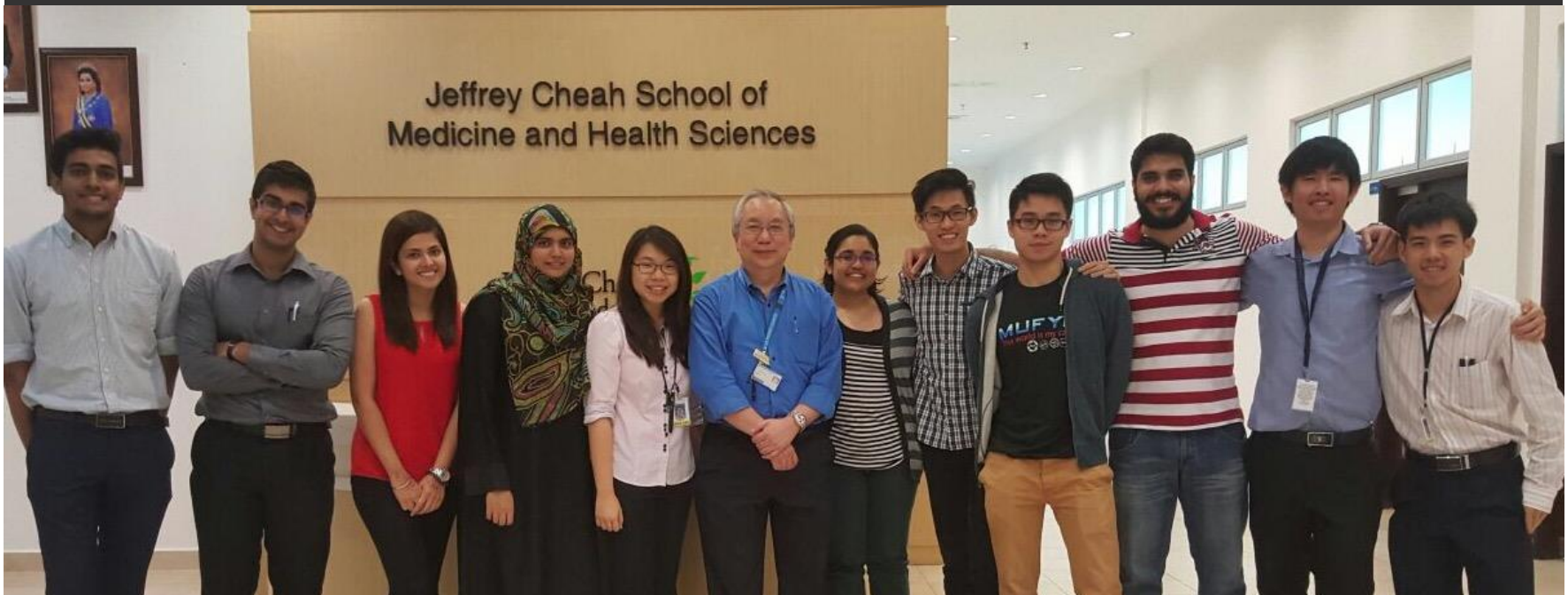
MONASH University

Medicine, Nursing and Health Sciences

Introduction to Immunisation

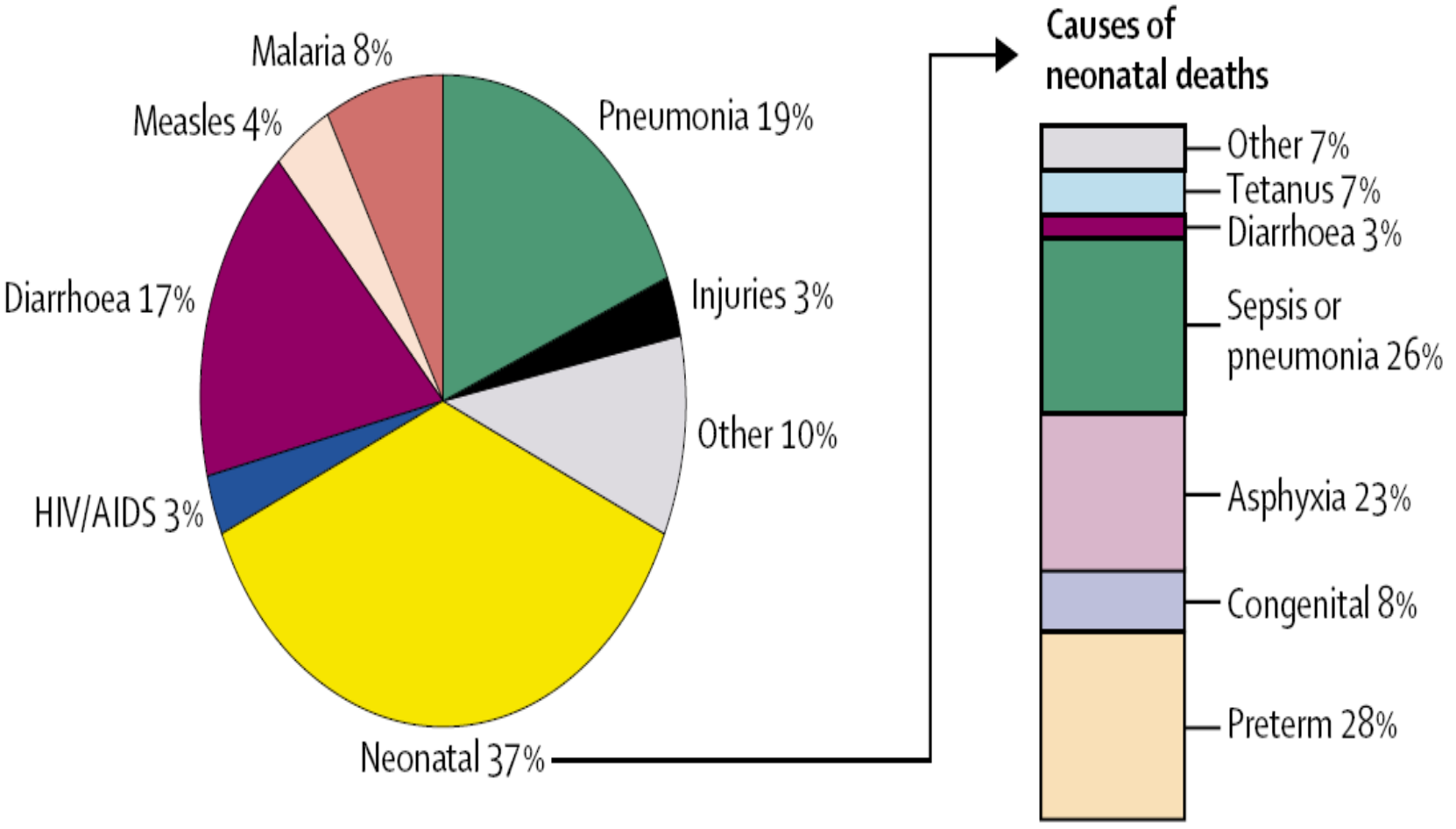
Assoc. Prof. Alex Tang
Clinical School Johor Bahru
Senior Consultant Paediatrician, KPJ Johor Specialist Hospital
www.alextang.org



Objective

- Overview of the immunisation schedules
- Basis of immunisation
- Infections
- Concerns of parents
- The cold chain

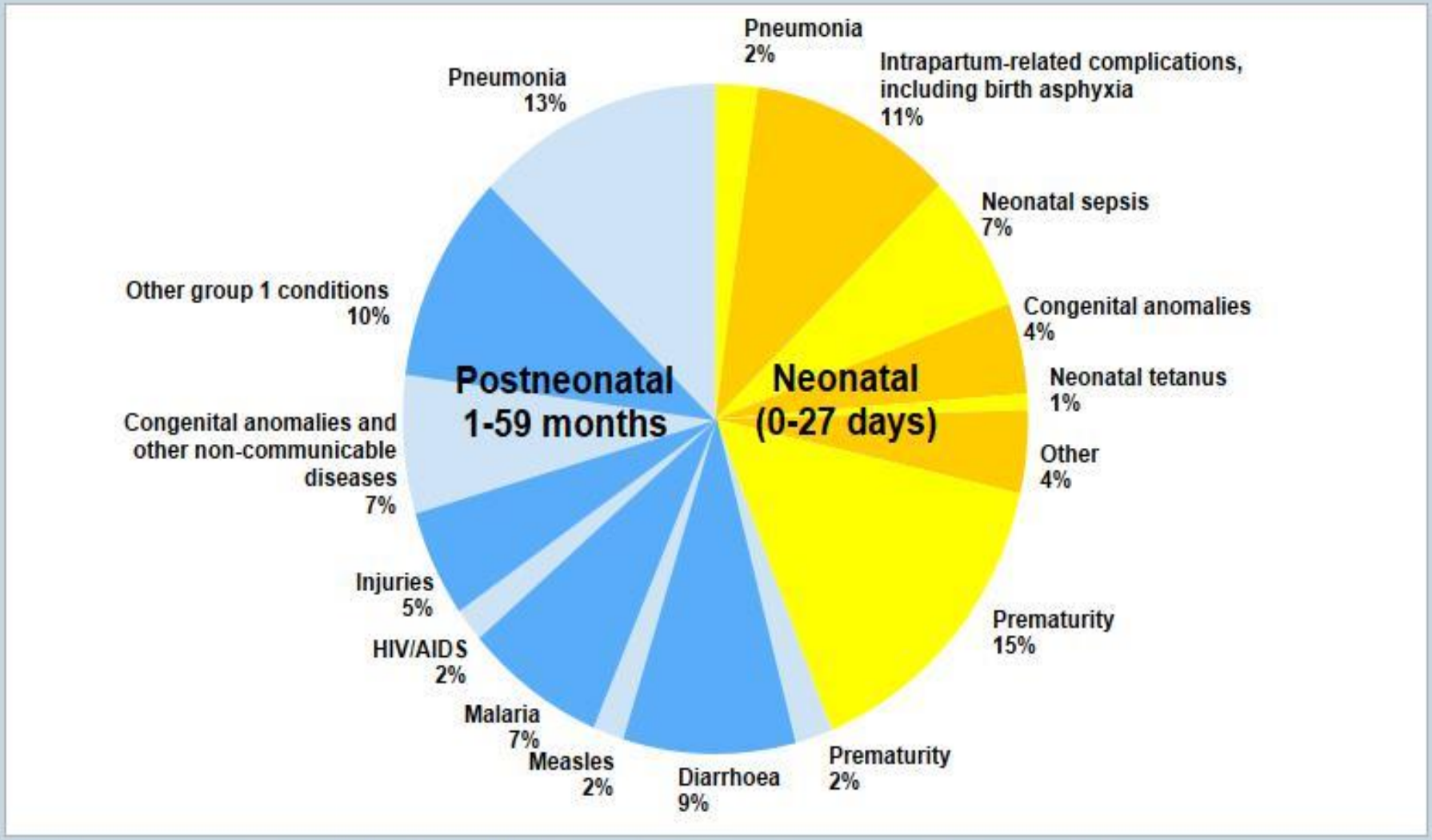
WHO: Major causes of death in children younger than age 5 years and in neonates



