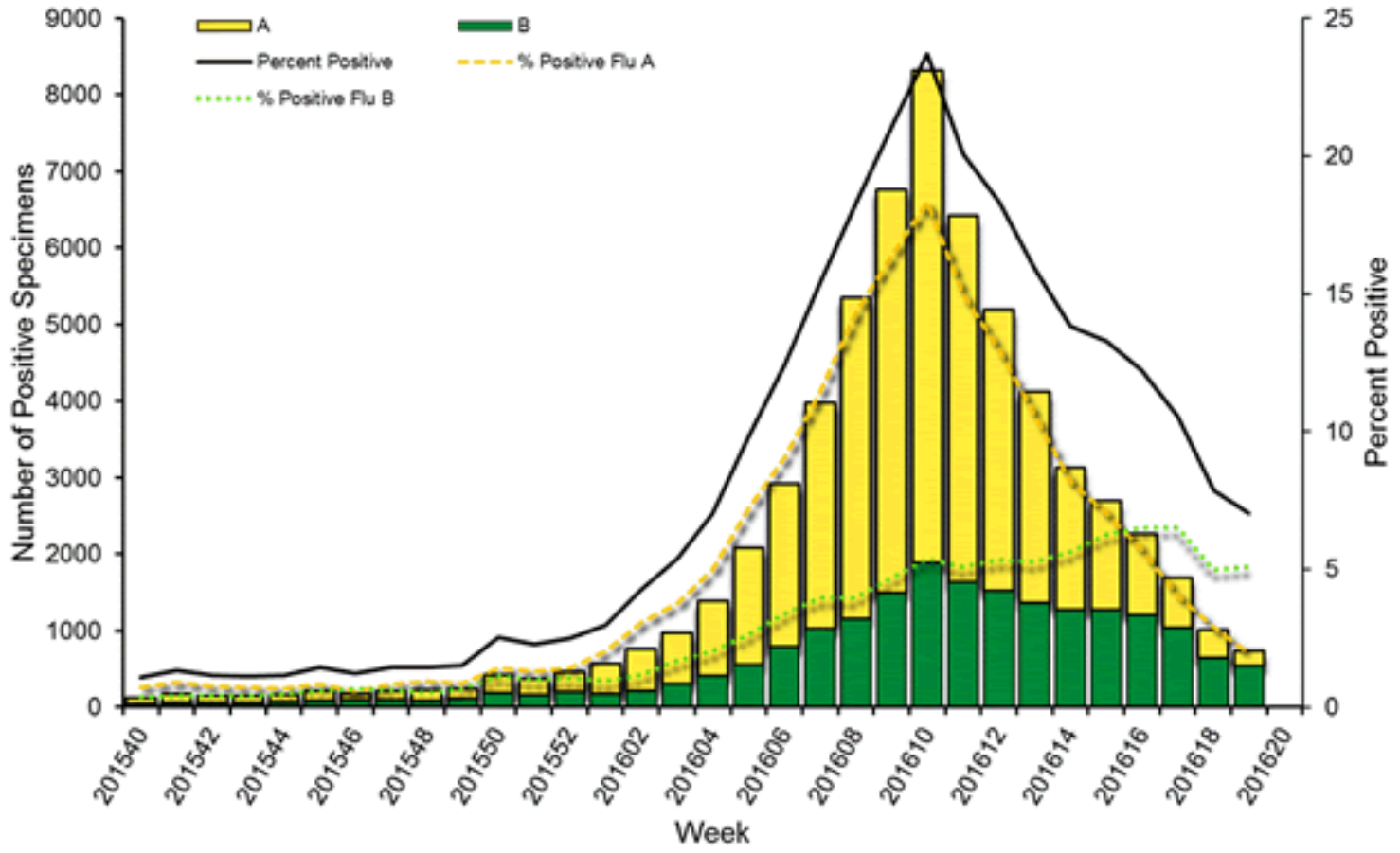
JULIE APPLEBY

FROM KHN KAISER HEALTH NEWS

- Flu vaccine should be given 2-6 weeks prior to anticipated peak of flu season
- Many suggest “Between Halloween and Thanksgiving” is ideal
- Studies suggest that very early vaccination, especially in the elderly, leads to waning immunity
  - Biggest falloff appears to be for Influenza A H3N2
- Other studies suggest some vaccine components can last years

