AAP Red Book 2018 Update

Orange County Immunization Coalition

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AAP Red Book Resources

- Hard copy provided to all AAP members for free
- Red Book Online subscription also included in membership
  - https://redbook.solutions.aap.org/
  - Login with AAP login & password
- AAP Red Book app for iOs and Android, also free for members

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Summary of changes

- All 240 chapters have been revised since 2015
- New chapters (3)
  - Zika
  - Chikungunya
  - Coagulase-negative staphylococcal infection *(not covered today)*
- "More important changes"
  - Liberalization of use of doxycycline for short-treatment durations
  - Extension of the age range for initiation of HPV vaccination
  - Prohibition on live-virus rotavirus vaccine for infants born to moms who received biologic response modifiers during pregnancy

Summary of changes – *additional revisions*

- Addition of reverse-sequence testing to congenital syphilis algorithm
- Harmonization of return-to-school recommendations between AAP *Managing Infectious Diseases in Child Care and Schools* (the Purple Book) and the specific chapters in the Red Book
- Shortening of return-to-school recommendation for GAS pharyngitis
- Reorganization of chapter on internationally adopted, refugee and immigrant children
- Addition of third dose of MMR during mumps outbreaks
- Updating of recommendations for IGRA and LTBI treatment

New Chapters in Section 3 – Summaries of Infectious Diseases

Zika and Chikungunya now separate chapters

- Symptoms

Features	Zika	Dengue	Chikungunya
Fever	++	+++	+++
Rash	+++	+	++
Conjunctivitis	++	-	-
Arthralgia	++	+	+++
Myalgia	+	++	+
Headache	+	++	++
Hemorrhage	-	++	-
Shock	-	+	-
Asymptomatic	up to 80%	up to 50%	<30%

Rabe, Ingrid MBCHB, MMed "Zika Virus- What Clinicians Need to Know?" (presentation, Clinician Outreach and Communication Activity (COCA) Call, Atlanta, GA, January 26 2016)

http://www.cdc.gov/zika/hc-providers/training/training.html

- Travel history
  - Similar geographic distribution for Zika, chikungunya, dengue

https://wwwnc.cdc.gov/travel/page/world-map-areas-with-zika

- Incubation period
  - Zika 3-14 days,CHKV 1-12 days

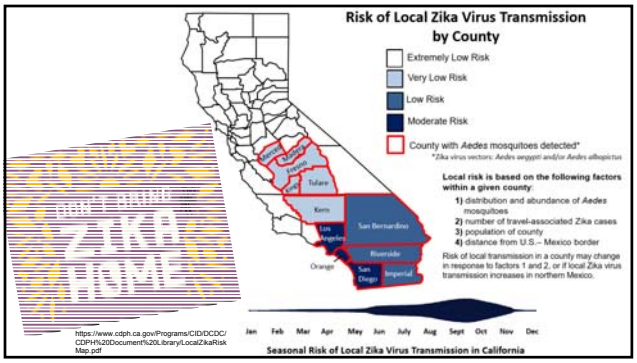
Zika and Chikungunya

- Testing – type of test depends on timing (and if pregnant [for Zika])
  - Polymerase chain reaction (PCR) testing of serum (for Zika also urine)
  - Serology – virus-specific IgM
    - Zika and dengue are flaviviruses; serology cross-reacts with each other (and WNV, St. Louis encephalitis, yellow fever, JEV)
      - Also false-positives can occur
      - Needs virus-specific confirmatory testing at CDPH (PRNT)
- Management:
  - Supportive care; no specific antiviral treatment. Avoid ASA and NSAIDS until dengue ruled out to reduce risk of hemorrhage
  - Zika: consult www.cdc.gov/zika for latest testing and f/u guidance
    - Neurodevelopmental issues may not be evident at birth – specialized follow-up is needed of all suspect congenital infections

Zika and Chikungunya Prevention

- Avoiding mosquito bites

- Guidance on insect repellents for children
  - Chapter on Prevention of Mosquitoborne and Tickborne Infections
- Abstain/use condoms after travel to Zika risk area
  - At least 3 months for men; 2 months for women
- Pregnant women should avoid travel to Zika risk areas; abstain from sex or use condoms for duration of pregnancy if partner traveled



Liberalization of use of doxycycline for short-treatment durations

Tetracycline class of antibiotics

- Tetracycline, minocycline, doxycycline
- Tetracyclines first came to market in 1940's
- Bacteriostatic, binds to 30S subunit of ribosome, inhibits bacterial protein synthesis
- Use historically limited in pediatrics due to reports of permanent dental discoloration in children < 8 years of age
  - Tetracyclines and colored degradation products incorporated in enamel (bind to calcium ions)
  - Effects during period of odontogenesis until completion of formation of enamel in permanent teeth (ends by 8 years of age)
  - Degree of staining depends on dosage, duration of therapy, stage of tooth mineralization/calcification, which drug

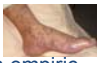
Tetracycline and teeth staining

- Prevalence of teeth staining among children who received tetracycline during odontogenesis 23-92%
- 1970 warning label against use of tetracyclines in children less than 8 years of age
- 1967 doxycycline came to market
  - inherited warning label from tetracycline against use in children

