Dilemmas in Vaccination

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BCG VACCINE
(BACILLE CALMETTE-GUÉRIN)

Q1. What is the efficacy of BCG vaccination?

- Meta-analysis of RCTs limited to children who received BCG vaccination as infants or children, with observation periods up to 12.5yr, the average protection against TB disease in the prospective studies was 51% (RR 0.49, CI 95% 0.34-0.7).
- BCG vaccination does NOT prevent pulmonary infection or reactivation.
- Vaccine efficacy varies geographically. In warm countries, pre-existing immunity to environmental mycobacteria interferes with BCG vaccine viability in the host, reducing the immune response to the vaccine.

Q2. What factors affect the variability in local responses after BCG vaccination?

- Age
- Immune status/genetics of recipient
- BCG vaccine strain

- Current BCG vaccine strains are descendants of the original *M.bovis* isolated by Calmette & Guérin in 1909. To prevent deviation from the original BCG strain, lypophilized seed lots of the vaccine strain have been kept by WHO since 1956.
- A number of BCG vaccine strains are available. The number of cultivable bacilli per dose & the biochemical composition of the vaccine vary considerably depending on the strain & production method of the BCG vaccine.
- In terms of efficacy, no BCG strain is better than another & there is no global consensus about the optimal strain for general use.

Q3. In the absence of a BCG scar, is repeat BCG vaccination indicated?

WHO Position paper:

- In the absence of a scar in children in HIGH-BURDEN countries, BCG vaccination is indicated.
- However, where there is appropriate documentation of BCG vaccination or those who remain negative on subsequent PPD testing, re-vaccination is of NO documented value.
- Strategy for booster BCG vaccination after the neonatal dose is of NO documented value.
- Note: neonates <6 weeks are regularly TST-negative.

Q4. What is the duration of protection following BCG vaccination?

- In Saudi Arabia, the protective efficacy of neonatal BCG vaccination against pulmonary, meningeal or disseminated TB was followed over a 20-year period & shown to be:

  82% in children <15 years

  67% in 15-24 years

  20% in persons 25-34 years

Q5. Are there any additional indications for BCG vaccine?

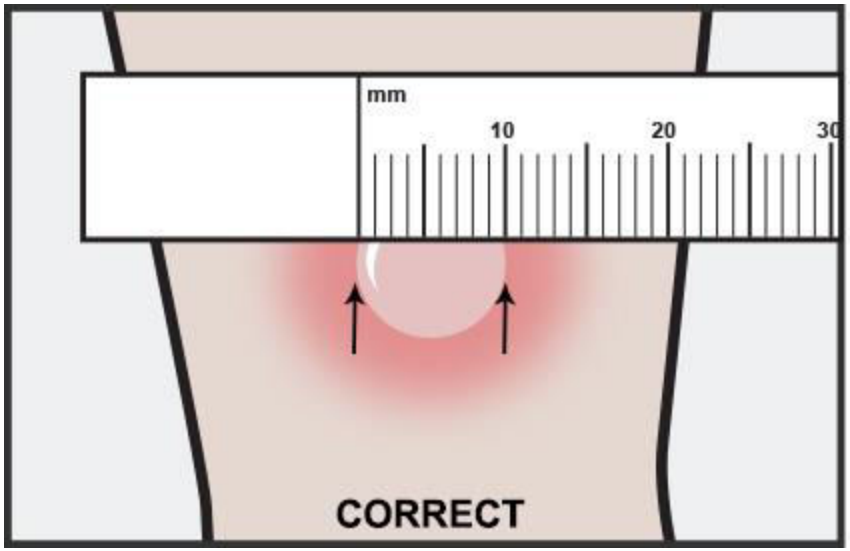
- BCG has proven efficacy in the control of leprosy (*M.leprae*) & also protects against Buruli ulcer (*M.ulcerans*).
- Treatment of bladder cancer.
- BCG vaccination in adults is not normally recommended but may be considered for PPD-negative persons in unavoidable & close contact with cases of MDR *M.tuberculosis* (WHO position paper).