Song JY, Cheong HJ, Hwang IS, et al. Long-term immunogenicity of influenza vaccine among the elderly: Risk factors for poor immune response and persistence. Vaccine 2010;28:3929–35

Influenza Positive Tests Reported to CDC by U.S. Clinical Laboratories, National Summary, 2015-2016 Season



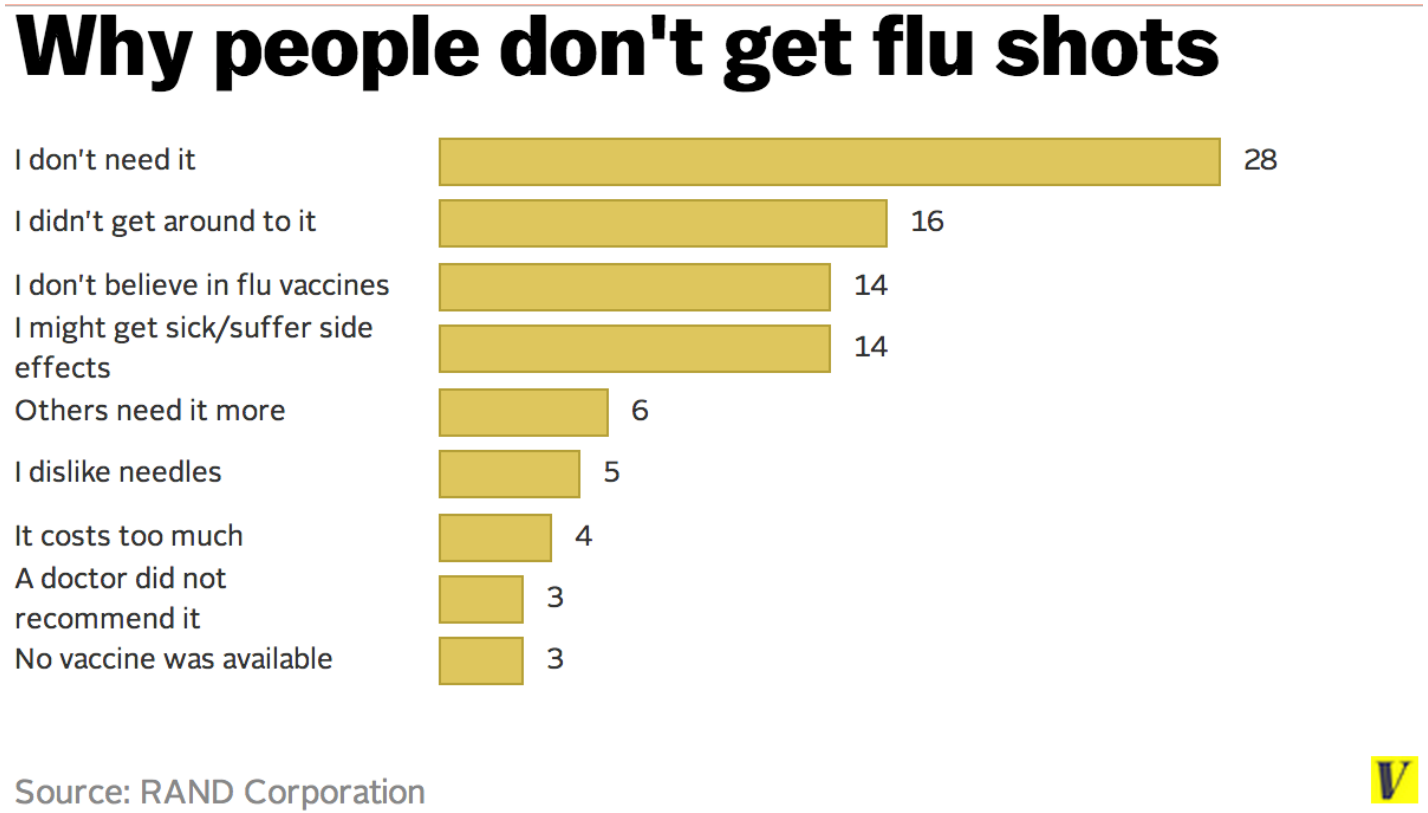
3.) Should we keep vaccinating even if the vaccine is a poor match?