Doxycycline and teeth staining – lack of evidence

- Doxycycline binds less readily to calcium than minocycline or tetracycline
- No published studies linking doxy to dental staining at dose/duration for rickettsial diseases
  - 1969 case series showed slight discoloration on one child's primary tooth / 25 children who received doxycycline as preterm infant; unknown dose/duration. Negligible staining
- Studies since looked at staining of permanent teeth with doxycycline use during odontogenesis
  - No reports of dental staining
  - Small sample sizes

No teeth staining from doxycycline use for RMSF



- Doxycycline is drug of choice for RMSF
- CDC and IHS: retrospective cohort of children with empiric treatment of RMSF with doxycycline
  - 250 children on American Indian reservation with high rates of RMSF
  - Blinded dentists inspected permanent teeth of 58 children who had doxy for suspected RMSF before 8th birthday and 213 children who did not
    - 58 children had average of 1.8 courses of doxycycline <8 y.o.
    - Looked for tooth staining, color, weakness in enamel
    - 0/58 had tetracycline-like staining
    - No difference seen between children w/doxy or without

Todd et al. *Journal of Pediatrics* 2015;166(5):1246-1251; image from www.cdc.gov/rmsf

Doxycycline use for RMSF

- Author conclusions (2015): "Healthcare provider confidence in use of doxycycline for suspected RMSF in children may be improved by modifying the drug's label"
- FDA label:

5 WARNINGS AND PRECAUTIONS

5.1 Tooth Development

The use of drugs of the tetracycline-class during tooth development (last half of pregnancy, infancy and childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown). This adverse reaction is more common during long-term use of the drugs but it has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. Doxycycline should not be used in this age group, except for anthrax, including inhalational anthrax (post-exposure), unless other drugs are not likely to be effective or are contraindicated.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/90431Orig1s010lbl.pdf

AAP revised recommendation: use of doxycycline

- Doxycyline can be administered for short durations (i.e., 21 days or less) without regard to the patient's age
- When used, patients should avoid excess sun exposure due to the photosensitivity associated with doxycycline
- Dosage: generally 4.4 mg/kg/day divided into 2 doses (up to 100 mg BID)
- Indications:



  - Typhus, RMSF, other rickettsial diseases, ehrlichiosis, anaplasmosis
  - Alternative for bite wounds in PCN-allergic patient (covers *P. multocida)*
  - Presumed atypical pneumonia, as alternative to macrolide
  - Lyme disease, relapsing fever (*Borrelia);* cholera

Section 2: Recommendations for Care of Children in Special Circumstances

Children in Out-of-Home Child Care School Health

Resources for Child Care / School Health

- AAP: Managing Infectious Diseases in Child Care and Schools: A Quick Reference Guide, 4th ed.
  - Easy to understand explanations
  - Quick reference sheets, exclusion and readmission criteria, sample letters and more
- "The Purple Book"

Resources for Child Care / School Health

- Caring for Our Children, National Health and Safety Performance Standards for Early Care and Education Programs, 3rd ed.
  - Free searchable database and downloadable pdf, http://nrckids.org/CFOC
- American Academy of Pediatrics, American Public Health Association, National Resource Center for Health and Safety in Child Care and Early Education

Resources for Child Care / School Health

www.healthychildcare.org/HealthyFutures.html

- Free on-line course
  - Based on *Managing Infectious Diseases*
  - Also available as an in-person training module which a "trainer" can facilitate for a group of providers
    - Trainer's guide, presentations and handouts
    - Includes video clips, activities, forms, pre- and post- assessments

Previous recommendations for group A strep pharyngitis

- CDC website "Treating an infected person with an antibiotic for 24 hours or longer generally eliminates their ability to transmit the bacteria. Thus, people with group A strep pharyngitis should stay home from work, school, or daycare until afebrile and until at least 24 hours after starting appropriate antibiotic therapy."
- 2015 Red Book: "Children with GAS pharyngitis…should not return to school or child care until at least 24 hours after beginning appropriate antimicrobial therapy"
- 1985 – based on 3 studies; low rate of GAS persistence even after 18 hours in these studies

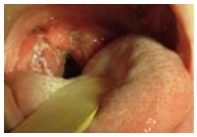
Reappraisal of return to school recommendation for GAS

- 111 children in office practice in Virginia 2013-2015 with sore throat, positive RADT (also positive for GAS by culture), randomly assigned to 2 treatment groups
  - A: 50 mg/kg/dose of amoxicillin suspension at initial visit; repeat dose one hour prior to office visit the next day (12-23h later), OR
  - B: 50 mg/kg/dose of amoxicillin suspension at initial visit only
- Throat cultures at office visit the next day (12-23h later)
  - A: 10% positive RADT vs B: 8% positive RADT (p=0.75)
  - 91% of all children had undetectable GAS in culture (A or B); failures random, not time related
- Authors' conclusion: "All children treated with amoxicillin for "strep throat" by 5 pm of day 1 may, if afebrile and improved, attend school on day 2."

Schwartz, Kim, Martin, Pichichero. *PIDJ* 2015;34:1302-1304

Return to child care/ school with group A strep pharyngitis

- 2017 Purple Book: "New evidence suggests children can return after only 12 hours of antibiotic treatment (rather than 24 hours)"
- 2018 Red Book:



School and Child Care

Children with GAS pharyngitis or skin infections should not return to school or child care until well appearing and at least 12 hours after beginning appropriate antimicrobial therapy. Close contact with other children during this time should be avoided.

