The Year's Top Articles in Infectious Diseases for the Practitioner

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Welcome

to Journal Watch...
The year, in context, with attitude

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Disclosure: Dr. Long is an associate editor of the *Red Book* 2018-2021 and *The Journal of Pediatrics*

Soon-to-be new parents come to your office for a first visit. In taking the histories of their health you learn that father has Crohn disease for which he is being treated with a monthly biologic response modifying (BRM) drug, Remicaide (infliximab). You make a note of this and relevance to the baby's care.

With regards to the baby's usually recommended vaccines, you should:

A. Give inactivated and live-virus vaccines on schedule
B. Give inactivated vaccines on schedule but delay live virus vaccines until father is off BRM therapy
C. Delay inactivated and live virus vaccines until father is off BRM therapy

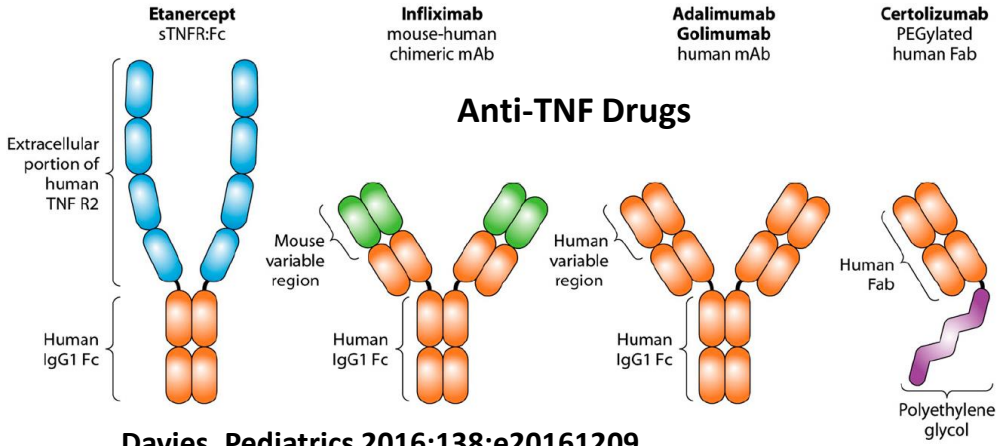
Soon-to-be new parents come to your office for a first visit.
In taking the histories of their health you learn that mother has rheumatoid arthritis for which she is being treated with a monthly BRM drug, Remicaide (infliximab).
You make a note of this and its relevance to the baby's care.

With regards to the baby's usually recommended vaccines, you should:

A. Give vaccines as in the preceding case in which father was being treated with a BRM drug

B. NOT give vaccines as in the preceding case in which father was being treated with a BRM drug

Bio Resp Mod Agents for JIA in Children	
Anti-TNF Therapy	
Etanercept	Embrel
Adalimumab	Humira
Infliximab	Remicade
Golimumab	Simponi
Anti-IL-6 Therapy	
Tocilizumab	Actemra
Anti-IL-1 Therapy	
Anakinra	Kineret
Canakinumab	Ilaris
Rilonacept	Arcalyst
Selective T-cell Co-stimulation Therapy	
Abatacept	Orencia



Davies. Pediatrics 2016;138:e20161209

Similarities between BRM Agents

- ✓ Target specific innate immune responses
- ✓ Dampen by blocking an excitatory cytokine or receptor, or upregulating an inhibitory pathway
- ✓ Large studies in adults, but small studies in children

Differences between BRM Agents

- ✓ Specific production and specific targets
- ✓ Avidity for target
- ✓ Downstream effects on inflammatory cascade
- ✓ Half-lives and routes of administration
- ✓ Propensity and specificity of infectious risks

Disease-Modifying Anti-rheumatic Drugs (DMARDs)	
Prednisone	Deltasone, prediSONE, etc.
Methotrexate	Rheumatrex, Trexall, etc.
Azathioprine	Imuran
6-Mercaptopurine	Purinethol
Cyclosporine	Gengraf, Neoral, SandIMMUNE