Table. Adjusted vaccine effectiveness estimates for influenza seasons from 2005-2016

Influenza Season†	Reference	Study Site(s)	No. of Patients§	Adjusted Overall VE (%)	95% CI
2004-05	Belongia 2009	WI	762	10	-36, 40
2005-06	Belongia 2009	WI	346	21	-52, 59
2006-07	Belongia 2009	WI	871	52	22 ,70
2007-08	Belongia 2011	WI	1914	37	22, 49
2009-10	Griffin 2011	WI, MI, NY, TN	6757	56	23, 75
2010-11	Treanor 2011	WI, MI, NY, TN	4757	60	53, 66
2011-12	Ohmit 2014	WI, MI, PA, TX, WA	4771	47	36, 56
2012-13	McLean 2014	WI, MI, PA, TX, WA	6452	49	43, 55
2013-14	Unpublished	WI, MI, PA, TX, WA	5990	51	43, 58
2014-15	ACIP presentation, Flannery	WI, MI, PA, TX, WA	9329	23	14, 31
2015-16*	ACIP presentation, Flannery	WI, MI, PA, TX, WA	7563	47*	39, 53*

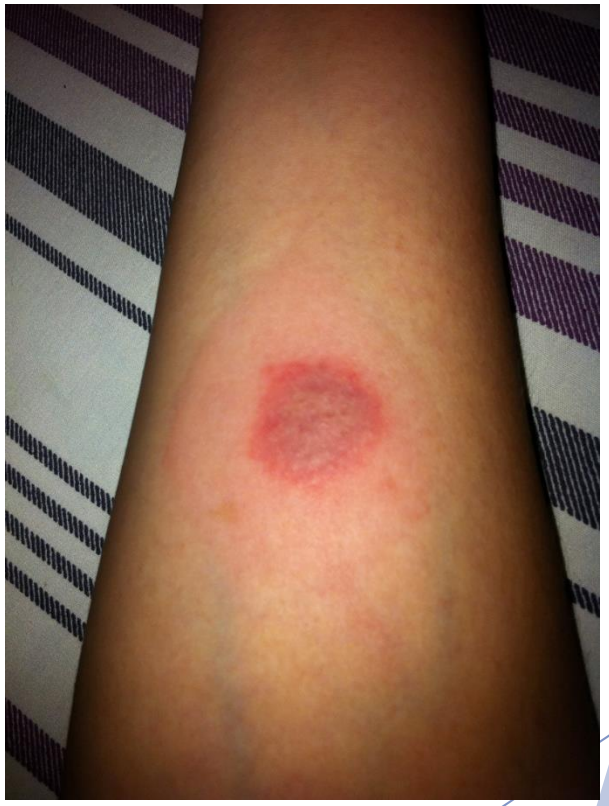
*Estimate from Nov 2, 2015–April 15, 2016.

4.) My patients think the flu vaccine makes them sick.



1.) Do we still use PPD testing? What are the cutoffs again?

- Tuberculin skin test (Mantoux TST)
  - Positive testing is induration at 48-72 hours after test placement
    - >15mm in the general population
    - >10mm in healthcare workers and those at high risk for exposure
    - >5mm in HIV+ patients and the immunocompromised



2.) What blood tests are available?