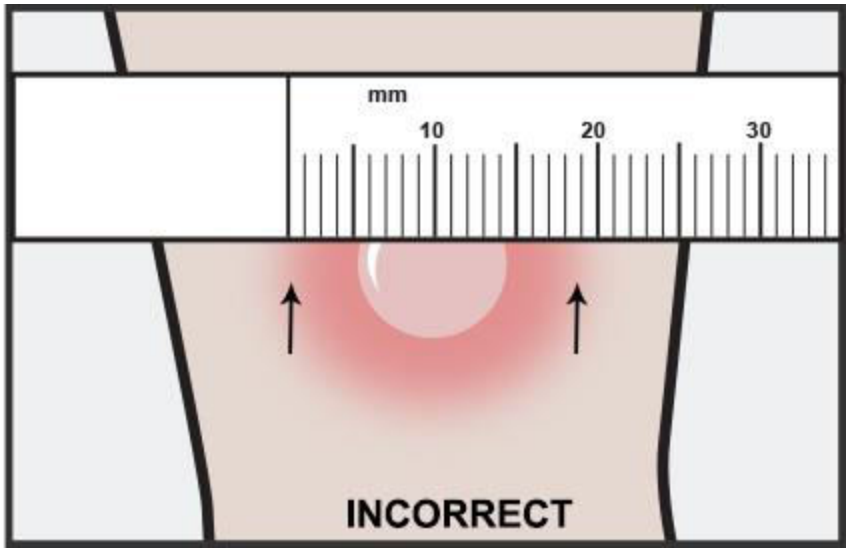
Q6. How to interpret a tuberculin skin test (TST/ PPD) in the context of BCG vaccination?

- Most individuals who have received BCG vaccine have a TST reaction of 3-19 mm in size at two to three months following vaccination. The reaction wanes with time. At >10 years post vaccination, it is generally <10 mm.
- The skin-test positivity on TST is a marker of delayed hypersensitivity against antigens of *M.tuberculosis* complex (*Mtb, M.africanum, M.ulcerans* and *M.bovis*). It does not necessarily indicate immunity to re-infection.
- Specificity of TST/PPD depends on:
  - Timing of previous exposure to BCG vaccine
  - Exposure to environmental mycobacteria
  - Host immune status
  - Adequacy of PPD test (5 tuberculin units of PPD, 0.1ml injected intra-dermally using a 27-gauge needle & 1ml syringe into the volar surface of forearm. Creation of palpable wheal 6-10mm in diameter is crucial to accurate testing- AAP Red Book 2015)

Ensure an interval of 28 days between administration of a live vaccine & PPD placement. Risk of false negative PPD readings due to interference of cell-mediated immunity from earlier live vaccine administration.

Q7. How to read a PPD test?





- Read 48-72hrs after placement.
- Measure induration, NOT erythema.
- Measure the transverse diameter.

Potential causes of false-negative tuberculin tests

Technical (potentially correctable)
Tuberculin material:
Improper storage (exposure to light or heat)
Contamination, improper dilution, or chemical denaturation
Administration:
Injection of too little tuberculin or too deeply (should be intradermal)
Administration more than 20 minutes after drawing up into the syringe
Reading:
Inexperienced or biased reader
Error in recording
Biologic (not correctable)
Infections:
Active tuberculosis (especially if advanced)
Other bacterial infection (typhoid fever, brucellosis, typhus, leprosy, pertussis)
HIV infection (especially if CD4 count <200)
Other viral infection (measles, mumps, varicella)
Fungal infection (South American blastomycosis)
Recent live-virus vaccination (measles, mumps, polio)
Immunosuppressive drugs (corticosteroids, tumor necrosis factor inhibitors, and others)
Metabolic disease (chronic renal failure, severe malnutrition, stress [surgery, burns])
Diseases of lymphoid organs (lymphoma, chronic lymphocytic leukemia, sarcoidosis)
Age (infants <6 months, older adults)

Definitions of positive tuberculin skin test (TST) results in infants, children, and adolescents*

Induration 5 mm or greater
Children in close contact with known or suspected contagious people with tuberculosis disease
Children suspected to have tuberculosis disease: ▪ Findings on chest radiograph consistent with active or previous tuberculosis disease ▪ Clinical evidence of tuberculosis disease¶
Children receiving immunosuppressive therapyΔ or with immunosuppressive conditions, including human immunodeficiency (HIV) infection
Induration 10 mm or greater
Children at increased risk of disseminated tuberculosis disease: ▪ Children younger than four years of age ▪ Children with other medical conditions, including Hodgkin disease, lymphoma, diabetes mellitus, chronic renal failure, or malnutrition
Children with likelihood of increased exposure to tuberculosis disease: ▪ Children born in high-prevalence regions of the world ▪ Children who travel to high-prevalence regions of the world ▪ Children frequently exposed to adults who are HIV infected, homeless, users of illicit drugs, residents of nursing homes, incarcerated, or institutionalized
Induration 15 mm or greater
Children age four years or older without any risk factors

* These definitions apply regardless of previous Bacille Calmette-Guérin immunization; erythema alone at TST site does not indicate a positive test result. Tests should be read at 48 to 72 hours after placement.
¶ Evidence by physical examination or laboratory assessment that would include tuberculosis in the working differential diagnosis (eg, meningitis).
Δ Including immunosuppressive doses of corticosteroids or tumor necrosis factor-alpha antagonists.