Lancet 2005; 365: 1147–52

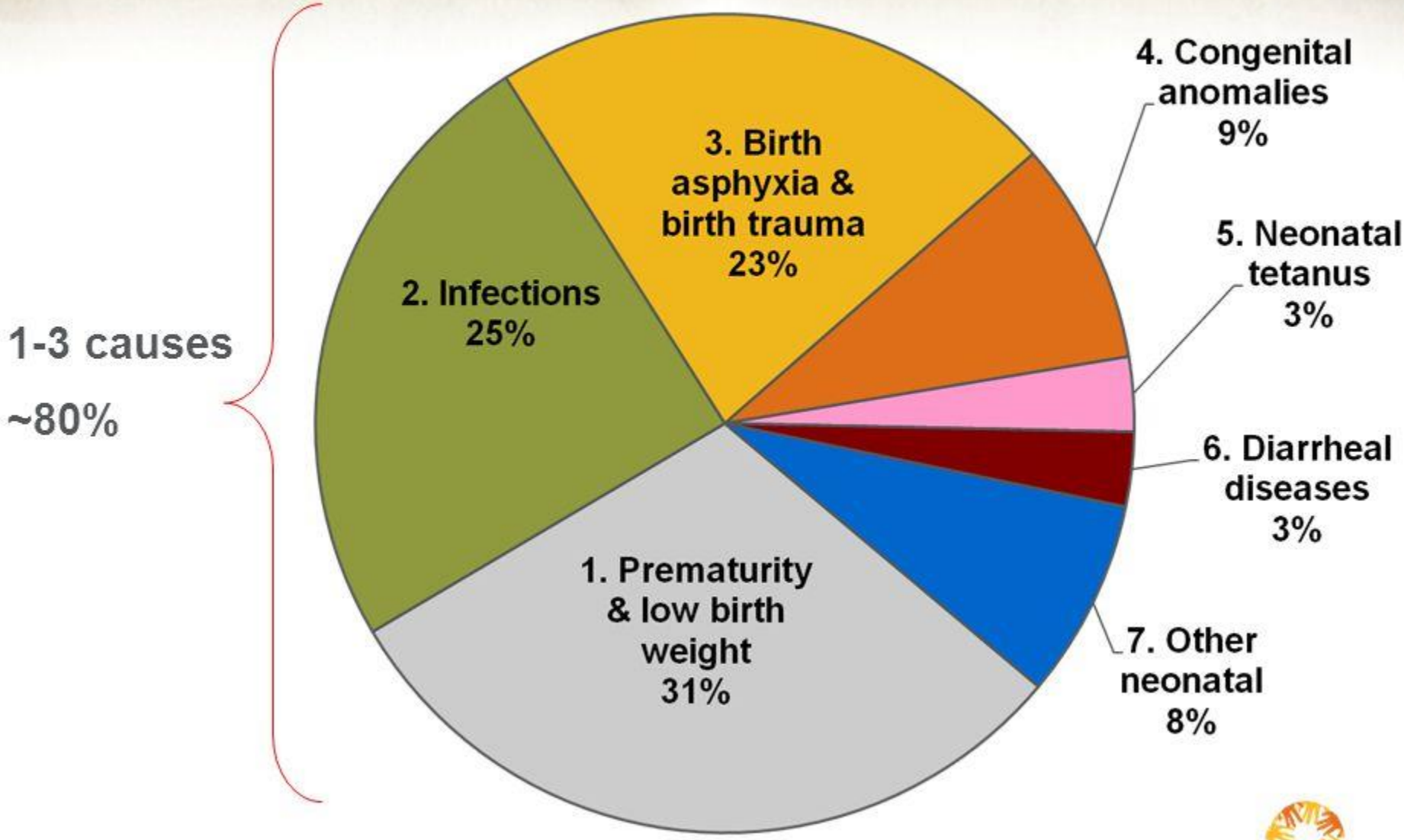
Causes of deaths among children under 5 years, 2013

World Health Organization



Source: CHERG-WHO methods and data sources for child causes of death 2000-2013 (Global Health Estimates Technical Paper WHO/HIS/HSI/GHE/2014.6.2)

Major Causes of Neonatal Deaths



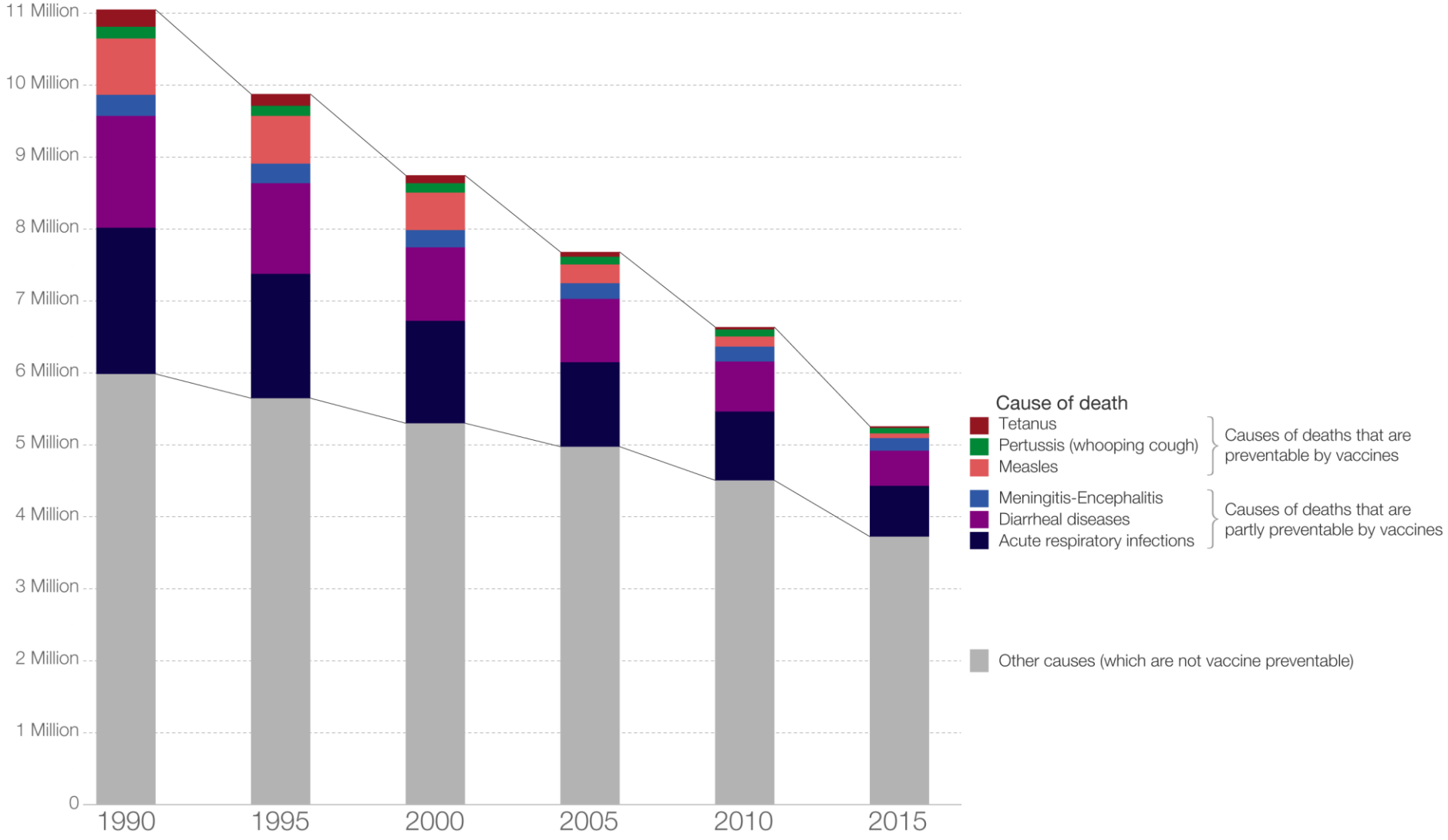
Source: *World Health Organization. The Global Burden of Disease: 2004 update. WHO, Geneva, 2008.*

care

Global number of child deaths per year – by cause of death

Our World in Data

Shown is the number of children younger than 5 years who died in a year. The height of the bar shows the total number of deaths with colored sections showing the number of children who died of diseases that are wholly or partially preventable by vaccines.
The number of child deaths for which there are vaccines available declined from 5.1 million deaths in 1990 to 1.5 million deaths 25 years later.



Data source: based on data from the *Institute for Health Metrics and Evaluation* (IHME)
The data visualization is available at OurWorldinData.org. There you find research and more visualizations on global development.

Vaccination schedule

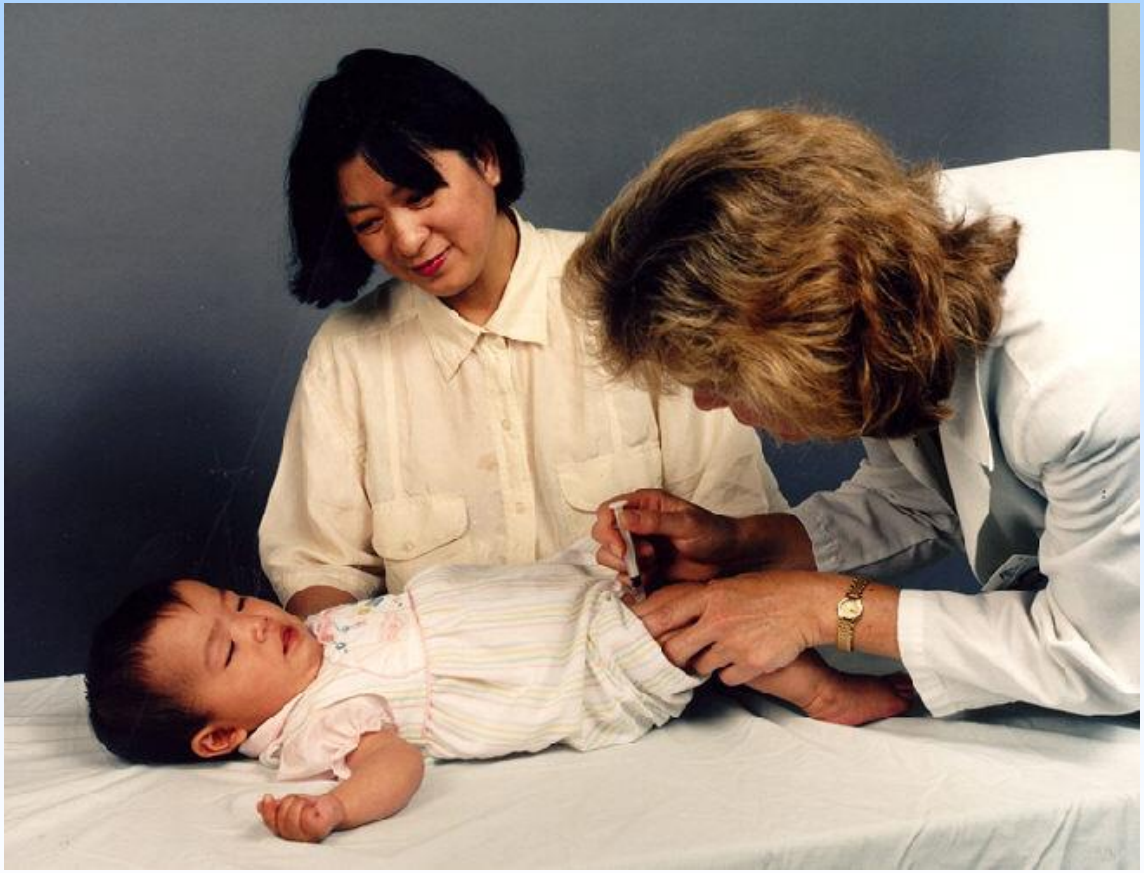


Photo from Centers for Disease Control and Prevention. *Childhood immunization* (1999) Public Health Image Library (PHIL) 982.