Return to school / child care after diarrhea

- 2015 and 2018 Red Book; similar wording in 2017 Purple Book
  - Children in Out-of-Home Child Care

Symptom(s)	Management
Diarrhea if stool not contained in diaper or if fecal accidents occur in a child who is normally continent, if stool frequency exceeds 2 stools above normal for that child, or stools contain blood or mucus	Medical evaluation for stools with blood or mucus; exclusion until stools are contained in the diaper or when toilet-trained children no longer have accidents using the toilet and when stool frequency becomes no more than 2 stools above that child's normal frequency for the time the child is in the program, even if the stools remain loose

Diarrhea in Section 3: Summaries of Infectious Diseases

- Language does not apply to diseases require clearance (through Public Health) for child care, sensitive situations

  Examples: Shiga-toxin producing *E. coli* (STEC)
  Salmonella non-typhoidal (some situations)
  Salmonella typhi (typhoid)
  Shigella

- For diarrheal diseases not needing clearance, follow same overarching guidance for diarrhea for out-of-home care:
  - 2015 examples: "until diarrhea has subsided" or "until they have become asymptomatic"
  - Updated 2018: "Infants and children should be excluded from child care centers until stools are contained in the diaper or when toilet-trained children no longer have accidents using the toilet and when stool frequency becomes no more than 2 stools above that child's normal frequency for the time the child is in the program, even if the stools remain loose. "

Section 2: Recommendations for Care of Children in Special Circumstances

Reorganization of chapter on internationally adopted, refugee and immigrant children

Internationally adopted, refugee and immigrant children

- Evaluate as soon as possible
  - Immunizations, screening for infectious diseases
  - AAP Immigrant Health Toolkit: www.aap.org/en-us/Documents/cocp_toolkit_full.pdf
- Internationally adopted children
  - Contact before arrival – acquire health records, immunizations
    - Some screening required by US Dept of State; not comprehensive
    - www.cdc.gov/immigrantrefugeehealth/
  - Immunizations for family before traveling to pick up child and for family members/caregivers who will interact with child after
- Refugees and asylees (~100/year → 39)
  - Some receive presumptive therapy overseas for intestinal pathogens, malaria
  - CDC recommended medical screening post arrival: www.cdc.gov/immigrantrefugeehealth/guidelines/domestic/domestic-guidelines.html
- Immigrants – recommendations depending on situation, includes above

Internationally adopted, refugee and immigrant children

- See also chapter on Children Who Received Immunizations Outside the United States or Whose Immunization Status is Unknown or Uncertain
- Consideration for Testing for Infectious Agents
  - Hepatitis A
  - Hepatitis B
  - Hepatitis C
  - Intestinal pathogens
  - Tissue parasites/eosinophilia
  - Syphilis
  - Tuberculosis
  - HIV
  - Chagas Disease (American Trypanosomiasis)
  - Other Infectious Diseases (e.g., skin infections, ectoparasites)

Suggested Screening Tests for Infectious Diseases in International Adoptees, Refugees, and Immigrants[a]

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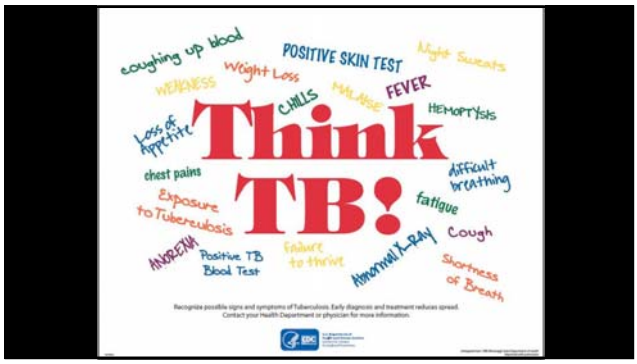
Felice Adler-Shohet, MD



Tuberculosis Definitions

- **LTBI**- Latent tuberculosis infection-*M. tuberculosis* infection with a positive TST or IGRA, no evidence of disease, CXR normal or with evidence of healed infection (eg, calcification in the lung, the hilar lymph nodes, or both).
- **Tuberculosis disease-** illness with symptoms, signs, or radiographic manifestations caused by *M tuberculosis* complex apparent.

2018 Red Book TB Chapter Changes

- New testing algorithms for IGRAs
- New LTBI treatment recommendations
- New rifampin dosing

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Diagnostic Tests

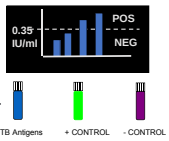
- TB skin test (TST)
- Interferon Gamma Release Assay (IGRA)

Diagnostic Tests

- Both methods rely on specific cellular sensitization after infection
- Conditions that decrease lymphocyte numbers or function can reduce the sensitivity of these tests

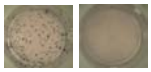
Diagnosis- IGRA

- **QuantiFERON® (QFT):**
  Whole blood incubated with MTB specific antigens -> free IFN-γ release is measured (ELISA)



QFT-TB Gold In-Tube

- **T-Spot®.*TB*:**
  T-cells incubated with MTB specific antigens; IFN-γ releasing cells are counted (ELISPOT-based technology)



Which Test is Best?