GENERAL VACCINE QUESTIONS

Q. 14mo old exposed to sibling with measles. Has not received the MMR vaccine. What next?

- Available data suggests that measles vaccine, if given within 72hrs of measles exposure, can protect against clinical disease (AAP; CDC).
- During measles outbreaks, additional doses of MMR vaccine should be considered regardless of MMR vaccine status (WHO).

Q. Your 7 month old patient is travelling to a country where there is an ongoing measles outbreak. What is your recommendation?

- Children 6-11 months of age in epidemic situations or before international travel to high-risk countries, should receive their MMR vaccination. This dose is <u>not</u> considered valid, & 2 valid doses administered on or after the 1st birthday are required for complete immunity (AAP Red Book; CDC).

Q. You are seeing a well-appearing 3 year old with primary varicella infection in your clinic. His father has never had chickenpox infection. Next step?

- Administration of varicella vaccine to people without evidence of immunity >1yr of age, including adults, as soon as possible after exposure (ideally between 72-120hrs post-exposure), may prevent or attenuate clinical disease (AAP Red Book; CDC).

Q. What is the recommended interval between vaccines?

- Injectable or nasally-administered live vaccines (BCG, nasal influenza, MMR, varicella, yellow fever vaccine) should either be co-administered the same day or separated by an interval of 28 days.
- Oral vaccines i.e., oral typhoid, cholera and RV vaccines can be co-administered the same day with or at any interval before or after other live vaccines (injectable or intranasal).
- Varicella vaccine:
  - Children 12mo to 12yr: 2 doses of vaccine at least 3 months apart.
  - Children ≥13yr & adults: 2 doses of vaccine at least 28 days apart.
- MMR vaccine:
  - 2 doses of MMR vaccine AFTER the 1st birthday are recommended. Minimal interval between doses is 28 days in any age group.

FIGURE 2. Catch-up immunization schedule for persons aged 4 months through 18 years who start late or who are more than 1 month behind—United States, 2017.

The figure below provides catch-up schedules and minimum intervals between doses for children whose vaccinations have been delayed. A vaccine series does not need to be restarted, regardless of the time that has elapsed between doses. Use the section appropriate for the child's age. Always use this table in conjunction with Figure 1 and the footnotes that follow.