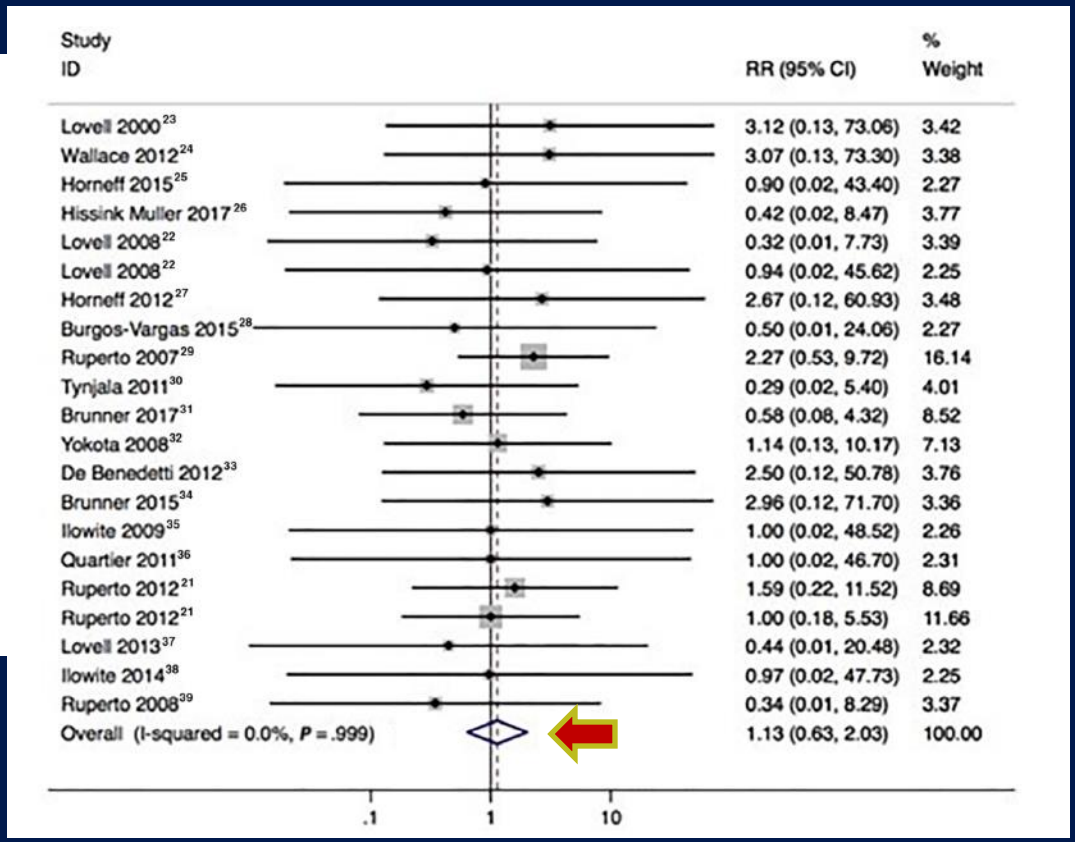
Risk of serious infections associated with biologic agents in juvenile idiopathic arthritis: A systematic review and meta-analysis.
Aeschlimann FA, Chong S-L, Lyons TW, Beinvogl BC, Goez-Mogollon LM, Tan S, Laxer RM.
J Pediatr 2019; 204: 162

Study

Serious infection in children with JIA in registered clinical trials of biologic agent compared with controls
(Study design = RCT, parallel design, withdrawal)

Results

21 studies, 1601 children, different BRMs
Duration of studies/follow up 4 – 54 weeks (median 18 weeks)
Serious infections in 17/810 BRM recipients vs 15/797 controls
Pooled BRMs RR 1.13 (95% CI 0.63, 2.03)



Conclusion

No demonstrable increased risk of BMRs for serious infection

What We Know about BRM Agents

- ✓ Highly effective in controlling disease, improving quality of life
- ✓ Therapies are long-term

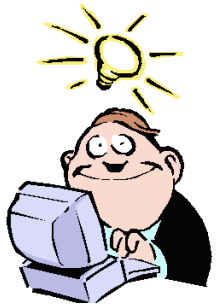
What We Don't Know about BRM Agents

- ✓ Long-term safety re malignancy and autoimmunity
- ✓ Even short term safety re uncommon infections
- ✓ Even short term safety re common infections in large numbers of patients

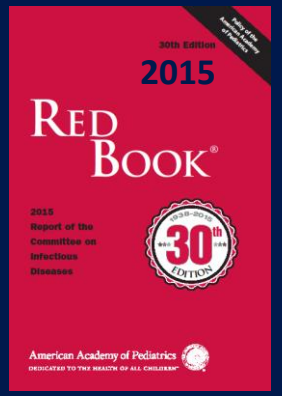
- **Disorders themselves are due to abnormal innate immune responses.**
- **Disorders themselves ↑risk for infections.**
- **Patients get BRM + DMARDs → ↑risk and confounding. No "like" patients in placebo-c or comparator studies .**
- **Drug trials are not real-world experience.**
- **Drug trials have insufficient numbers/durations to capture enough exposures to assess real risk.**

Risks of serious infections in children treated with biologic response-modifying drugs