- Recent prospective study in people at high risk for LTBI from the TB Epidemiology Studies Consortium
- Each enrollee tested with TST, QFT and T-SPOT
- There were 8,018 foreign-born people tested ≥ 5 yo and 463 < 5 yo
  - 66% of them BCG vaccinated
- LTBI prevalence was 38% in ≥ 5 yo and 4.2% in < 5yo

Stout, JE et al. Thorax. 2018 Jul 7

Which Test is Best?

- In a foreign-born population ≥ 5 yo
  - TST sensitivity 75%, specificity 70%
  - TST positive predictive value 61%
  - Of 1000 people, 39% with TST+ don't have LTBI and 25% of LTBI missed
  - IGRA sensitivity 71%, specificity 99%
  - IGRA positive predictive value 98%
  - Of 1000 people 2% with IGRA+ don't have LTBI and 29% of LTBI missed

Stout, JE et al. Thorax. 2018 Jul 7

Which Test is Best?

- In a foreign-born population < 5 yo
  - TST sensitivity 75%, specificity 74%
  - TST positive predictive value 10%
  - Of 1000 people 90% with TST+ don't have LTBI and 25% of LTBI missed
  - QFT sensitivity 70%, specificity 99%
  - IGRA positive predictive value 74%
  - Of 1000 people 26% with QFT+ don't have LTBI and 30% of LTBI missed
  - T-SPOT results similar

Stout, JE et al. Thorax. 2018 Jul 7

Which Test is Best?

- For foreign- born persons ≥ 5 yo TST little better than coin flip in predicting LTBI but IGRA had high positive predictive values
- For foreign-born children < 5 yo prevalence of LTBI was low so TST PPV of 10% means almost all positive TST were false positives
- Study results suggest serial testing (TST followed by IGRA) or IGRA better for foreign born/BCG vaccinated
- If TST+ and IGRA- in asymptomatic unexposed child LTBI is very unlikely especially if child had BCG

Which Test is Best?

- Retrospective review of **laboratory-confirmed TB disease** in children ≤ 18 yo in California
- Of 95 children who had both TST and IGRA, no significant difference in sensitivity
- Use of both tests increased sensitivity over TST alone
- In children 2-4 yo as well as children < 2 yo sensitivity of TST and IGRA were the same
- In 5-18 yo TST had inferior sensitivity compared with IGRA

Kay AW et al. Pediatrics. 2018;141(6):e20173918

Comparison of TST and IGRA

Characteristic	TST	IGRA
Antigens used	Many; PPD	3 (QFT) or 2 (T-SPOT)
Sample	ID injection	Blood draw
Patient visits required	2	1
Distinguish between LTBI and TB disease	No	No
Cross-reactivity with BCG	Yes	No
Cross-reactivity with NTM	Yes	Only rare species
Differing positive values by risk	Yes (5-10-15)	No
Causes boosting	Yes	No
Subject to boosting by previous TST	Yes	Possible
Durability over time (stays positive with or without treatment)	Yes	Unknown
Difficulties with test reproducibility	Yes	Yes
Relative cost	Lower	Higher
Location of need for trained staff	"Bedside"	Laboratory
Estimated specificity in BCG-unvaccinated children	95% to 100%	90% to 95%
Estimated specificity in BCG-vaccinated children	49% to 65%	89% to 100%
Estimated sensitivity (confirmed TB disease)	75% to 85%	80% to 85%
Estimated sensitivity (clinical TB disease)	50% to 70%	60% to 80%

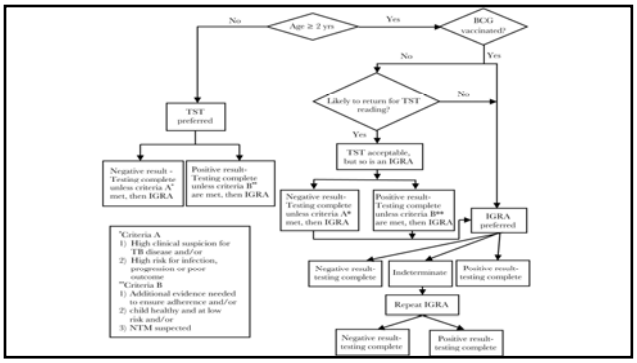
Starke JR. Pediatrics Dec. 2014

Diagnosis-2018 AAP Red Book

- TST preferred in children < 2 yo
- Either TST or IGRA for children ≥ 2 yo
- IGRA preferred in ≥ 2 yo who received BCG vaccine
- IF BCG vaccinated child ≥ 2 yo has a positive TST, IGRA can be performed to see if TST+ due to BCG or LTBI
- Indeterminate tests cannot be used to make decisions
- Use with caution in immunocompromised patients
- Neither IGRA or TST is perfect nor do they distinguish between LTBI and TB disease, use clinical judgement!