Vaccine	Minimum Age for Dose 1	Minimum Interval Between Doses			
		Dose 1 to Dose 2	Dose 2 to Dose 3	Dose 3 to Dose 4	Dose 4 to Dose 5
Children age 4 months through 6 years					
Hepatitis B[1]	Birth	4 weeks	8 weeks *and* at least 16 weeks after first dose. Minimum age for the final dose is 24 weeks.		
Rotavirus[2]	6 weeks	4 weeks	4 weeks[2]		
Diphtheria, tetanus, and acellular pertussis[3]	6 weeks	4 weeks	4 weeks	6 months	6 months[3]
Haemophilus influenzae type b[4]	6 weeks	4 weeks if first dose was administered before the 1st birthday. 8 weeks (as final dose) if first dose was administered at age 12 through 14 months. No further doses needed if first dose was administered at age 15 months or older.	4 weeks[4] if current age is younger than 12 months **and** first dose was administered at younger than age 7 months, **and** at least 1 previous dose was PRP-T (ActHib, Pentacel, Hiberix) or unknown. 8 weeks *and* age 12 through 59 months (as final dose)[4] • if current age is younger than 12 months **and** first dose was administered at age 7 through 11 months; OR • if current age is 12 through 59 months **and** first dose was administered before the 1st birthday, **and** second dose administered at younger than 15 months; OR • if both doses were PRP-OMP (PedvaxHIB; Comvax) **and** were administered before the 1st birthday. No further doses needed if previous dose was administered at age 15 months or older.	8 weeks (as final dose) This dose only necessary for children age 12 through 59 months who received 3 doses before the 1st birthday.	
Pneumococcal[5]	6 weeks	4 weeks if first dose administered before the 1st birthday. 8 weeks (as final dose for healthy children) if first dose was administered at the 1st birthday or after. No further doses needed for healthy children if first dose was administered at age 24 months or older.	4 weeks if current age is younger than 12 months and previous dose given at <7 months old. 8 weeks (as final dose for healthy children) if previous dose given between 7-11 months (wait until at least 12 months old); OR if current age is 12 months or older and at least 1 dose was given before age 12 months. No further doses needed for healthy children if previous dose administered at age 24 months or older.	8 weeks (as final dose) This dose only necessary for children aged 12 through 59 months who received 3 doses before age 12 months or for children at high risk who received 3 doses at any age.	
Inactivated poliovirus[6]	6 weeks	4 weeks[6]	4 weeks[6]	6 months[6] (minimum age 4 years for final dose).	
Measles, mumps, rubella[8]	12 months	4 weeks			
Varicella[9]	12 months	3 months			
Hepatitis A[10]	12 months	6 months			
Meningococcal[11] (Hib-MenCY ≥6 weeks; MenACWY-D ≥9 mos; MenACWY-CRM ≥2 mos)	6 weeks	8 weeks[11]	See footnote 11	See footnote 11	
Children and adolescents age 7 through 18 years					
Meningococcal[11] (MenACWY-D ≥9 mos; MenACWY-CRM ≥2 mos)	Not Applicable (N/A)	8 weeks[11]			
Tetanus, diphtheria; tetanus, diphtheria, and acellular pertussis[12]	7 years[12]	4 weeks	4 weeks if first dose of DTaP/DT was administered before the 1st birthday. 6 months (as final dose) if first dose of DTaP/DT or Tdap/Td was administered at or after the 1st birthday.	6 months if first dose of DTaP/DT was administered before the 1st birthday.	
Human papillomavirus[13]	9 years	Routine dosing intervals are recommended.[13]			
Hepatitis A[10]	N/A	6 months			
Hepatitis B[1]	N/A	4 weeks	8 weeks **and** at least 16 weeks after first dose.		
Inactivated poliovirus[6]	N/A	4 weeks	4 weeks[6]	6 months[6]	
Measles, mumps, rubella[8]	N/A	4 weeks			
Varicella[9]	N/A	3 months if younger than age 13 years. 4 weeks if age 13 years or older.			

NOTE: The above recommendations must be read along with the footnotes of this schedule.

Vaccine doses administered 4 days or fewer before the minimal interval or age can be counted as valid. However, this 4-day exception does not apply to rabies vaccine due to the unique schedule for this vaccine.

Q. A new 4mo patient comes for a vaccination visit. Rotavirus vaccine was given at 2mo, but the type is not documented. What RV vaccine would you choose?

- If *any* dose in the series was RotaTeq, or vaccine type was unknown, a total of 3 doses of rotavirus vaccine should be administered (CDC, ACIP).

Q. Is it safe to interchange vaccine products?

- Licensed vaccines from different manufacturers are considered interchangeable by most experts when administered according to their recommended indications
- There are minimal data on safety & interchangeability of DTaP vaccines from different manufacturers. However, when the previous DTaP product is not known or available, any of the DTaP vaccines may be used according to licensure for dose & age (AAP Red Book, CDC).

Q. “Aluminum in vaccines causes brain damage!”

- Aluminum salts are added to inactivated vaccines as adjuvants, which work to boost our immune response.
- Facts:
  - The total aluminum exposure from vaccines in the first 6 months of life is <5 mg
  - Breastfed infants ingest 7mg daily of aluminum.
  - Formula-fed infants ingest as much as 38- 112 mg per day of aluminum.

Acknowledgement: Dr. Hosam Tatari

Q. A mother comments that “mercury in vaccines caused my child’s autism”.

Q. What is thiomersal?

- Thiomersal is the most widely-used preservative for vaccines.
- Thiomersal is a compound containing ethyl mercury used to prevent bacterial and fungal growth in some inactivated vaccines in multi-dose vials.

Q. Why do vaccines need preservatives?

- Preservatives inhibit growth of bacterial and fungal contaminants, which may be introduced during repeated use of a multi-dose vial. Multi-dose vials are used in many countries because they require less storage space in the cold-chain and lead to less wastage, both of which have a significant impact on program costs. In many countries, for inactivated vaccines supplied in multi-dose vials, the presence of a preservative is a regulatory requirement.