Abinum, M. Newcastle upon Tyne, UK Rheum 2018;57:211

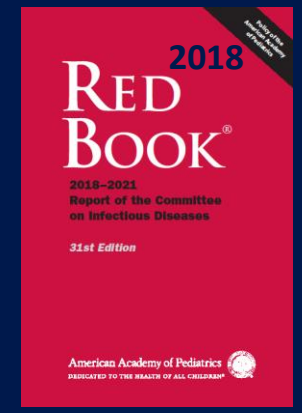


- ➢ **Although meta-analyses are reassuring, there is good evidence that BRMs ↑severe infections, especially when combined with other DMARDs.**
- ➢ **To some extent, these patients reproduce experiments of nature.**
- ➢ **We should use our knowledge of patients with rare single gene defects to predict further dysregulation by targeted modulation of these patients' already diseased immune systems.**



Patients treated with BRMs are at ↑risk of infections caused by *M tuberculosis*, non-TB mycobacteria, molds and endemic fungi (eg, *Histoplasma*, *Pneumocystis*), *Legionella*, *Listeria* and other intracellular pathogens, as well as lymphomas and other cancers. [BRMs] also potentially permit reactivation of infections that have been controlled, as well as lead to an inadequate immune response to new pathogens that require cell-mediated immunity for control.

- ❖ Patients receiving BRMs are considered highly immunosuppressed.
- ❖ Live virus vaccines are contraindicated.
- ❖ Inactivated vaccines should be given as recommended, including IIV.
- ❖ Table "Recommendations for Evaluation Prior to Initiation of BRMs"
  - -- Inactivated vaccines at least 2 weeks prior to BRM
  - -- Live vaccines at least 4 weeks prior to BRM



Infectious Complications With the Use of Biologic Response Modifiers in Infants and Children

H. Dele Davies, MD, FAAP, COMMITTEE ON INFECTIOUS DISEASES **Pediatrics 2016; 138:e20161209**

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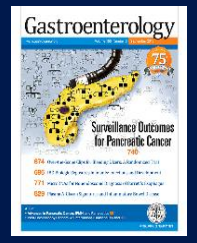


Concentrations of Adalimumab and Infliximab in Mothers and Newborns, and Effects on Infection

Mette Julsgaard,[1,2] Lisbet A. Christensen,[1] Peter R. Gibson,[3] Richard B. Gearry,[4] Jan Fallingborg,[5]

Gastroenterology 2016;151:110–119

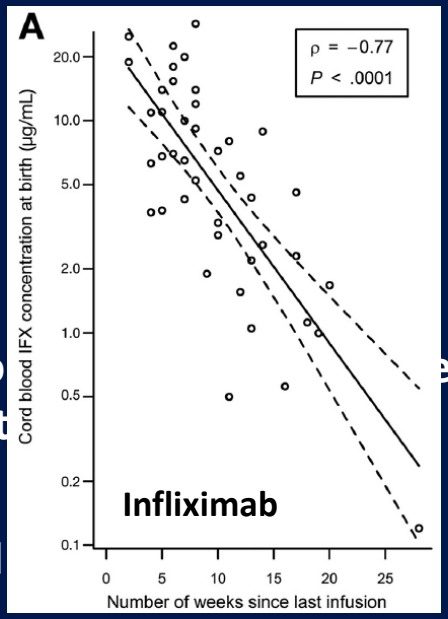
The Methods

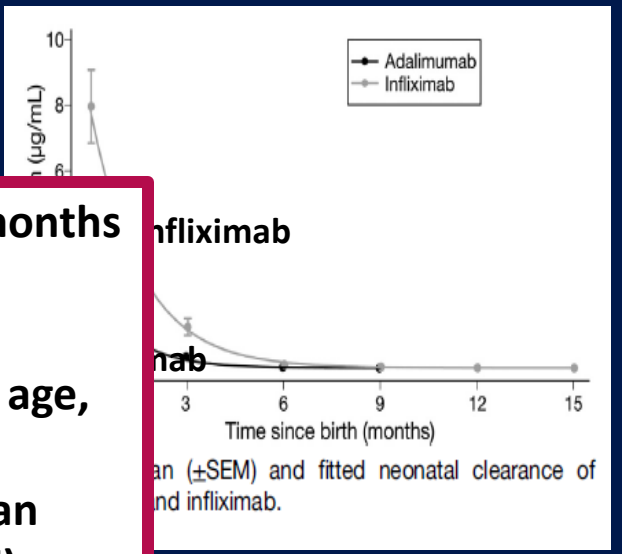
80 pregnant women (Denmark. Australia, NZ) receiving TNFI agents (adalimumab [Humira] o e]
Measured serum drug concentrations @ delivery in mother, in cord and in infants q 3 mo unt

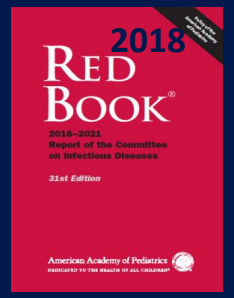
The Findings

The shorter the time from last exposure → ↑ maternal concentration @ delivery and in cord
Ratio of infant : mother concentration at birth = 1.21 for adalimumab
1.97 for infliximab