Malaysian National Immunisation Schedule

VACCINES	AGE (Months)										(Years)		
	0	1	2	3	5	6	9	12	18	21	7	13	15
BCG	D1												
Hepatitis B	D1	D2				D3							
DTaP			D1	D2	D3				B				
Hib			D1	D2	D3				B				
Polio (IPV)			D1	D2	D3				B				
Measles (Sabah Only)						D1							
MMR							D1	D2					
MR											B		
DT											B		
OPV													
HPV (Girls Only)												D1 D2	
Tetanus													B
JE (Sarawak Only)							D1			D2			

Primary Dose Booster Dose

Optional Vaccines in Malaysia

Vaccine	Month								
	0	1	2	3	4	5	6	12	15
Pneumococcal Vaccine									
Chickenpox Vaccine									
Hepatitis A Vaccine									
Rotavirus									

VACCINATION SCHEDULE BY THE HEALTH MINISTRY

Age: Newborn
Vaccine:
- Bacillus Calmette–Guérin (BCG)
- 1st dose: Hepatitis B

Age: 1 month old
Vaccine: 2nd dose: Hepatitis B

Age: 2 months old
Vaccine: 1st dose:
- Diphtheria, tetanus, acellular pertussis (DTaP)
- Haemophilus influenzae b (Hib)
- Inactivated poliovirus (IPV)

Age: 3 months old
Vaccine: 2nd dose:
- DTaP
- Hib
- IPV

Age: 6 months old
Vaccine: 3rd dose:
- Hepatitis B
- Measles (Sabah only)

Age: 12 months old
Vaccine: 1st dose:
- Measles, mumps and rubella (MMR)
- 2nd dose: JE (Sarawak only)

Age: 4 years old
Vaccine: 4th dose:
- JE (Sarawak only)

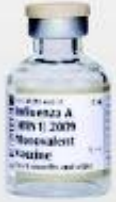
Age: 6 weeks old
Rotavirus

Age: 2 months old
Rotavirus

Age: 5 months old
Vaccine: 3rd dose:
- DTaP • Hib • IPV

Age: 10 months old
Vaccine: 1st dose:
- Japanese Encephalitis (JE) (Sarawak only)

Age: 6 months old
Influenza



Age: 10 months old
Hepatitis A

Age: 18 months old
Vaccine: 4th dose:
- DTaP • Hib • IPV

3rd dose: • JE (Sarawak only)

Age: 12 months old
Chicken pox

Age: 7 years old
Vaccine:
- BCG (optional — only if no scar found)
- Diphtheria, tetanus (DT booster)
- 2nd dose of MMR

Age: 13 years old
Vaccine:
- Human papillomavirus (HPV) with three doses within six months (2nd dose one month after first dose, third dose six months after first dose)

Age: 15 years old
Vaccine: Tetanus (TT)

OPTIONAL VACCINES IN MALAYSIA

Most paediatricians will recommend additional or optional vaccinations in addition to the ones mandated by the Health Ministry. Parents can choose to administer them to their children based on their doctor's advice.

INFOGRAPHIC NST

National Childhood and Adolescent Immunisation Schedule, Singapore
For persons aged 0 to <18 years

Vaccination against	Birth	1 month	3 months	4 months	5 months	6 months	12 months	15 months	18 months	6-7 years^	10-11 years^^
Tuberculosis	BCG										
Hepatitis B*	HepB (D1)	HepB (D2)			HepB (D3)#						
Diphtheria, Tetanus, Pertussis			DTaP (D1)	DTaP (D2)	DTaP (D3)				DTaP (B1)		Tdap (B2)
Poliovirus			OPV (D1)	OPV (D2)	OPV (D3)				OPV (B1)	OPV (B2)	OPV (B3)
Measles, Mumps, Rubella							MMR (D1)	MMR (D2)##			
Pneumococcal Disease**			PCV (D1)		PCV (D2)		PCV (B1)				
Human Papillomavirus		*Recommended for females 9 to 26 years; three doses are required at intervals of 0, 2, 6 months*									
Influenza		*Recommended annually for all children aged 6 months to <5 years and children aged 6 months to <18 years in high-risk groups****									

National Immunisation Registry, Health promotion Board, Singapore, update 23/06/2011

Australian Government Department of Health and Ageing National Immunisation Program Schedule (1 Feb 2013-30 June 2013)

Birth	Hepatitis B (hepB)
2 months	• Hepatitis B, diphtheria, tetanus, acellular pertussis (whooping cough), *Haemophilus influenzae* type b, inactivated poliomyelitis (polio) (hepB-DTPa-Hib-IPV) • Pneumococcal conjugate (13vPCV) • Rotavirus
4 months	• Hepatitis B, diphtheria, tetanus, acellular pertussis (whooping cough), *Haemophilus influenzae* type b, inactivated poliomyelitis (polio) (hepB-DTPa-Hib-IPV) • Pneumococcal conjugate (13vPCV) • Rotavirus
6 months	• Hepatitis B, diphtheria, tetanus, acellular pertussis (whooping cough), *Haemophilus influenzae* type b, inactivated poliomyelitis (polio) (hepB-DTPa-Hib-IPV) • Pneumococcal conjugate (13vPCV) • Rotavirus
12 months	•*Haemophilus influenzae* type b (Hib) • Meningococcal C (MenCCV) • Measles, mumps and rubella (MMR)
18 months	• Varicella (chickenpox)
4 years	• Diphtheria, tetanus, acellular pertussis (whooping cough) and inactivated poliomyelitis (polio) (DTPa-IPV) • Measles, mumps and rubella (MMR)

Australian Government Department of Health and Ageing National Immunisation Program Schedule (From July 2013)

Birth	Hepatitis B (hepB)
2 months	• Hepatitis B, diphtheria, tetanus, acellular pertussis (whooping cough), *Haemophilus influenzae* type b, inactivated poliomyelitis (polio) (hepB-DTPa-Hib-IPV) • Pneumococcal conjugate (13vPCV) • Rotavirus
4 months	• Hepatitis B, diphtheria, tetanus, acellular pertussis (whooping cough), *Haemophilus influenzae* type b, inactivated poliomyelitis (polio) (hepB-DTPa-Hib-IPV) • Pneumococcal conjugate (13vPCV) • Rotavirus
6 months	• Hepatitis B, diphtheria, tetanus, acellular pertussis (whooping cough), *Haemophilus influenzae* type b, inactivated poliomyelitis (polio) (hepB-DTPa-Hib-IPV) • Pneumococcal conjugate (13vPCV) • Rotavirus
12 months	•*Haemophilus influenzae* type b (Hib) • Meningococcal C (MenCCV) • Measles, mumps and rubella (MMR)
18 months	•Measles, mumps, rubella and varicella (chickenpox) (MMRV)
4 years	• Diphtheria, tetanus, acellular pertussis (whooping cough) and inactivated poliomyelitis (polio) (DTPa-IPV) • Measles, mumps and rubella (MMR)

2016 Recommended Immunizations for Children from Birth Through 6 Years Old

Vaccine	Birth	1 month	2 months	4 months	6 months	12 months	15 months	18 months	19–23 months	2–3 years	4–6 years
HepB	HepB				HepB						
RV			RV	RV	RV						
DTaP			DTaP	DTaP	DTaP		DTaP				DTaP
Hib			Hib	Hib	Hib	Hib					
PCV			PCV	PCV	PCV	PCV					
IPV			IPV	IPV	IPV						IPV
Influenza (Yearly)*					Influenza (Yearly)*						
MMR						MMR					MMR
Varicella						Varicella					Varicella
HepA§						HepA§					

Is your family growing? To protect your new baby and yourself against whooping cough, get a Tdap vaccine in the third trimester of each pregnancy. Talk to your doctor for more details.

Shaded boxes indicate the vaccine can be given during shown age range.

NOTE: If your child misses a shot, you don't need to start over, just go back to your child's doctor for the next shot. Talk with your child's doctor if you have questions about vaccines.

FOOTNOTES:

* Two doses given at least four weeks apart are recommended for children aged 6 months through 8 years of age who are getting an influenza (flu) vaccine for the first time and for some other children in this age group.

§ Two doses of HepA vaccine are needed for lasting protection. The first dose of HepA vaccine should be given between 12 months and 23 months of age. The second dose should be given 6 to 18 months later. HepA vaccination may be given to any child 12 months and older to protect against HepA. Children and adolescents who did not receive the HepA vaccine and are at high-risk, should be vaccinated against HepA.

If your child has any medical conditions that put him at risk for infection or is traveling outside the United States, talk to your child's doctor about additional vaccines that he may need.

SEE BACK PAGE FOR MORE INFORMATION ON VACCINE-PREVENTABLE DISEASES AND THE VACCINES THAT PREVENT THEM.

For more information, call toll free
1-800-CDC-INFO (1-800-232-4636)
or visit
http://www.cdc.gov/vaccines

CDC

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

AMERICAN ACADEMY OF FAMILY PHYSICIANS
STRONG MEDICINE FOR AMERICA

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

2015 Recommended Immunizations for Children from 7 Through 18 Years Old

These shaded boxes indicate when the vaccine is recommended for all children unless your doctor tells you that your child cannot safely receive the vaccine.

These shaded boxes indicate the vaccine should be given if a child is catching-up on missed vaccines.

These shaded boxes indicate the vaccine is recommended for children with certain health conditions that put them at high risk for serious diseases. Note that healthy children **can** get the HepA series[6]. See vaccine-specific recommendations at www.cdc.gov/vaccines/pubs/ACIP-list.htm.

FOOTNOTES

[1] Tdap vaccine is recommended at age 11 or 12 to protect against tetanus, diphtheria and pertussis. If your child has not received any or all of the DTaP vaccine series, or if you don't know if your child has received these shots, your child needs a single dose of Tdap when they are 7 -10 years old. Talk to your child's health care provider to find out if they need additional catch-up vaccines.

[2] All 11 or 12 year olds – both girls *and* boys – should receive 3 doses of HPV vaccine to protect against HPV-related disease. The full HPV vaccine series should be given as recommended for best protection.

[3] Meningococcal conjugate vaccine (MCV) is recommended at age 11 or 12. A booster shot is recommended at age 16. Teens who received MCV for the first time at age 13 through 15 years will need a one-time booster dose between the ages of 16 and 18 years. If your teenager missed getting the vaccine altogether, ask their health care provider about getting it now, especially if your teenager is about to move into a college dorm or military barracks.

[4] Everyone 6 months of age and older—including preteens and teens—should get a flu vaccine every year. Children under the age of 9 years may require more than one dose. Talk to your child's health care provider to find out if they need more than one dose.

[5] Pneumococcal Conjugate Vaccine (PCV13) and Pneumococcal Polysaccharide Vaccine (PPSV23) are recommended for some children 6 through 18 years old with certain medical conditions that place them at high risk. Talk to your healthcare provider about pneumococcal vaccines and what factors may place your child at high risk for pneumococcal disease.

[6] Hepatitis A vaccination is recommended for older children with certain medical conditions that place them at high risk. HepA vaccine is licensed, safe, and effective for all children of all ages. Even if your child is not at high risk, you may decide you want your child protected against HepA. Talk to your healthcare provider about HepA vaccine and what factors may place your child at high risk for HepA.