Q. Which vaccines do NOT contain thiomersal ?

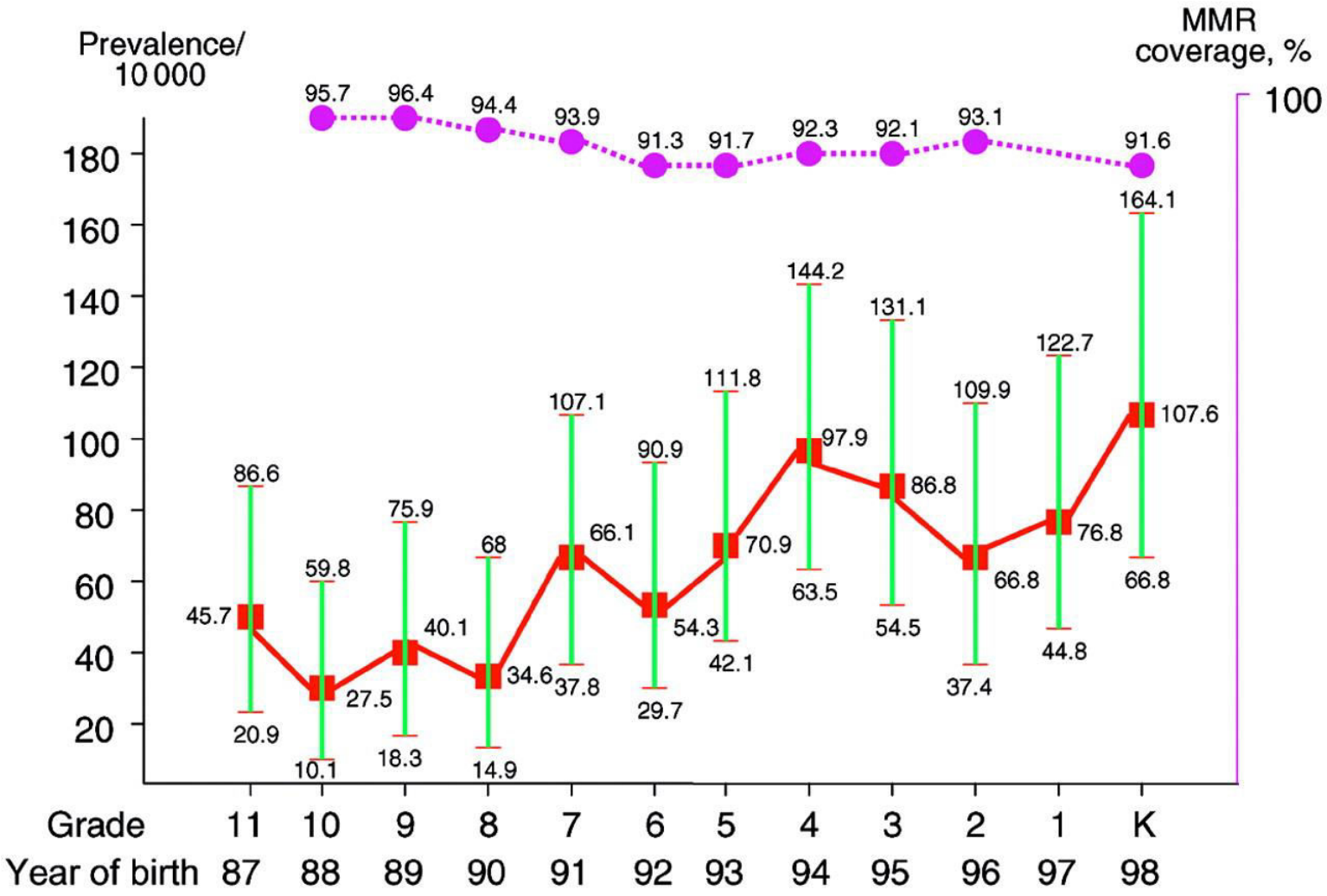
- Live vaccines, such as OPV, yellow fever vaccine and MMR vaccines, do not contain thiomersal, because it would kill the immunizing component. In inactivated vaccines, when only single-dose presentations are available from a particular manufacturer, there is no thiomersal component in sufficient concentration required to prevent contamination of a vial because those presentations are not meant to be reused.

Q. Is there a difference between ethyl mercury (thiomersal) & methyl mercury?

- Expert consultation and data presented to WHO Global Advisory Committee on Vaccine Safety (GACVS) indicate that the pharmacokinetic profile of ethyl mercury is substantially different to that of methyl mercury. In particular, the half-life of ethyl mercury is short (6 days) compared with 40-50 days for methyl mercury, making exposure to ethyl mercury in blood comparatively brief and preventing accumulation when vaccines are administered at least four weeks apart. Further, ethyl mercury is actively excreted via the gut, unlike methyl mercury, which accumulates in the body. This rapid elimination of ethyl mercury has been confirmed in all studies reviewed, even those that looked at low birth-weight infants.