Mean time from last exposure to drug clearance in infants = 4.0 mo for adalimumab
7.3 mo for infliximab
No drug > 12 months







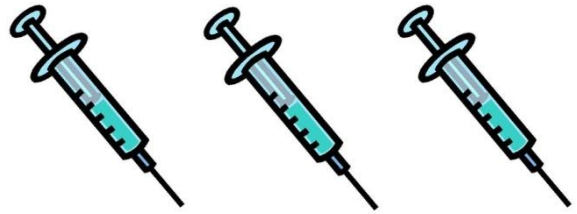
Until further data are available …

- ✓ Rotavirus vaccine should be avoided in U.S. infants for the first 12 months *after the final in utero exposure* to a BRM.
  Catch-up of RV vaccine is not recommended at 12 months.
- ✓ Because MMR, V & MMRV vaccines are recommended at 12 mos of age, BRM in mother does not affect receipt at the recommended time.
- ✓ For measles prevention <12 months, IGIV 400mg/kg is preferred in an outbreak setting (as is the current rec for highly immunosuppressed).
- ✓ International travel of infants ***should be discouraged*** for 12 months following the final in utero exposure to a BRM.

A family is about to travel to France.
Parents both had one dose of MMR.
4 yr old had 2 doses of MMR.
7 month old infant due for first MMR at 12 months of age.

Which is the correct MMR immunization strategy

A. No MMR is indicated because no one is “behind”
B. No MMR is indicated because France has little measles
C. MMR is indicated for parents only
D. MMR is indicated for parents and 7 mo old



Subacute Sclerosing Panencephalitis: The Devastating Measles Complication That Might Be More Common Than Previously Estimated.

Wendorf KA[1], Winter K[1], Zipprich J[1], Schechter R[1], Hacker JK[2], Preas C[2], Cherry JD[3], Glaser C[4], Harriman K[1].

CID 2017;65:226

What We Knew?

Subacute sclerosing encephalitis (SSPE) is a fatal complication of measles, with symptom onset years after measles, with progressive cognitive and motor deterioration.

Incidence SSPE U.S. prior to measles vaccine 1 : 100,000 measles cases

A consistent risk factor for SSPE was measles before the 2nd birthday

After U.S. universal vaccination U.S. SSPE↓↓. No cases vaccine virus SSPE.

Measles eliminated in the Americas, but endemic elsewhere

Intro measles into U.S. is related to travel. Person-to-person trans within US re level vaccination

The Question

Sought to describe current epi and risk factors of CA SSPE cases 1998 –2015

The Study

Cases ascertainment: CA Encephalitis Project
CA death certificates
CDC notification measles RNA/antigen in CSF from CA specimen

The Findings

Total of 17 cases SSPE (71% febrile rash illness; all <15 months of age, 67% with exposure in CA)

Median age of SSPE = 12 years

Incidence SSPE per measles case

1 : 1367 for children <5 years
1 : 609 for children <12 months

A healthy 7-month old infant is brought for advice and any immunizations required in preparation to travel to Japan in 2 weeks to visit with extended family.
He has received routine vaccines on schedule including the 6-month injections. It's October, influenza vaccine has arrived.

You provide advice about behaviors and precautions.
You plan to give MMR to protect against measles, as well as influenza vaccine.

Do you have specific additional recommendations ?

A. Nothing in addition to vaccines given and general precautions
B. Standard immunoglobulin(IG) should be administered IM, just prior to travel to protect against hepatitis A
C. A dose of hepatitis A vaccine should be given
D. A dose of varicella vaccine should be given

Hepatitis A Facts

- Nonenveloped RNA virus, can survive in environment for prolonged periods at low pH and across freezing – moderate temperatures
- Transmitted by person-to-person (fecal-oral), contaminated water, ice, shellfish from sewage-contaminated water, fruits, vegetables, other foods
- HAV-infected young children usually are asymptomatic but are sources for adults.
- Universal immunization HepA vaccine in U.S. @1 yr

Recommended Immunization Schedule - United States, 2018

	Birth	1 mo	2 mos	4 mos	6 mos	9 mos	12 mos	15 mos
	1st dose	←2nd dose→			←3rd dose→			
			1st dose	2nd dose	See footnote 2			
			1st dose	2nd dose	3rd dose			←4th dose→
			1st dose	2nd dose	See footnote 4		←3rd or 4th dose, See footnote 4→	
			1st dose	2nd dose	3rd dose		←4th dose→	
			1st dose	2nd dose	←3rd dose→			
					Annual vaccination (IIV) 1 or 2 doses			
Measles, mumps, rubella[8] (MMR)					See footnote 8		←1st dose→	
Varicella[9] (VAR)							←1st dose→	
Hepatitis A[10] (HepA)							←2 dose series, See footnote 10→	

Hepatitis A vaccine (minimum age 12 months)