For more information, call toll free 1-800-CDC-INFO (1-800-232-4636) or visit http://www.cdc.gov/vaccines/teens

CDC
U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

AMERICAN ACADEMY OF FAMILY PHYSICIANS
STRONG MEDICINE FOR AMERICA

KPJ JOHOR
SPECIALIST HOSPITAL
39-B, JALAN ABDUL SAMAD, 80100 JOHOR BAHRU, JOHOR, MALAYSIA.
TEL : +607-225 3000 (50 Lines) FAX : +607-224 8213

ACCREDITED HOSPITAL

DR. ALEX TANG TUCK HON
(MMC Full Reg. No. 24171)

CONSULTANT PAEDIATRICIAN
MD(M'sia), DCH(Glasgow), MRCP(UK), M.Min(M'sia)
FRCP(Edin), FCCP(USA), AM(M'sia)

Tel : 07-225 3000 (HOSPITAL)
: 07-225 3014 (CLINIC)
Fax : 07-224 8213 / 07-225 3014
Email : draltang@yahoo.com

Your Ref :

Our Ref :

Date :

Recommended Immunisation Schedule

Age (month)	Immunisation	
1	• General checkup. No injection 普检。无注射	
2	• Triple antigen+polio+Hep B+ Hib (6 in 1) 三种并合针, 小兒麻痺症, 乙型肝炎及脑膜炎疫苗（6 合 1） • Rotavirus 轮状病毒口服疫苗	
3	• Pneumococcal (PncV) 肺炎链球菌疫苗	
4	• Triple antigen+polio+Hep B+ Hib (6 in 1) 三种并合针, 小兒麻痺症, 乙型肝炎及脑膜炎疫苗（6 合 1） • Rotavirus 轮状病毒口服疫苗	
5	• Pneumococcal (PncV) 肺炎链球菌疫苗	
6	• Triple antigen+polio+Hep B+ Hib (6 in 1) 三种并合针, 小兒麻痺症, 乙型肝炎及脑膜炎疫苗（6 合 1） • ±Rotavirus 轮状病毒口服疫苗	
7	• ±Pneumococcal (PncV) 肺炎链球菌疫苗	
9	• MMR 麻疹，腮腺炎及風疹	
12	• MMR-Chickenpox/MMR 麻疹，腮腺炎及風疹 /水痘	
13	• ±Chickenpox 水痘 (see above)	
15	• Booster Pneumococcal (PncV) 肺炎链球菌疫苗	
18	• Booster Double antigen+polio+ Hib 二種并合針, 小兒麻痺症及脑膜炎疫苗	

Years		
6	• Booster Double antigen+polio 二種并合針及小兒麻痺症 • MMR 麻疹，腮腺炎及風疹	
9-13	• HPV (for girls) 人类乳头状瘤病毒疫苗	
15	• Tetanus 破伤风	

(updated Jan 2016)

Types of vaccines

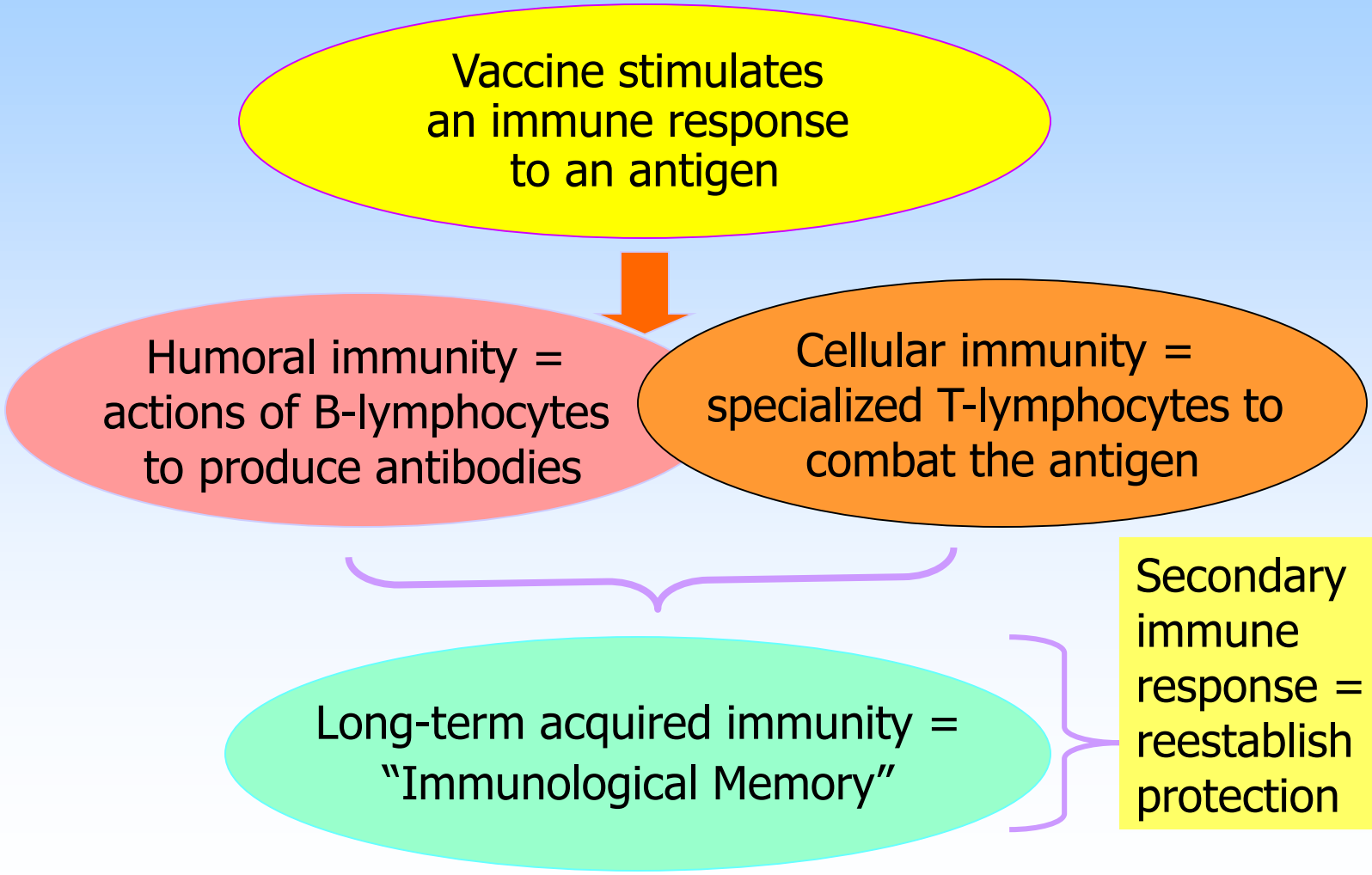
Live vaccines	Live Attenuated vaccines	Killed Inactivated vaccines	Toxoids	Cellular fraction vaccines	Recombinant vaccines
•Small pox variola vaccine	•BCG •Typhoid oral •Plague •Oral polio •Yellow fever •Measles •Mumps •Rubella •Intranasal Influenza •Typhus	•Typhoid •Cholera •Pertussis •Plague •Rabies •Salk polio •Intra-muscular influenza •Japanise encephalitis	•Diphtheria •Tetanus	•Meningococcal polysaccharide vaccine •Pneumococcal polysaccharide vaccine •Hepatitis B polypeptide vaccine	•Hepatitis B vaccine

Vaccination successes

- Vaccination has:
  - Eradicated smallpox[5]
  - Nearly eradicated polio[8]
  - Controlled many major diseases[3]

Ref 3: Plotkin, p 1
Ref 5: AAP, p 554
Ref 8: CDC, p 721

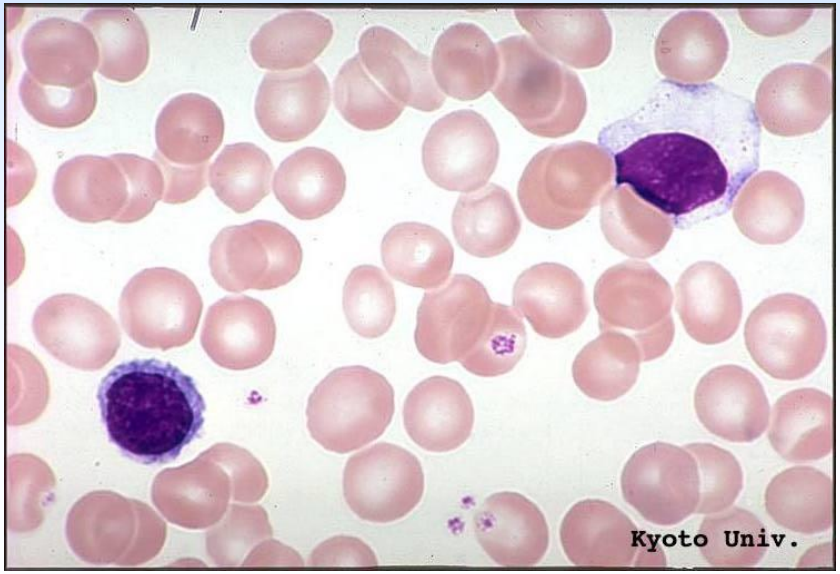
Immunological Memory



The Main Cell Types in the Immune Response

Phagocytes
- Monocytes
- Macrophages
- Polymorphonuclear neutrophils (PMNs)

Lymphocytes
- B cells
- T cells
  - Helper
  - Killer
- Natural Killer cells



Indirect Effect of Vaccination

Vaccines help to reduce the spread of disease through indirect effect, sometimes called “herd immunity” or “community immunity.”

- Once a person is vaccinated against a disease, they are less likely to develop it as well as pass it on to someone who is not immunized.

Disease	R0	Threshold (%)
Mumps	4-7	75–86
Polio	5-7	80–86
Smallpox	5-7	80–85
Diphtheria	6-7	85
Rubella	6-7	83–85
Pertussis	12-17	92–94
Measles	12-18	83–94

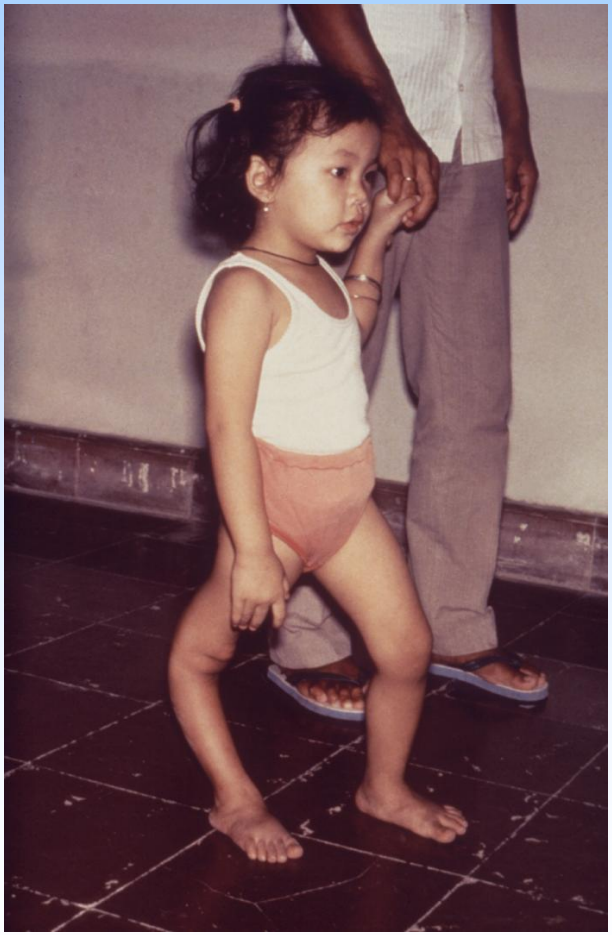
Vaccine-Preventable Diseases and the Vaccines that Prevent Them