- TB blood testing – Interferon Gamma Release Assay
  - QuantiFERON TB Gold In-Tube test (3rd gen 2007)
  - T-spot TB test (2008)
  - Updated guidelines for use June 25, 2010
- POSITIVE – Patient is likely to have been infected with TB bacteria. Additional testing is needed to determine if patient has active TB or LTBI
- NEGATIVE – Infection with TB bacteria is unlikely
- INDETERMINATE – Patient status could not be ascertained, testing should be repeated
  - Possible mishandling, possible patient immunosuppression, concurrent drug effect, poor mitogen response

IGRAs cont'd.

- June 25, 2010 – MMWR published guidelines on the use of IGRAs for TB testing
- How it works:
  - The QFT-GIT assay is an ELISA-based, whole-blood test that uses peptides from three TB antigens (ESAT-6, CFP-10, and TB7.7) in an in-tube format. The result is reported as quantification of IFN-gamma in international units (IU) per mL. An individual is considered positive for *M. tuberculosis* infection if the IFN-gamma response to TB antigens is above the test cut-off after subtracting the background IFN-gamma response in the negative control.
- Sensitivity and specificity are similar to a properly placed PPD test, with some advantages and disadvantages.

QuantiFERON package insert

3.) What are the advantages and disadvantages of TB blood tests?

- Advantages of the test:
  - Requires a single patient visit to draw a blood sample.
  - Results can be available within 24 hours.
  - Does not boost responses measured by subsequent tests, which can happen with tuberculin skin tests (TST).
  - Is not subject to reader bias that can occur with TST.
  - **Is not affected by prior BCG vaccination.**

- Disadvantages and limitations of the test:
  - Blood samples must be processed within ~24 hours after collection while white blood cells are still viable.
  - There is limited data on the use of QFT-GIT in children younger than 17 years of age, among persons recently exposed to M. tuberculosis, and in immunocompromised patients.
  - Errors in collecting or transporting blood specimens or in running and interpreting the assay can decrease the accuracy and potentially lead to indeterminate results.
  - False positive results can occur with Mycobacterium szulgai, Mycobacterium kansasii, and Mycobacterium marinum.

4.) What if one test is positive and the other test is negative?

- What if Mantoux TST is negative and quantiferon is positive?
- What if Mantoux TST is positive and quantiferon is negative?
- What if quantiferon is positive and it is repeated and it is negative?

- Age >50
- HIV status?
- Foreign born? BCG vaccine?

5.) What is the recommended treatment for LTBI? When can my patient start their anti-TNF agents?

- Generally treatment is with 9mo of isoniazid 300mg p.o. daily with 50mg of vitamin B6 daily
  - Rifampin 600mg p.o. daily x 4mo is also a consideration in some
- Goal is to get “as much LTBI Rx as possible” in these patients before starting anti-TNF agents
  - Risk, benefit assessment
  - Case-by-case if patient already on anti-TNFs as to if they should be held and for how long

Drug(s)	Duration	Dose	Frequency	Total Doses
Isoniazid (INH)	9 months	Adult: 5 mg/kg Children: 10-20 mg/kg Maximum dose: 300 mg	Daily	270
		Adult:15 mg/kg Children: 20-40 mg/kg Maximum dose: 900 mg	Twice weekly	76
	6 months	Adult: 5 mg/kg Children: Not recommended Maximum dose: 300 mg	Daily	180
		Adult: 15 mg/kg Children: Not recommended Maximum dose: 900 mg	Twice weekly	52
Isoniazid (INH) and Rifapentine (RPT)	3 months	Adults and Children 12 and over: **INH:** 15 mg/kg rounded up to the nearest 50 or 100 mg; 900 mg maximum **RPT:** 10.0–14.0 kg 300 mg 14.1–25.0 kg 450 mg 25.1–32.0 kg 600 mg 32.1–49.9 kg 750 mg *≥50.0 kg 900 mg maximum*	Once weekly	12
Rifampin (RIF)	4 months	Adult: 10 mg/kg Maximum dose: 600 mg	Daily	120