Diagnosis-2018 AAP Red Book

- In BCG vaccinated child
  - Strategy 1- TST: If negative, no more testing; if positive do IGRA
  - Strategy 2- IGRA only
  - If TB exposure consider child infected if either test +
- Child soon to be immune compromised
  - If no TB risk factor do either TST or IGRA
  - If TB risk factor do both TST and IGRA and evaluate and treat if either test +



2018 Red Book TB Chapter Changes

- New testing algorithms for IGRAs
- New LTBI treatment recommendations
- New rifampin dosing

Treatment of LTBI

- Red Book 2015 recommended 9 months of INH
- Recent studies have challenged that as a first line regimen

Treatment for Preventing Tuberculosis in Children and Adolescents

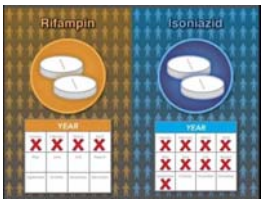
- Randomized trial of 12 weekly doses of isoniazid and rifapentine (3HP) vs 9 months daily INH (9H) in children 2-17 yo with LTBI
- 905 children evaluable for efficacy
- Completion rates: 3HP-88%, 9H-81%
- Development of TB- 3HP- 0/471, 9H- 3/434
- Grade 3 AE- 3HP- 3/539, 9H- 1/493 (NS)

3HP was at least as effective, safe, and had a higher completion rate than 9 mo INH

Villarino et al. JAMA Pediatr 2015; 247-55

Safety and Side Effects of Rifampin versus Isoniazid in Children

- Open-label, randomized trial comparing 4 mo RIF (4R) to 9 mo INH (9H) for children with LTBI



Diallo and Menzies et al. N Engl J Med 2018; 379:454-463

Table 2. Completion of Treatment.

Variable	Rifampin (N=422)	Isoniazid (N=407)	All Participants (N=829)	Adjusted Difference (95% CI)*
	number (percent)			*percentage points*
Treatment completed: ≥80% of doses	345 (81.8)	334 (82.1)	679 (81.9)	13.6 (7.9 to 19.3)
Treatment completed within allowed time: per protocol	360 (85.3)	311 (76.4)	671 (80.9)	13.4 (7.5 to 19.3)
Received 80–89% of doses	7 (1.7)	8 (2.0)	15 (1.8)	
Received 90–100% of doses	353 (83.6)	303 (74.4)	656 (79.1)	
Treatment completed but not within time allowed per protocol	5 (1.2)	3 (0.7)	8 (1.0)	
Treatment not completed	57 (13.5)	93 (22.9)	150 (18.1)	
Death	1 (0.2)	0	1 (0.1)	
Pregnancy	0	1 (0.2)	1 (0.1)	
Treatment never started per participant decision	10 (2.4)	14 (3.4)	24 (2.9)	
Treatment started but stopped early per participant decision	46 (10.9)	78 (19.2)	124 (15.0)	−11.9 (−17.3 to −6.6)
Received 50–79% of doses	22 (5.2)	24 (5.9)	46 (5.5)	
Received 1–49% of doses	24 (5.7)	54 (13.3)	78 (9.4)	

Additional Findings

- No significant differences between groups in rates of adverse events (AE)
- Fewer than 5% of children had an AE deemed possibly related to study drug and all were minor
- TB disease diagnosed in 2 children in the INH group during 542 person-years of follow up and no child in the RIF group during 562 person-years

Better Completion of Pediatric Latent Tuberculosis Treatment Using 4 Months of Rifampin in a US-based Tuberculosis Clinic

- 4R vs 9H from 2006 to 2015 in kids
- Retrospective, nonrandomized observational study
- Drug toxicity 4R-1.5%, 9H-0.7% (NS)
- No known treatment failures

Table 2. LTBI Treatment Completion Rates Stratified by Demographic and Clinical Characteristics

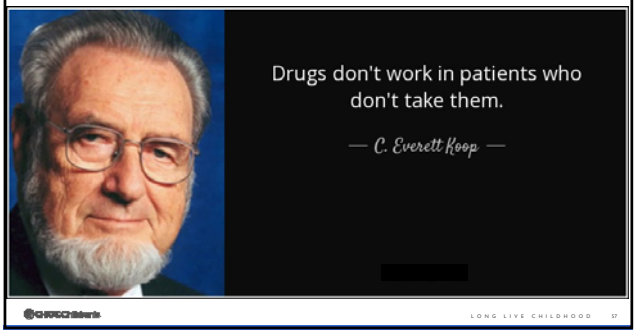
	Treatment Regimen[a] Completion (proportion, %)				p-value[b]
	4R (n=395)	%	9H (n=779)	%	
All patients	330/395	83.5	536/779	68.8	<0.001
Age Range (years)					
0-1	29/38	76.3	19/37	51.4	0.024
2-4	17/26	65.4	75/102	75.5	0.41
5-9	58/65	89.2	116/153	75.8	0.024
10-14	99/113	87.6	222/305	72.8	0.001
15-17	127/153	83	104/182	57.1	<0.001

Gaensbauer et al. Pediatr Infect Dis J 2018;37:224

Completion Rate and Safety of Tuberculosis Treatment with Shorter Regimens

- Retrospective review of actual practice 2014-17
- N=667: 3HP- 283, 4R- 132, 9H- 252
- Completion rates: 9H- **53%** (SAT), 3HP- 97% (DOT), 4R- 84% (SAT)
- AEs were more common with 9H including 2 children with significant hepatotoxicity (none with 3HP or 4R)
- One case of TB disease in 16 yo getting 3HP but thought to be hiding then spitting out the medication

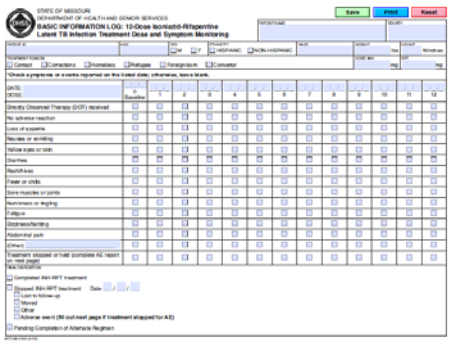
Cruz and Starke. Pediatrics 2018;141:e20172838