Disease	Vaccine	Disease spread by	Disease symptoms	Disease complications
Chickenpox	Varicella vaccine protects against chickenpox.	Air, direct contact	Rash, tiredness, headache, fever	Infected blisters, bleeding disorders, encephalitis (brain swelling), pneumonia (infection in the lungs)
Diphtheria	DTaP* vaccine protects against diphtheria.	Air, direct contact	Sore throat, mild fever, weakness, swollen glands in neck	Swelling of the heart muscle, heart failure, coma, paralysis, death
Hib	Hib vaccine protects against *Haemophilus influenzae* type b.	Air, direct contact	May be no symptoms unless bacteria enter the blood	Meningitis (infection of the covering around the brain and spinal cord), intellectual disability, epiglottitis (life-threatening infection that can block the windpipe and lead to serious breathing problems), pneumonia (infection in the lungs), death
Hepatitis A	HepA vaccine protects against hepatitis A.	Direct contact, contaminated food or water	May be no symptoms, fever, stomach pain, loss of appetite, fatigue, vomiting, jaundice (yellowing of skin and eyes), dark urine	Liver failure, arthralgia (joint pain), kidney, pancreatic, and blood disorders
Hepatitis B	HepB vaccine protects against hepatitis B.	Contact with blood or body fluids	May be no symptoms, fever, headache, weakness, vomiting, jaundice (yellowing of skin and eyes), joint pain	Chronic liver infection, liver failure, liver cancer
Influenza (Flu)	Flu vaccine protects against influenza.	Air, direct contact	Fever, muscle pain, sore throat, cough, extreme fatigue	Pneumonia (infection in the lungs)
Measles	MMR** vaccine protects against measles.	Air, direct contact	Rash, fever, cough, runny nose, pinkeye	Encephalitis (brain swelling), pneumonia (infection in the lungs), death
Mumps	MMR**vaccine protects against mumps.	Air, direct contact	Swollen salivary glands (under the jaw), fever, headache, tiredness, muscle pain	Meningitis (infection of the covering around the brain and spinal cord) , encephalitis (brain swelling), inflammation of testicles or ovaries, deafness
Pertussis	DTaP* vaccine protects against pertussis (whooping cough).	Air, direct contact	Severe cough, runny nose, apnea (a pause in breathing in infants)	Pneumonia (infection in the lungs), death
Polio	IPV vaccine protects against polio.	Air, direct contact, through the mouth	May be no symptoms, sore throat, fever, nausea, headache	Paralysis, death
Pneumococcal	PCV vaccine protects against pneumococcus.	Air, direct contact	May be no symptoms, pneumonia (infection in the lungs)	Bacteremia (blood infection), meningitis (infection of the covering around the brain and spinal cord), death
Rotavirus	RV vaccine protects against rotavirus.	Through the mouth	Diarrhea, fever, vomiting	Severe diarrhea, dehydration
Rubella	MMR** vaccine protects against rubella.	Air, direct contact	Children infected with rubella virus sometimes have a rash, fever, swollen lymph nodes	Very serious in pregnant women—can lead to miscarriage, stillbirth, premature delivery, birth defects
Tetanus	DTaP* vaccine protects against tetanus.	Exposure through cuts in skin	Stiffness in neck and abdominal muscles, difficulty swallowing, muscle spasms, fever	Broken bones, breathing difficulty, death

* DTaP combines protection against diphtheria, tetanus, and pertussis.
** MMR combines protection against measles, mumps, and rubella.

Last updated January 2016 • CS261834-D •

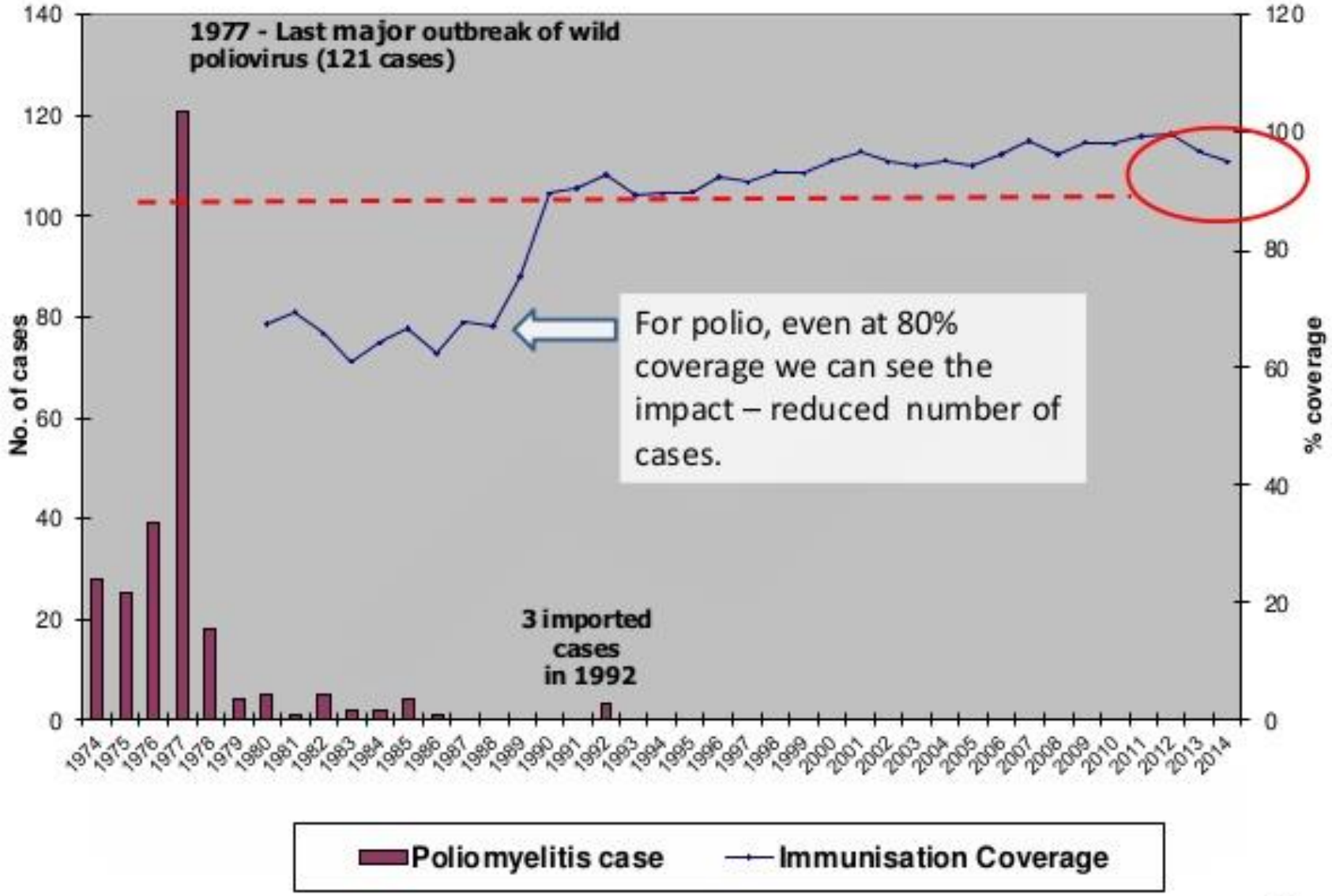
Polio



CDC

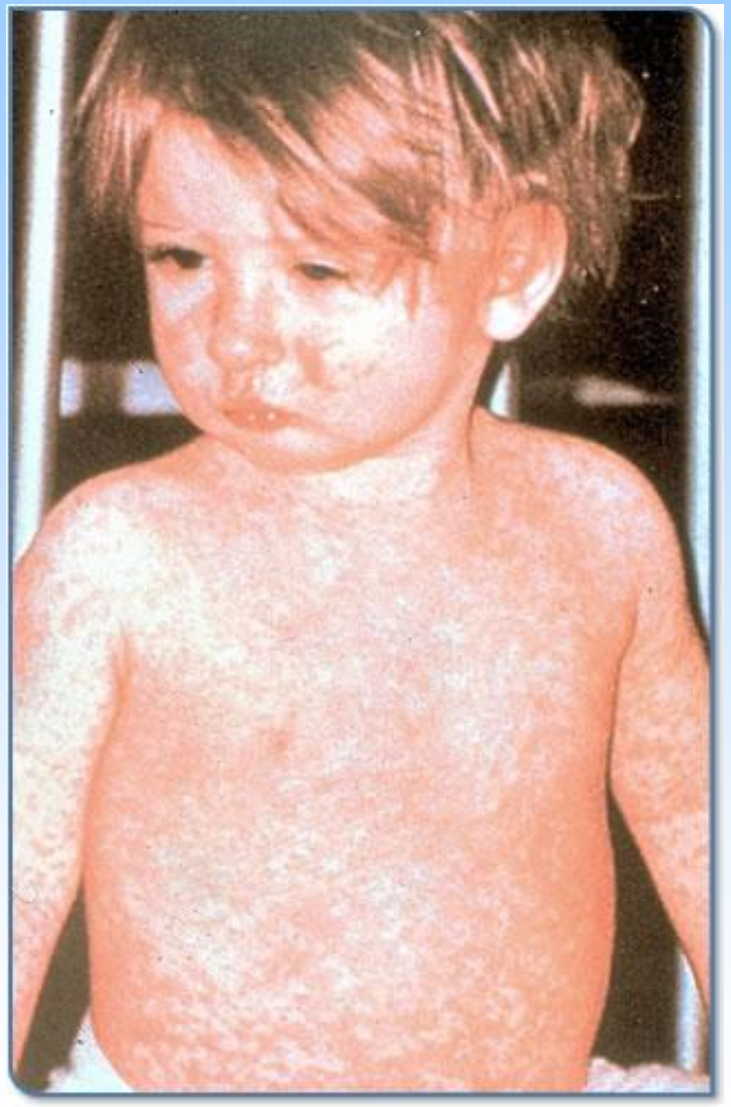
- Affects the nervous system and spinal cord, causing paralysis
- ≈1/200 infections lead to paralysis
- Two types of vaccine
- In 1994, wild polio transmission was interrupted in the Americas

Poliomyelitis in Malaysia , 1974 - 2015



MMR – THE FACTS

- Measles, Mumps & Rubella
- Short memories of deadly Measles epidemic
- 1990 – 45 million Measles; 1 million dead
- 32.8/100,000 (1987) – 2.6/100,000 (1997)
- National epidemic 1999-2000; 10 deaths
- 2004 – PI 270 cases in 6 mths.
- 2 deaths, 45 pneumonia, 8 bro. obliterans