Routine vaccination: 2 doses separated by 6-18 mos, between 1st and 2nd birthdays
(If a series is started before the 2nd birthday should be completed even if dose 2 @ >24 months)

Catch-up vaccination: Anyone ≥ 2 years of age may receive HepA vaccine if desired.
(Minimum interval between doses is 6 months)

Hepatitis A and Travel

- HAV is common wherever there is inadequate sanitation and limited access to clean water.
  High endemicity: Africa and Asia
  Intermediate: Central/So America, Eastern Europe, ± Asia
  Low endemicity: U.S. and Western Europe
- HAV is among most common travel-acquired infections. Occurs in travelers to developing countries even with standard itinerary, accommodations, eating behaviors.
- Difficult to predict risk by map or habit.
- Two monovalent HepA vaccines (Vaqta, Havrix) approved for use ≥ 12 months of age

- ✓ Traveling infants 6–11 months should be given HepA vaccine.
- ✓ At age ≥12 months such infants still need 2 doses at least 6 mos apart

Previous Recommendations Hep A vaccine for Travel

- ✓ All susceptible people ≥ 12mos–40 years traveling for any purpose, frequency or duration to countries with high or intermediary HAV endemicity should be vaccinated before departure.
- ✓ Those <12 month[X] with immuno-suppression shou[X] given IGIM.
- ✓ Because risk assessment is complex and because of foodborne HAV even in countries with low endemicity, some experts advise that all people traveling outside the U.S. consider HepA vaccination regardless of destination.

- ✓ All susceptible people ≥12 mos–any age traveling … should be given HepA vaccine.
- ✓ People >40 years also may be given IG (.1–.2mg/kg) at provider's risk assessment.

A healthy 7-month old infant is brought for advice and any immunizations required in preparation to travel to Japan in 2 weeks to visit with extended family.
He has received routine vaccines on schedule including the 6-month injections.

You provide advice about behaviors and precautions.
You plan to give MMR to protect against measles, as well as influenza vaccine.

Do you have specific recommendations to protect against hepatitis A?

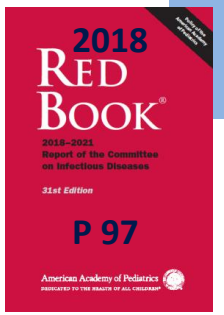
A. There is nothing in addition to general precautions

B. Standard immunoglobulin(IG) should be administered IM, just prior to travel to protect against hepatitis A

C. A dose of hepatitis A vaccine should be given

D. A dose of varicella vaccine should be given

A 17-year-old boy in your practice since infancy is going to volunteer at a local hospital and has had some serum antibody tests performed. Because of the result, he has been told that he needs some vaccines. You check his records and confirm that he received every recommended vaccine on the schedule, on time.



You should advise that

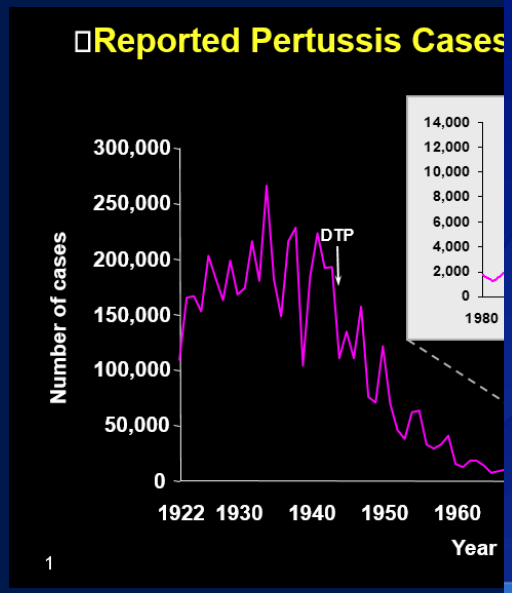
A. No vaccine
B. MMR vaccine
C. Varicella vaccine
D. Hepatitis B vaccine
E. More than one of t