Treatment of LTBI in 2018 Red Book

- Concern that completion rates for 9H can be as low as 50%
- Listed first is 3HP, then 4R and lastly 9H
- No preference listed but says "Most experts consider isoniazid-rifapentine to be the preferred regimen…"
- 3HP cannot be used in children under 2 years because of lack of PK data for rifapentine
- Consider using directly observed therapy for 3HP
- Drug interaction may limit use of rifamycins

Drug	Dosage	Maximum dose
INH	15 mg/kg rounded to nearest 50/100 mg in patients ≥ 12 years	900 mg
	25 mg/kg rounded to the nearest 50/100 mg in patients 2-11 years	
Rifapentine	10.0 – 14.0 kg = 300 mg	900 mg
	14.1 – 25.0 kg = 450 mg	
	25.1 – 32.0 kg = 600 mg	
	32.1 – 49.9 kg = 750 mg	
Rifapentine tablets can be crushed and administered with semi-solid food for children unable to swallow pills		



2018 Red Book TB Chapter Changes

- New testing algorithms for IGRAs
-
- New LTBI treatment recommendations

- New rifampin dosing

Rifampin Dosing

- Target serum concentration (C_{max}) of 8µg/ml
- CSF to serum ratio of 0.04-0.11
- WHO changed recommended RIF dosing in 2009 from 10mg/kg to 15 mg/kg
- Several PK studies since then have shown higher doses are needed to achieve appropriate C_{max} especially in infants, toddlers and TB meningitis cases
  - Schaaf et al. BMC Med, 2009
  - Verhagen et al. Trop Med Int Health, 2012
  - Savic et al. Clin Pharm Ther, 2015

Rifampin Dosing

- Standard Treatment
  - 2015: 10-20 mg/kg/day
  - 2018: 15-20 mg/kg/day
- Infants, Toddlers and serious forms of TB at any age (e.g. meningitis, disseminated)
  - 2015: 10-20 mg/kg/day
  - 2018: 20-30 mg/kg/day

Summary

- IGRAs can be used in children as young as 2 yo and are preferred in BCG vaccinated individuals
- 3HP (in children ≥ 2 yo), 4R and 9H are all acceptable regimens for treatment of LTBI in children
- Rifampin dosing has increased to
  - Routine 15-20 mg/kg/day
  - Infants, toddlers and serious infections 20-30 mg/kg/day

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Changes to HPV Vaccine Recommendations

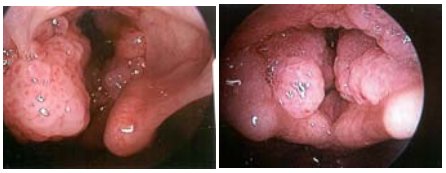
- **The AAP recommends starting the series between 9-12y, at an age that the provider deems optimal.**
- When HPV vaccine is begun at 9-10y, MCV4 and Tdap are still recommended at 11-12y.
- HPV vaccine is recommended for females up to 26y and males up to 21y; it can be given in males up to 26y.
- There is no recommendation regarding 9vHPV for those who previously completed 4v or 2vHPV vaccines.
- Evidence of past HPV exposure is not a contraindication.

Changes to HPV Vaccine Recommendations

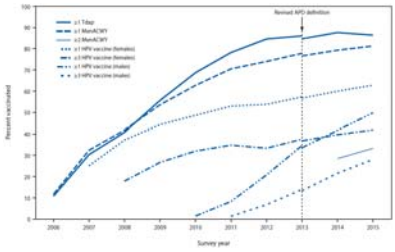
- >97% of healthy vaccine recipients develop antibodies to HPV vaccine types after vaccination.
- Antibody titers are higher in adolescents 9-15y c/w 16-26y.
- Vaccine type HPV decreased by ~60% in 14-19y girls in the first 6 years of the vaccination program. (Up to 90% in countries with high uptake, such as Australia)
- Incidence of genital warts in 4vHPV-immunized cohorts has been reduced by 90%.
- HPV vaccines have not been proven to have therapeutic effect on existing HPV infection.

Impact and Effectiveness of the Quadrivalent Human Papillomavirus Vaccine: A Systematic Review of 10 Years of Real-world Experience. *Clinical Infectious Diseases*, Volume 63, Issue 4, 15 August 2016, Pages 519–527

Pediatric Recurrent Respiratory Papillomatosis



CDC - NIS Teen Data

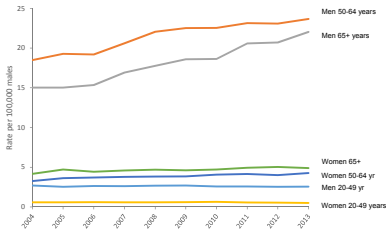


Cancers Caused by HPV per Year, U.S., 2009-2013

Cancer site	Percentage probably caused by any HPV type	Number probably caused by any HPV type		
		Female	Male	Both Sexes
Cervix	91%	10,600	0	10,600
Vagina	75%	600	0	600
Vulva	69%	2,500	0	2,500
Penis	63%	0	700	700
Anus	91%	3,200	1,600	4,800
Rectum	91%	500	200	700
Oropharynx	70%	2,000	9,600	11,600
TOTAL		19,400	12,100	31,500