MMR vaccine coverage & rates of Pervasive Developmental Disorder

Fombonne *et al.* Pediatrics 2006. Vol 118; Issue 1



Eric Fombonne et al. Pediatrics 2006;118:e139-e150

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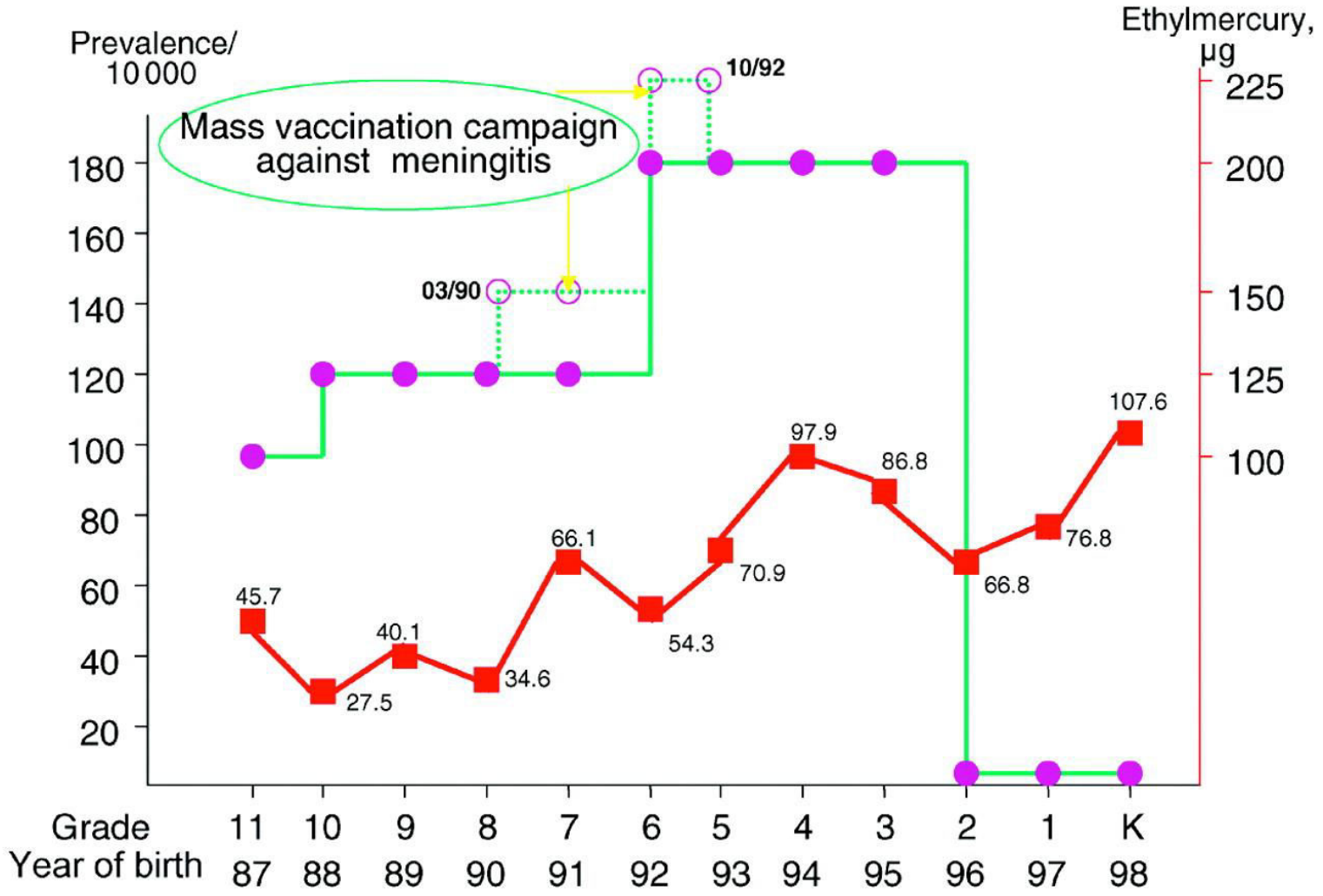
Ethylmercury exposure & rates of Pervasive Developmental Disorder

Fombonne *et al.* Pediatrics 2006. Vol 118; Issue 1



Eric Fombonne et al. Pediatrics 2006;118:e139-e150

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- What is WHO's position on the use of thiomersal in vaccines ?
- WHO supports continued use of thiomersal as an inactivating agent and preservative for vaccines.
- The reasons for this position are as follows:
  - regular review by WHO's Global Advisory Committee on Vaccine Safety of new studies relating to the safety of thiomersal in vaccines over more than a decade has not provided any evidence to suggest a possible health hazard with the amounts of thiomersal currently used in vaccines; and
  - the use of multi-dose vials remains the best option for routine immunization programmes in many countries because they are safe and effective, they limit the required storage capacity and waste, and help reduce vaccine costs.