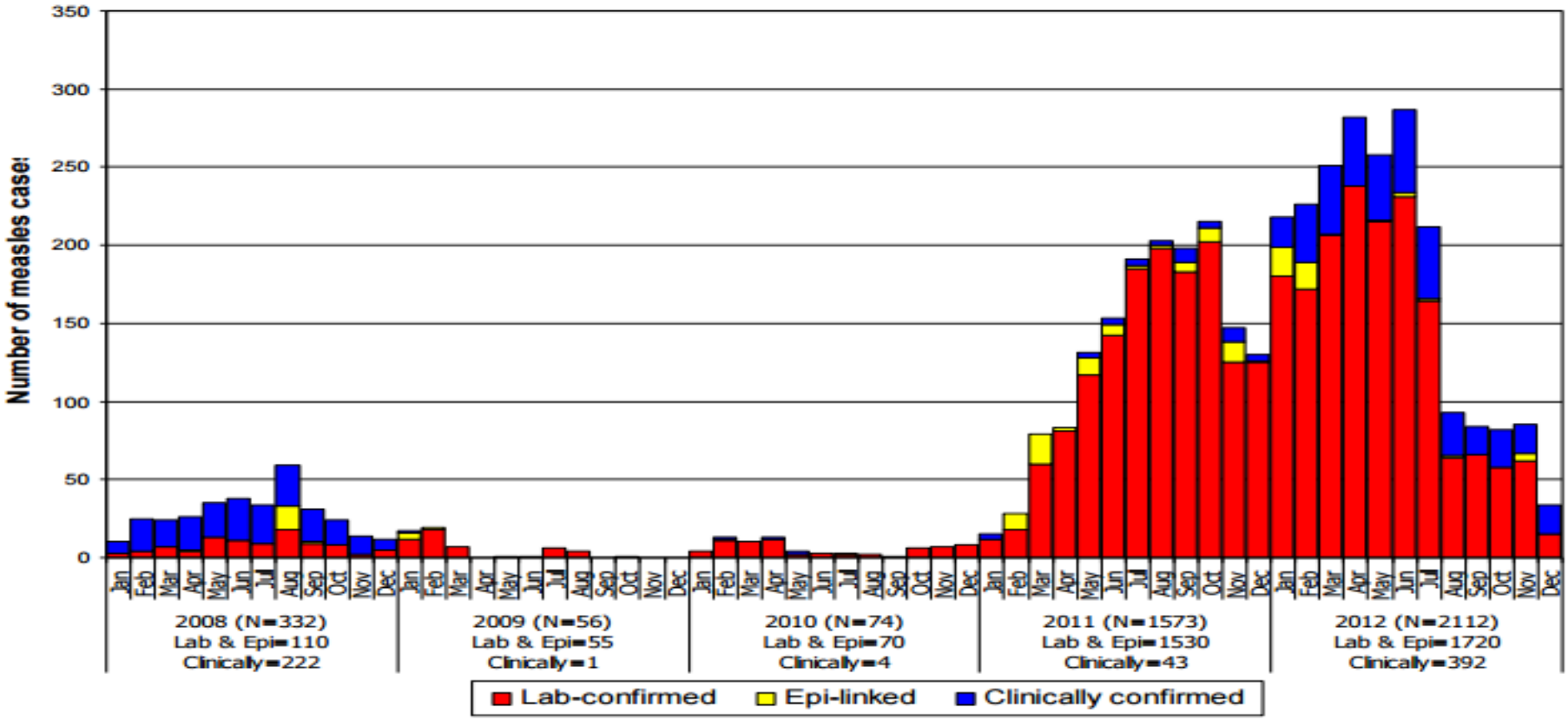


Measles Vaccine in Malaysia

- Measles life attenuated vaccine was first introduced to Malaysia on 1982.
- Malaysia registered 8727 cases of measles in 1980 and this number dropped to 483 in 1998. Most of the cases occurred before the eligible age of immunisation.
- In 2002, measles, mumps and rubella (MMR) was introduced [(3)].

- Malaysia managed to have a coverage rate of 95% for the MMR on 2009.
- In recent years, parent's refusal to vaccination has increased measles in Malaysia from 68 cases in 2010 to 1378 cases in 2011.
- MMR vaccine was thought to be associated with autism or other neurological disorders but it was proven wrong (

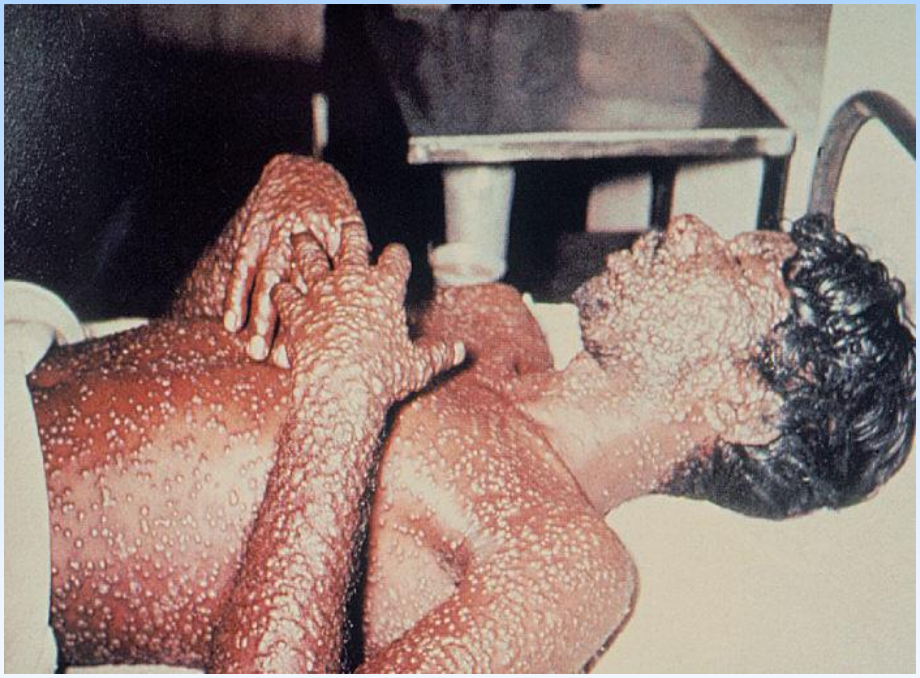
Confirmed measles cases by month of onset, Malaysia, 2008–2012 [1]



Source: National measles and rubella monthly country reports

[1] Reports received for January toDecember 2012

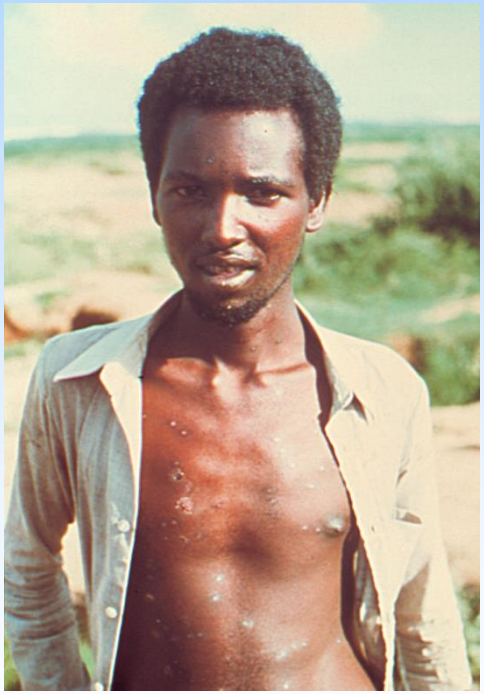
Smallpox



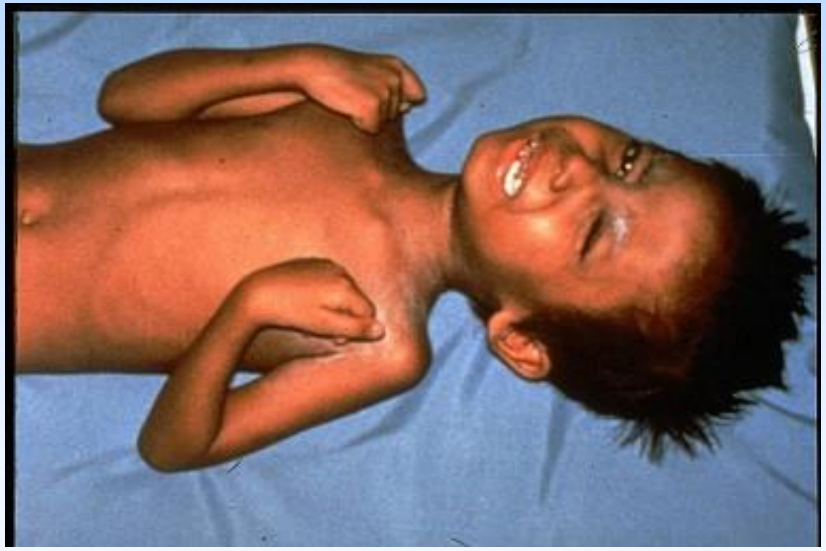
CDC/Barbara Rice

- Caused by variola virus
- A deadly disease
- Most survivors scarred with residual facial marks, some left blind

Last Person Infected with Naturally Occurring Smallpox in Somalia in 1977



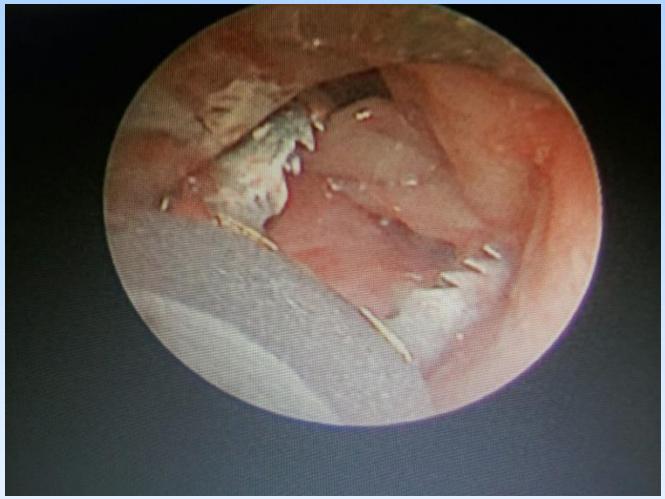
Tetanus

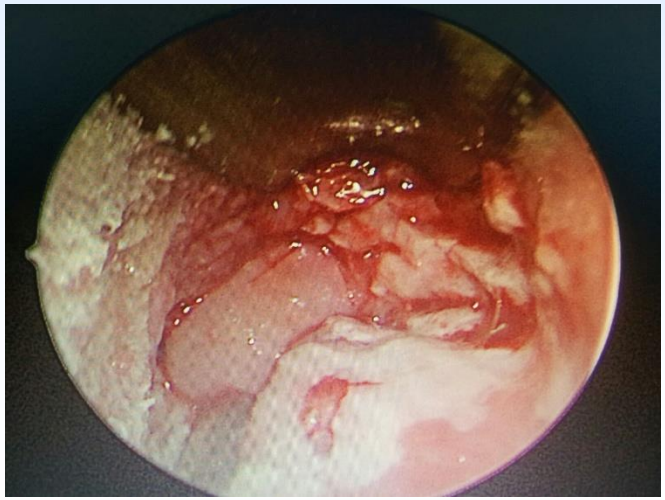


CDC

- Known as lockjaw
- Caused by *Clostridium tetani*
  - Releases a toxin causing muscle spasms
  - May lead to death by suffocation
- Neonatal tetanus occurs most often in developing countries