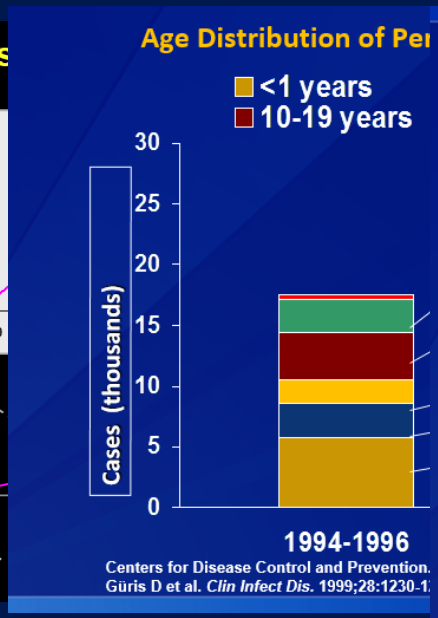
Evidence of Immunity to M, M, R, V

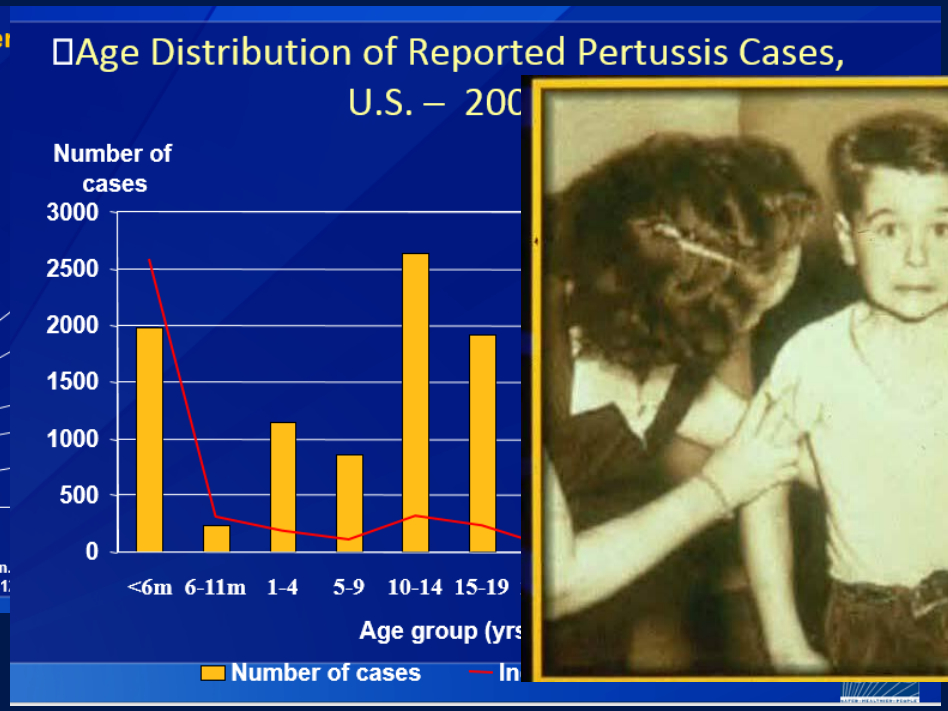
- ✓ Laboratory confirmed infection
  OR
- ✓ Laboratory evidence of immunity (Ab+)
  OR
- ✓ Documented receipt of 2 doses M, M, V (1 dose for R) vaccine, appropriately spaced, on after the 1st birthday
  OR
- ✓ Physician diagnosed disease (V only)
  OR (for elders)
- ✓ ± Birth prior to 1957 for M & M
- ✓ Not birth prior to 1957 for R
- ✓ Not birth prior to 1980 [or any yr] for V

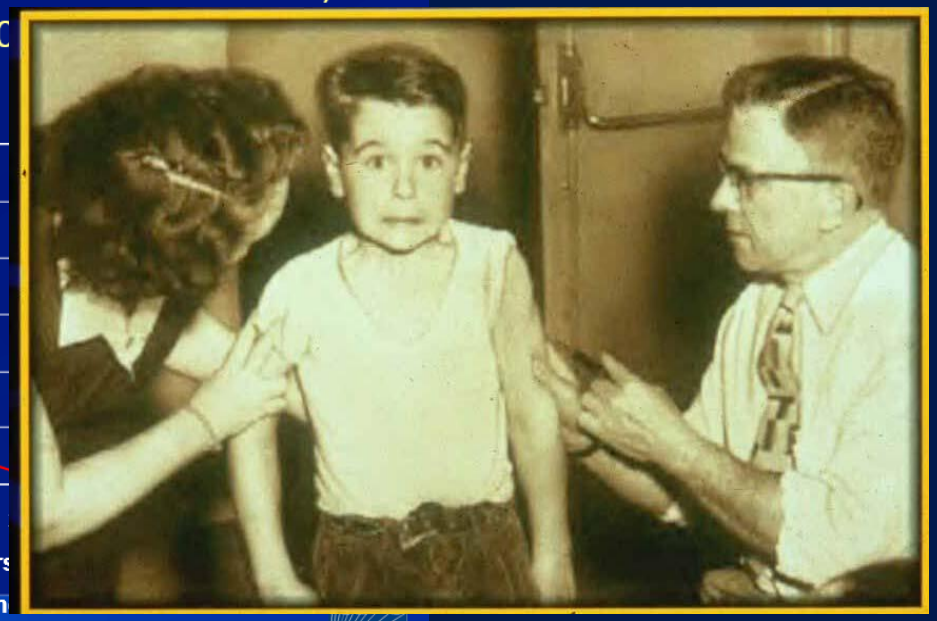
Evidence of Immunity to Hepatitis B

- ✓ Serum antibody to HepB surface antigen (HBsAb+)