Q. Too many vaccines ”overload” the immune system

TABLE 2. Number of Immunogenic Proteins and Polysaccharides Contained in Vaccines Over the Past 100 Years

1900		1960		1980		2000	
Vaccine	Proteins	Vaccine	Proteins	Vaccine	Proteins	Vaccine	Proteins/ Polysaccharides
Smallpox*	~200	Smallpox	~200	Diphtheria	1	Diphtheria	1
Total	**~200**	Diphtheria†	1	Tetanus	1	Tetanus	1
		Tetanus‡	1	WC-Pertussis	~3000	AC-Pertussis¶¶	2–5
		WC-Pertussis§	~3000	Polio	15	Polio	15
		Polio‖	15	Measles¶	10	Measles	10
		Total	**~3217**	Mumps#	9	Mumps	9
				Rubella**	5	Rubella	5
				Total	**~3041**	Hib††	2
						Varicella‡‡	69
						Pneumococcus§§	8
						Hepatitis B‖‖	1
						Total	**123–126**

Addressing Parents' Concerns: Do Multiple Vaccines Overwhelm or Weaken the Infant's Immune System?

Paul A. Offit, MD*; Jessica Quarles‡; Michael A. Gerber, MD§; Charles J. Hackett, PhD‖;
Edgar K. Marcuse, MD¶; Tobias R. Kollman, MD#; Bruce G. Gellin, MD**; and Sarah Landry‡