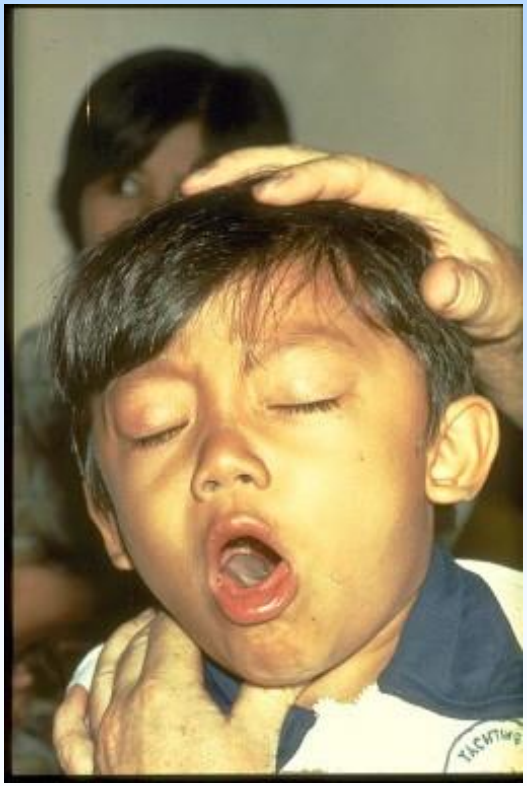
Diphtheria





- Caused by *Corynebacterium diphtheriae*
- Affects upper respiratory tract, also other organs
- Mortality rate 5-10 percent
  - If early treatment, < 1 percent

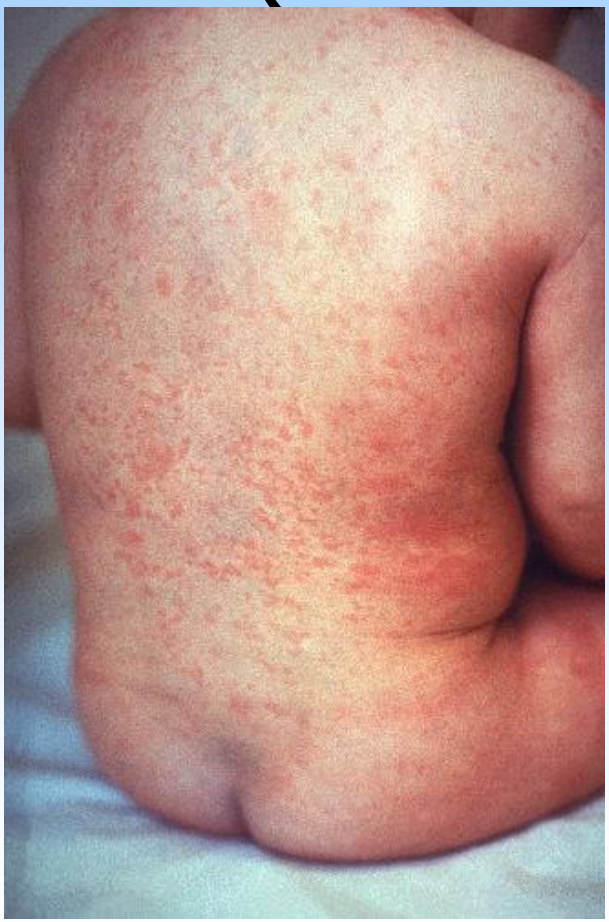
Pertussis ("Whooping Cough")



CDC

- Caused by *Bordetella pertussis*
- Characteristic cough
- Three phases
  - Catartrhal phase
  - Paroxysmal phase
  - Convalescent phase
- Greatest risk in infants and young children

Rubella ("German Measles")



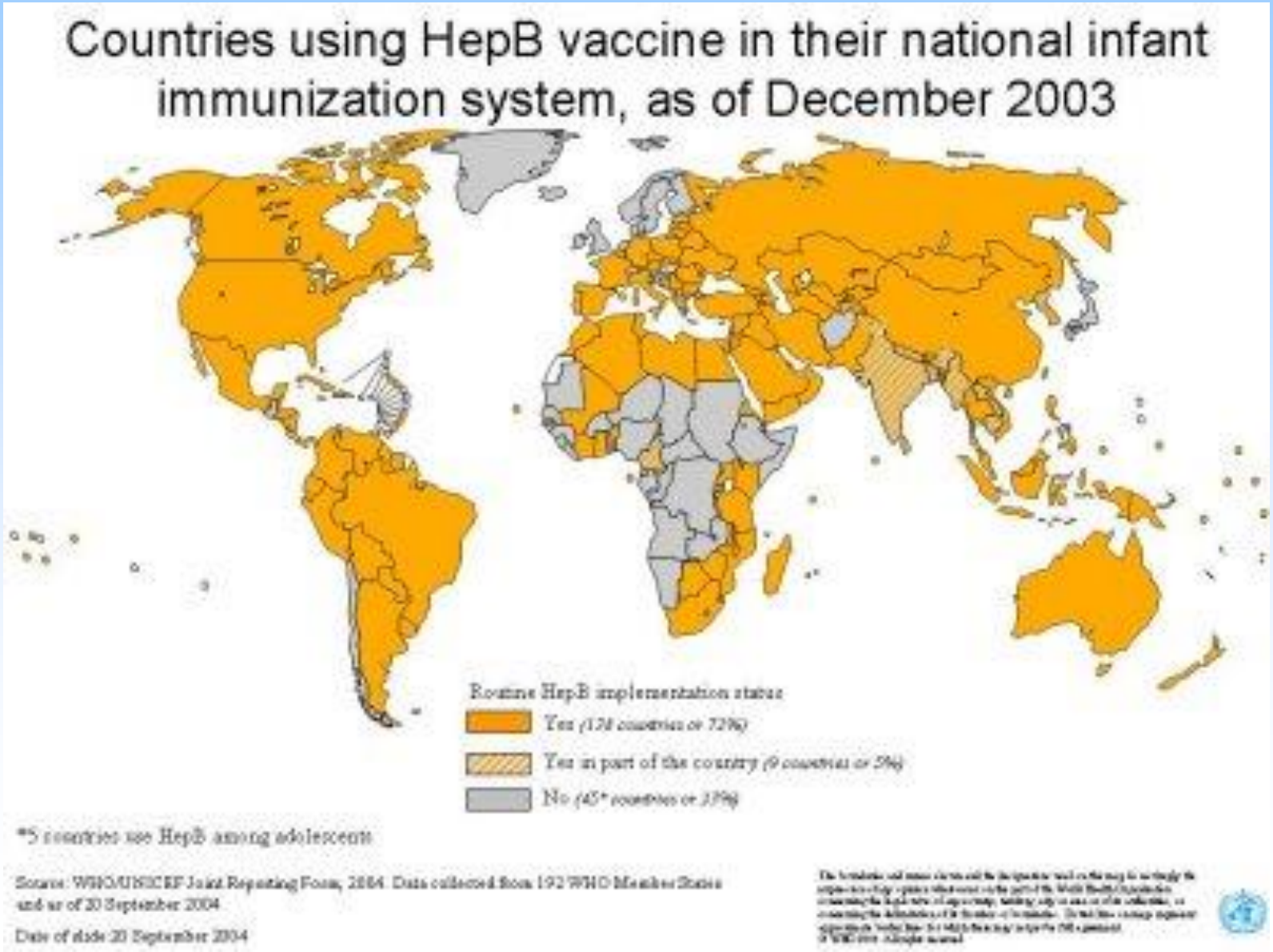
CDC

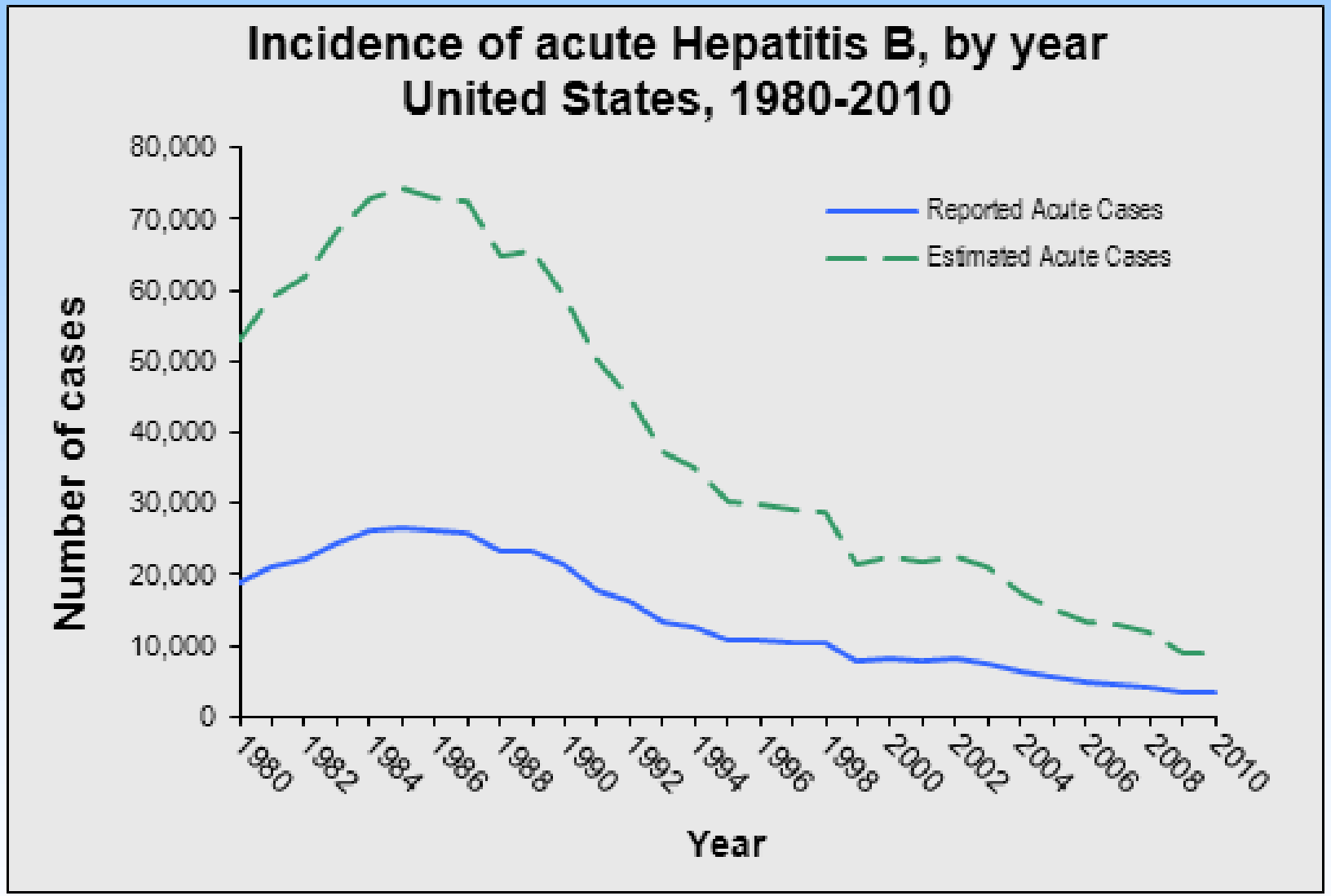
- A generally mild childhood disease caused by a virus
- Infection during pregnancy may result in fetal infection (congenital rubella syndrome)
  - Multiple defects in infants
    - Brain, Heart, Hearing, Liver

Incidence Diphtheria, Measles and Pertussis Malaysia 1980-2016

	1980	1990	2000	2012	2013	2014	2015	2016
Diphtheria	131	9	1	0	4	2	4	31
Measles	8'727	563	6'187	1'868	195	221	1'318	1'569
Pertussis	97	24	42	217	222	500	939	298