Based on Viens et al. MMWR 2016. https://www.cdc.gov/cancer/hpv/statistics

HPV-Associated Oropharyngeal Cancer: Increasing Incidence



Source: North American Association of Central Cancer Registries, 2016

Biologic Response Modifiers

- Drugs which are antibodies to proinflammatory cytokines or proteins that bind to cytokine receptors
- Considered highly immunosuppressive and live-virus vaccines are contraindicated during therapy
- Infants exposed in utero to maternally administered biologic response modifiers can have detectable drug concentrations for many months, resulting in concern for immunosuppression among infants in the 12 months after the last maternal dose
- Some are more efficiently passaged transplacentally in the 2nd and 3rd trimesters c/w 1st trimester
  - Pediatrics. 2016 Aug;138(2). pii: e20161209. doi: 10.1542/peds.2016-1209. Epub 2016 Jul 18. **Infectious Complications With the Use of Biologic Response Modifiers in Infants and Children.**

Changes to Rotavirus Vaccine Recommendations

- **Until further data are available, and considering that rotavirus disease is rarely life-threatening in the US, rotavirus vaccines should be avoided for the 12 mos after in utero exposure to a biologic response modifier.**
- In addition, international travel should be avoided during this time (MMR)

Changes to MMR Vaccine Recommendations

- **People previously vaccinated with 2 doses of MMR who are identified by public health as at increased risk for mumps because of an outbreak should receive a 3rd dose of MMR to improve protection against mumps disease and related complications.**
- The current routine recommendation for 2 doses of MMR vaccine appears to be sufficient for mumps control in the general population, but insufficient for preventing mumps outbreaks in prolonged, close-contact settings, even where coverage with 2 doses of MMR vaccine is high. Waning of vaccine-induced immunity with time after receipt of the second vaccine dose in high intensity exposure settings typical of outbreaks contributes to this higher risk for mumps disease in these settings. Protection against severe disease, however, is maintained.

Data to Support Changes to MMR Vaccine Recommendations

- 3 epidemiologic studies provided evidence regarding use of a 3rd dose of MMR vaccine for prevention of mumps, all conducted in outbreak settings among populations with high coverage with 2 doses of MMR vaccine (schools and a university).
- All studies reported lower attack rates among persons who received the third dose during the outbreak compared with persons who had received 2 doses before the outbreak.
- Incremental vaccine effectiveness of the third versus the second MMR dose in these studies ranged from 61% to 88%,
- This study also found that students who had received 2 doses of MMR vaccine ≥13 years before the outbreak had nine or more times the risk for contracting mumps than did those who had received the second dose within the 2 years preceding the outbreak.

MMWR January 12, 2018 / 67(1);33–38

Unknown or Uncertain Immunization Status Children Who Received Immunizations Outside the US

- In general, only written documentation should be accepted.
- Immigrant children should meet ACIP recommendations for poliovirus vaccination, which require protection against all 3 types with IPV or trivalent OPV (tOPV).
- Some countries may have provided monovalent or bivalent OPV as part of polio vaccination campaigns.
- **If OPV was administered before April 1, 2016, it may be counted as tOPV. If after, it does not count unless specified as tOPV**.
- Serologic testing for polio is not recommended.

Immunization in Immunocompromised Children

- Chapter has been extensively rewritten.
- Information on inactivated vaccines, primary and secondary immunodeficiencies, household members of immunocompromised pts, and biologic response modifiers has been updated.
- Table detailing immunization of children with primary and secondary immune deficiencies has been expanded.
- **Immunization of HIV-infected children with MCV4 beginning at 2 months of age has been added.**
- Information is now fully harmonized with IDSA and the CDC.

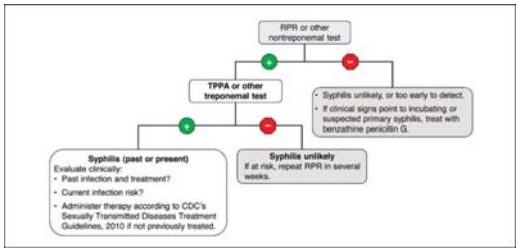
Active Immunization of People Who Recently Received Immune Globulin or Other Blood Products

- Certain live-virus vaccines may have diminished immunogenicity when administered within 2 weeks before or up to 11 months after IG
- No interference with LAIV, oral rotavirus, oral typhoid as well as OPV and yellow fever vaccines.
- **Table has been updated to include Botulinum Immune Globulin (Baby BIG) and CMV hyperimmune globulin (6 month interval).**
- **Measles prophylaxis has been updated (vaccine, IGIM, IGIV), including preference for MMR over IGIM in vaccine eligible individuals <72h.**
- No interference from monoclonal ab's such as palivizumab.