Reasons for Changes in Pertussis Epidemiology In the DTwP Era

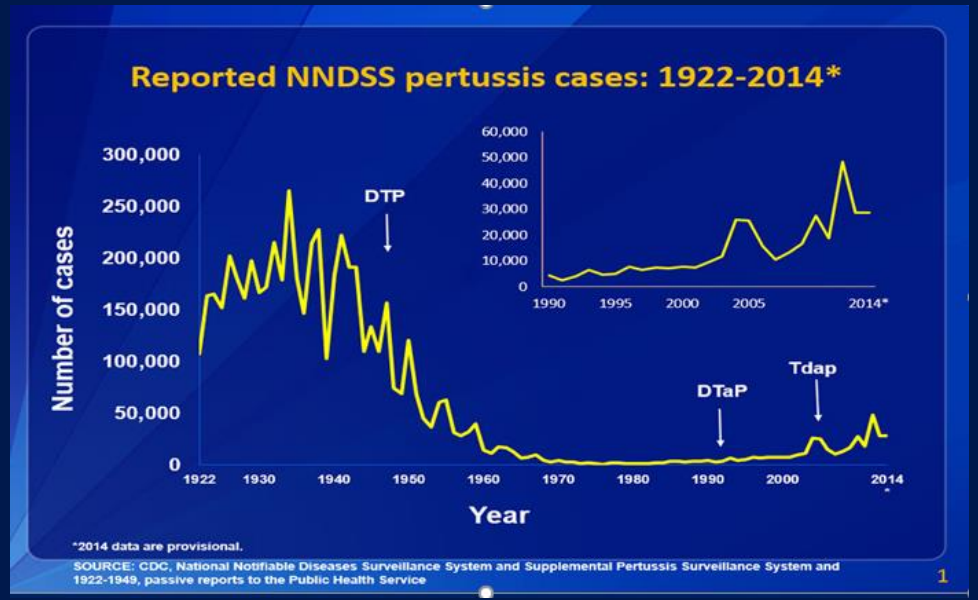
Pertussis in Adolescents and Adults

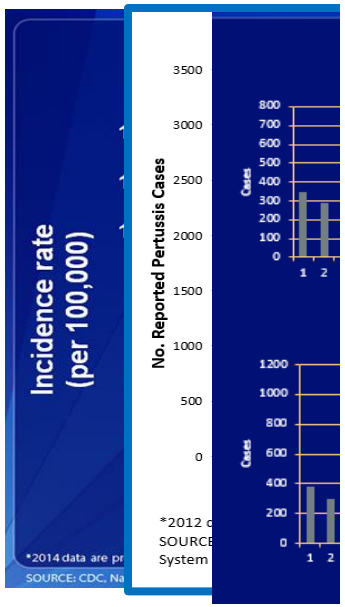
- ✓ Partial control: Fewer natural
- ✓ Partial control: Organism
- ✓ Failure to vaccinate: ↑ Su
- ✓ Vaccine failure: ↑ S
- ✓ Waning vacc immunity: ↑ S

WRONG

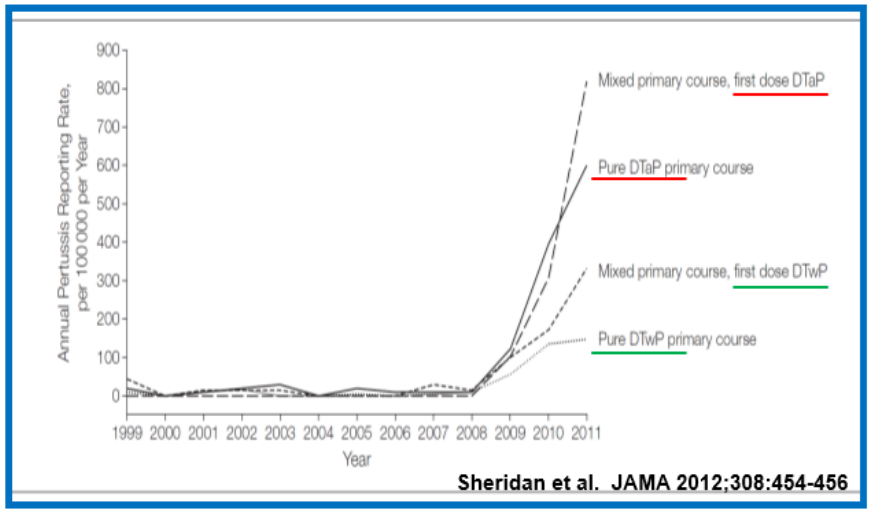
Pertussis in Young Infants

- ✓ Waned mat immunity: ↓Transplacental Ab
- ✓ Vaccine schedule: Susceptible ≤3–4mo