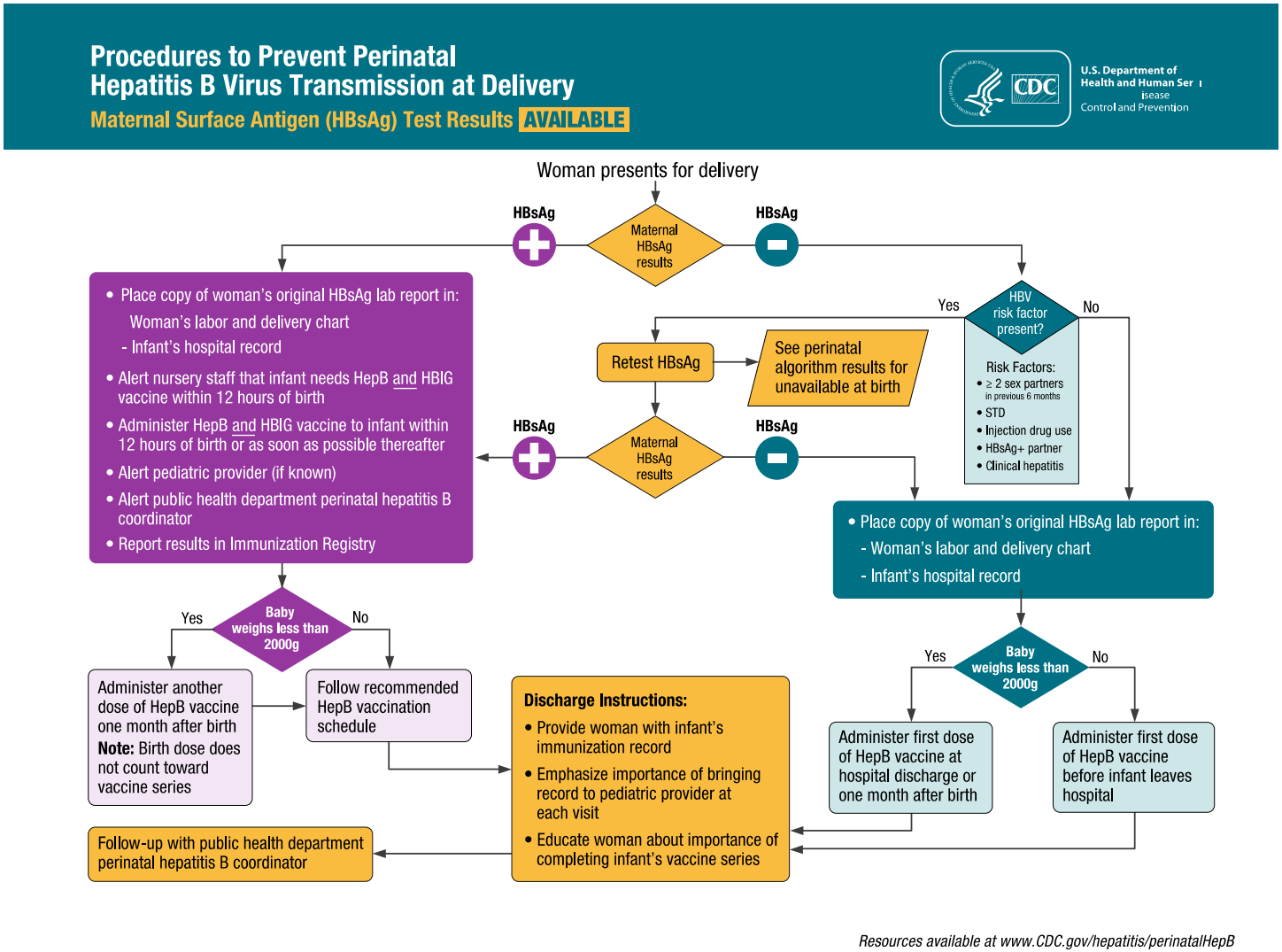
Pediatrics 2002. Vol 109; No 1

Acknowledgement: Dr. Hosam Tatari

Q. I have a patient with sickle cell disease. What are vaccination considerations in asplenic children?

- Children >2yr of age who have completed the full course of PCV13 vaccination should receive a dose PPSV23 vaccine at least 8 weeks after the last PCV13 dose.
- PPSV23 should be repeated *every 5 years.*
- Annual influenza vaccination for asplenic children & household contacts (to reduce the risk of secondary bacterial infections)
- Quadrivalent meningococcal conjugate vaccine (Aramen or Menactra) is recommended at the age-appropriate schedule.
- **Caution: do not administer PCV13 & Menactra at the same time. Menactra interferes with antibody production after PCV13 vaccination & these should be separated by 4 weeks. No precautions needed for Aramen vaccine.

Q. Neonate's mother is HepB sAg POSITIVE. What next?



Resources available at www.CDC.gov/hepatitis/perinatalHepB

- Key Points:
  - Both HBIG *and* HepB vaccine need to be given within 12hrs of birth (CDC) (*24hr, WHO).
  - For infants <2000gm, the birth dose of HepB vaccine doesn't count towards the vaccine series. Give additional dose of HepB vaccine at 1mo of age.
  - Both need to be given at different injection sites.
  - Hepatitis B *cannot* be transmitted by breastfeeding.
  - Check infant's HepB sAg and sAb between 9-12 months of age.
  - No indication to delay BCG vaccine (NHS, UK).

Risk of vertical transmission of HepB: Without prophylaxis

Maternal Status	Transmission Rate
HBsAg (+) , HBeAg (+)	70%-90%
HBsAg(+) , HBeAg (-)	10%-40%

CDC.MMWR.December 23, 2005 / 54(RR16);1-23
WHO. Weekly Epidemiol Rec. 2009;84(40):405-20

Risk of vertical transmission of HepB:

Immunoprophylaxis	Protective efficacy in preventing perinatal HBV infection
Hepatitis B Vaccine + HBIG (birth dose +2 doses)	85-95%
Hepatitis B Vaccine (birth dose + 2-3 doses)	70-95%

CDC.MMWR.December 23, 2005 / 54(RR16);1-23
WHO. Weekly Epidemiol Rec. 2009;84(40):405

Q. My patient sustained a crush injury & I'm uncertain regarding tetanus immunization.

- Clean or minor wounds. Human tetanus immunoglobulin (HTIG) is *not* indicated:
  - **Receipt of <3 doses** (or unknown) of tetanus-containing vaccine. Give vaccine.
  - **Receipt of ≥3 doses** of tetanus-containing vaccine, no need for booster unless last dose was >10yrs ago.

- All other wounds i.e., contaminated with dirt, feces, soil, or saliva; puncture wounds; avulsions; wounds resulting from missiles, crushing, burns, or frostbite:
  - **Receipt of <3 doses** (or unknown) of tetanus-containing vaccine. Give vaccine & HTIG
  - **Receipt of ≥3 doses** of tetanus-containing vaccine, booster indicated if last dose was ≥5yrs ago. HTIG not indicated.

- 250 units of HTIG intramuscularly at a different site than tetanus toxoid.
- Intravenous immune globulin (IVIG) should be administered if human tetanus immune globulin is not available.

THANK YOU!