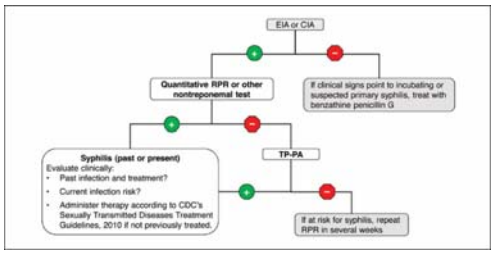
Not Yet in the Red Book…

- A single dose of hepatitis A vaccine should be administered to infants age 6-11 months of age traveling to countries outside the United States for which protection against hepatitis A is recommended on CDC's Traveler's health website (https://wwwnc.cdc.gov/travel/). Infants should then receive the full 2-dose hepatitis A vaccine series at ≥12 months of age as recommended.
- Rationale:
  - IG hard to obtain
  - Timing of IG complicates MMR administration

Changes to Congenital Syphilis Management Algorithm



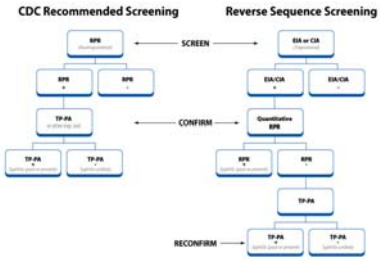
Reverse Sequence Screening (RSS) for Syphilis

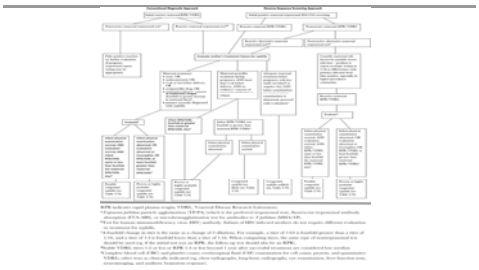


Rationale for Reverse Sequence Screening (RSS) for Syphilis

- Automated (high throughput)
- Low cost in high volume settings
- Less lab occupational hazard (pipetting)
- No false negatives due to prozone reaction
- Objective results
- Some EIA/CIAs detect IgM antibodies; potentially useful for diagnosis of early syphilis

Reverse Sequence Screening (RSS) for Syphilis





Immunization Update Resource Slides

Timing of Vaccines and the Immunization Schedule

- Recent data that administration of Menactra 1 month after Daptacel reduces meningococcal antibody response to Menactra.
- Menactra should be given >4 weeks after PCV13.
- The epidemiology of increased risk of seizure among recipients of concurrent influenza vaccine and PCV13 has been updated to describe an increased risk in children 6-24 mos x 24h, ~1 per 2200 doses. Simultaneous administration is still recommended.
- HibMenCY has been removed from the US market.

Hypersensitivity Reactions after Immunization Immediate Type Allergic Reactions

- Data have shown that IIV and LAIV are well tolerated by those who have an egg allergy, including severe allergy.
- New paragraph on gelatin allergy – those with history of food allergy to gelatin may develop anaphylaxis after receipt of gelatin-containing vaccines (e.g., MMR, varicella, some influenza vaccines, yellow fever, rabies vaccines). These pts should be evaluated by an allergist for skin testing.
- Yeast allergy – rare, but theoretically possible with recombinant vaccines made with Saccharomyces cerevisiae (HPV, HBV). Pts should be evaluated by an allergist prior to vaccination.
- Latex allergy – Some vaccine vial stoppers and syringe plungers contain latex. Info available on the CDC website.

Hypersensitivity Reactions after Immunization Delayed Type Allergic Reactions

- Most cell-mediated, delayed type allergic reactions are due to small molecules.
- Thimerosol – temporary swelling at the injection site. Not a contraindication.
- Aluminum – sterile abscesses/ nodules at injection site. Sometimes due to inadvertant subcutaneous injection rather than IM. May recur with subsequent doses. Not a contraindication unless severe.
- Antimicrobial agents – many vaccines contain trace amts of streptomycin, neomycin, or polymixin B leading to an injection site papule. Not a contraindication. (If there is a history of anaphylaxis to one of these agents, allergy referral warranted). No US vaccines contain penicillin, cephalosporins, or fluoroquinolones.

Passive Immunization

- IGIV dosing for replacement in ab deficiency has been updated.
- Management options for reactions to IGIV have been expanded.
- 4 IGSC products licensed in the US have been added.
- A table has been added to aid in the determination of which route of IG is most appropriate for a given patient.

Immunization in American Indian/ Alaska Native Children and Adolescents

- Permissive language for chemoprophylaxis of close contacts of an index case with Hia has been added.
- The epidemiology of rotavirus and HPV has been added.

International Travel

- Information on booster dose recommendations for yellow fever vaccine and for JE vaccine has been added.
- Information on the new oral cholera vaccine (Vaxchora) has been incorporated.

Managing Injection Site Pain

- Physical/ Psychological techniques:
  - Holding the child upright; administering the most painful vaccine last; providing tactile stimulation
  - Aspiration prior to injection is not necessary
  - Infants -Breast feeding, sweet solutions
  - Children – distractions (pinwheels, bubbles), deep breathing, toys
  - Adolescents – seated or lying down in case of syncope
- Pharmacologic techniques:
  - LMX4 (30 mins); EMLA (60 mins); ethyl chloride spray (15 secs)
  - Routine preemptive administration of acetaminophen is not recommended

General Information Updates

- Updated vaccine resources
- "Countering Vaccine Hesitancy" has been added
- VAERS chapter has updated information on monitoring of VAERS reports and reporting of adverse events. On June 30, 2017, the CDC and FDA implemented VAERS 2.0, which includes a new VAERS reporting form and new submission processes.
- Information on 21st Century Cures and on pregnant women has been added to the Vaccine Injury Compensation chapter