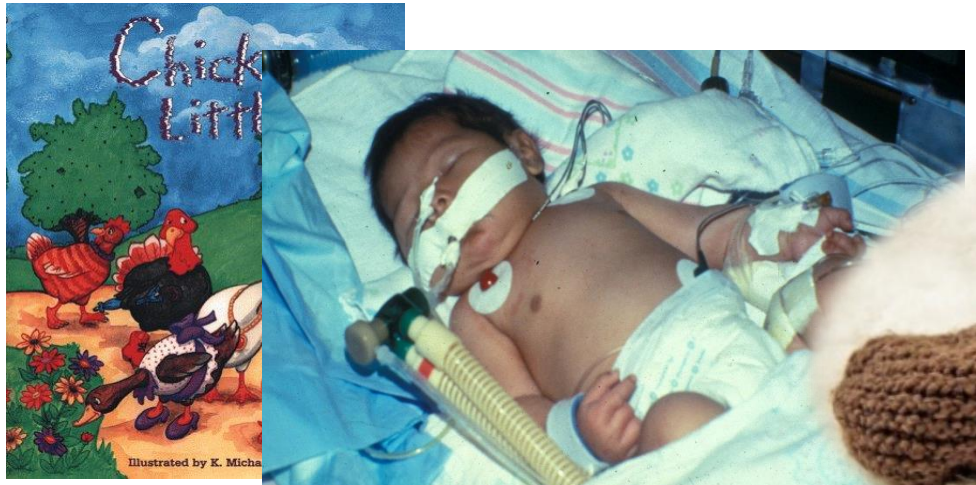


Pertussis Reporting Rates 1999-2011 by Primary Pertussis Vaccine(s) Received for Children Born in 1998, Australia



Reasons for Changes in Pertussis Epidemiology In the DTaP/Tdap Era

- ✓ Replacement Dose 4, Dose 3 in 1992
- ✓ Replacement Doses 1-2-3 in 1997
- ✓ By 2000 all children Dose 1 DTaP
- ✓ Rising cases is the effect of an aging cohort of children with all doses aP
- ✓ Although DTaP and Tdap effective, response → immediate waning



High mortality from pertussis is in 0-3 month olds
Tdap in pregnancy provides >90% protection to age 3 mo
Immunization rate is <60% (MMWR Sept 28, 2018)

- ✓ Tdap during every pregnancy preferably between 27 and 36 weeks

Enlightenments from Recent Pertussis Vaccine Studies

JAMA Ped

ity and Safety of Monovalent Acellular
cine at Birth
l Clinical Trial

JAMA Ped 2018;Sep epub

y Nolan, MB, BS, PhD; Helen Marshall, MB, BS, MD;
ma Gibbs, MSc; Kirsten Perrett, MB, BS, PhD; Peter McIntyre, MB, BS, PhD

DTaP at birth → interference/blunted responses to infant vaccines
440 Australian newborns Glaxo aP v HBV @ <5d (no mat Tdap this preg)

- ✓ Detectable Pert Ab @ 10 wks 93% v 51%
- ✓ Blunting Abs some other vaccines @ 8 mos

The Journal of Infectious Diseases

Maternal Vaccination With a Monocomponent Pertussis Toxoid Vaccine Is Sufficient to Protect Infants in a Baboon Model of Whooping Cough

JID 2018;218:217

Parul Kapil,[1] James F. Papin,[2] Roman F. Wolf,[2,a] Lindsey I. Zimmerman,[1] Leslie D. Wagner,[1] and Tod J. Merkel[1]

Concern re repeated Tdap each pregnancy
Pertussis-toxoid-only (Ptx) vaccine vs placebo to pregnant baboons
Challenged their 5-wk-old infants: Outcomes + colonization and disease

- ✓ All challenged infants were heavily colonized
- ✓ No disease in infants of Ptx-vaccinated mothers

The Journal of Infectious Diseases

Live Attenuated Pertussis Vaccine BPZE1 Protects Baboons Against *Bordetella pertussis* Disease and Infection

JID 2018;216:117

Camille Locht,[1,2,3,4] James F. Papin,[5] Sophie Lecher,[1,2,3,4] Anne-Sophie Debrie,[1,2,3,4] Marcel Thalen,[6] Ken Solovay,[6] Keith Rubin,[6] and Nathalie Mielcarek[1,2,3,4]

Administration of nasal pertussis vaccine (BPZE1) attenuated by inactivating PT, dermonecrotic toxin and tracheal cytotoxin
Subsequent challenge of vaccinated v naïve w virulent B. pertussis

- ✓ Vaccinated v naïve had 100% protection vs disease and >99% reduction in bacterial burden

Tdap each pregnancy
(CDC 10/24/12)

Better implementation
of current recs

Change timing DTaP
or Tdap Schedule? No
Routine Tdap > 1 No

Better vaccine?
Oh YES