Hepatitis B

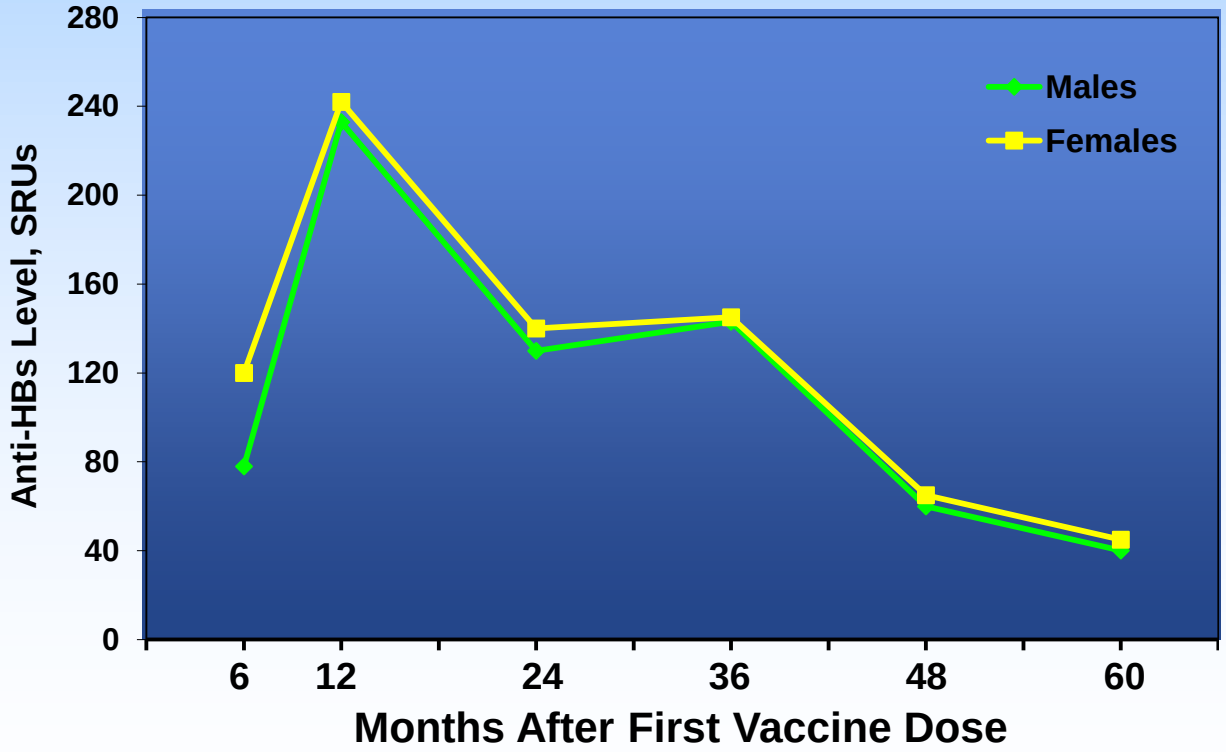

Countries using HepB vaccine in their national infant immunization system, as of December 2003
Routine HepB implementation status
Yes (138 countries or 72%)
Yes in part of the country (9 countries or 5%)
No (45* countries or 23%)
*5 countries use HepB among adolescents
Source: WHO/UNICEF Joint Reporting Form, 2004. Data collected from 192 WHO Member States as of 20 September 2004
Date of slide: 20 September 2004



http://www.cdc.gov/hepatitis/statistic.html (accessed 20 Oct 2011)

Hepatitis B Immune Response Level Through 5 Years Post-Vaccination[1]

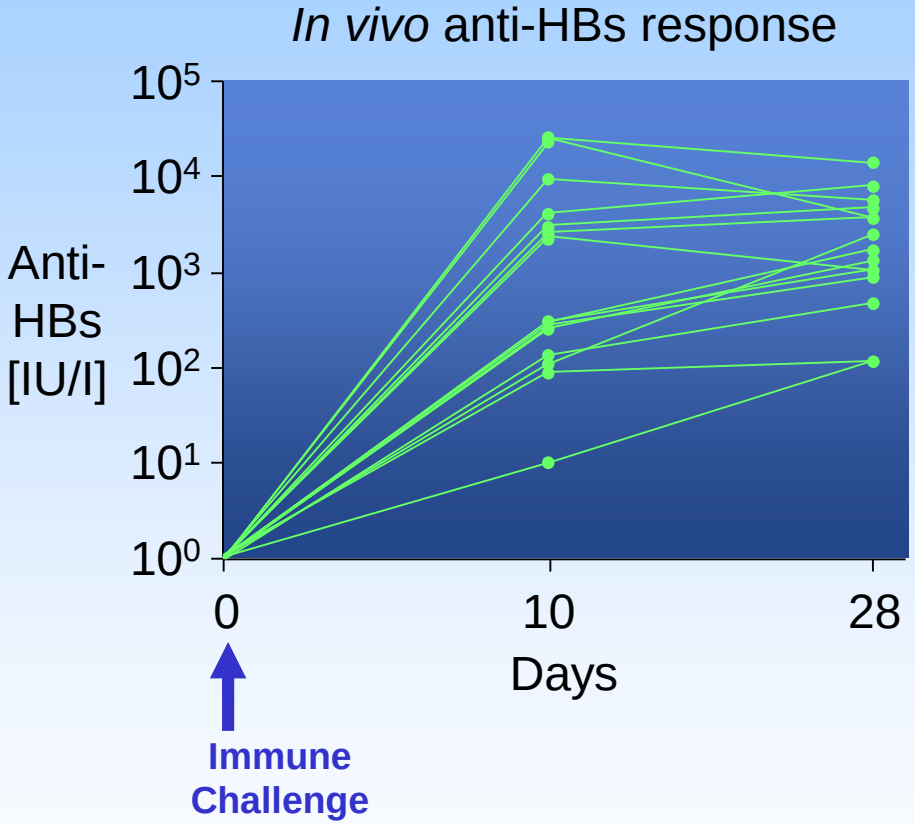
- Protection against hepatitis B virus (HBV) is based on the presence of specific antibodies against anti-HBs antigen.[2]
  - Anti-HBs levels disappear in 10-50% of vaccinees after a few years.[2]
  - No booster has been recommended to date.[3]



1. Wainwright RB, McMahon BJ, Bulkow LR, et al. *JAMA*. 1989;261:2362–2366. 2. Bauer T and Jilg W. *Vaccine*. 2006;24:572-577. 3. Mast E, Mahoney F, Kane M, Margolis H. Hepatitis B vaccine. In: Vaccine, 4th Ed. Plotkin SA, Orenstein WA editors. Elsevier Inc. USA publisher; 2004.

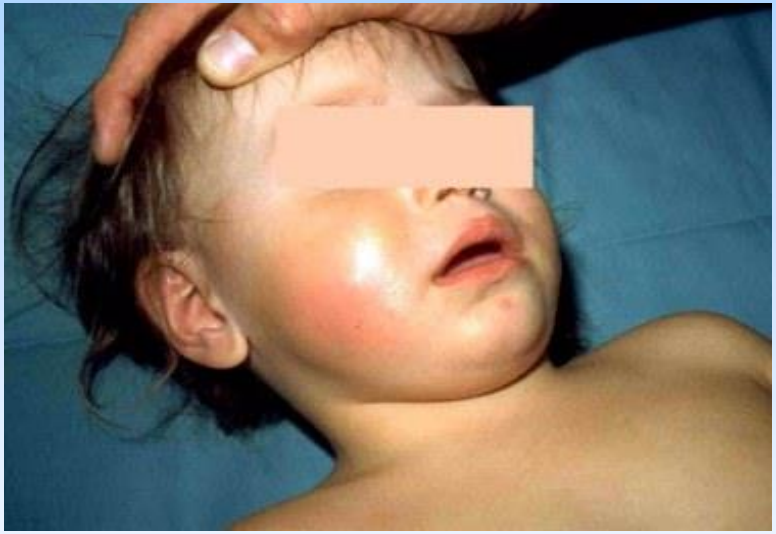
Anti-HBs After Immune Challenge[1]

- Immune memory persists beyond the time at which anti-HBs levels may no longer be detectable.
- Immune memory leads to a rapid anamnestic response after exposure to HBV, which prevents acute infection (and disease).



1. Bauer T, Jilg W. *Vaccine*. 2006;24:572–577.

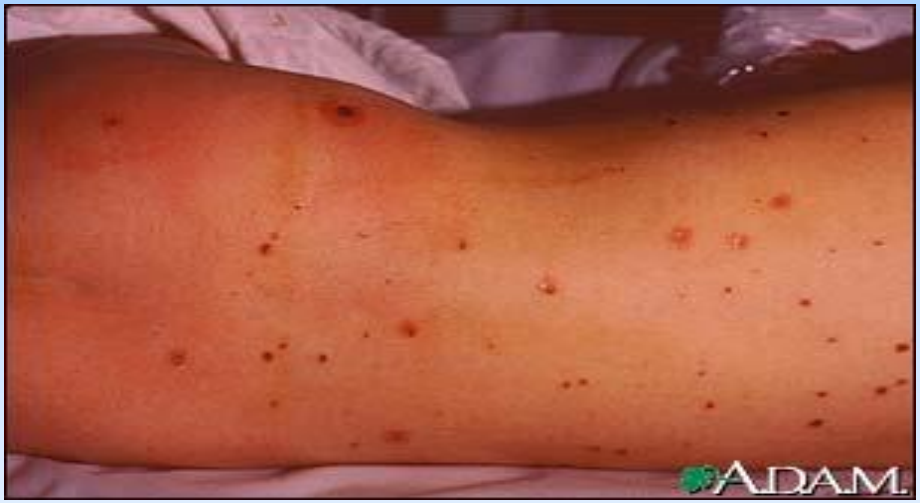
Haemophilus influenzae type b (Hib)



AAP

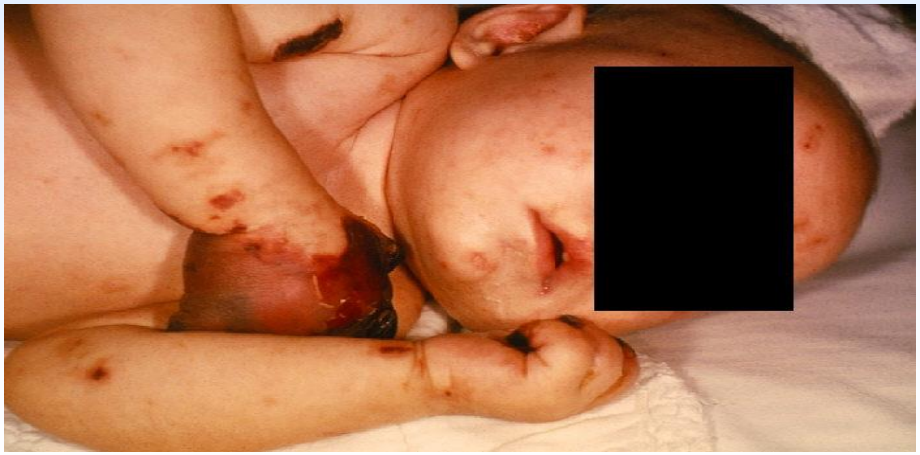
- Causes severe infection in many organs
- Before routine use of effective vaccines, Hib was the leading cause of bacterial meningitis in young children

Neisseria Meningitidis



National Library of Medicine

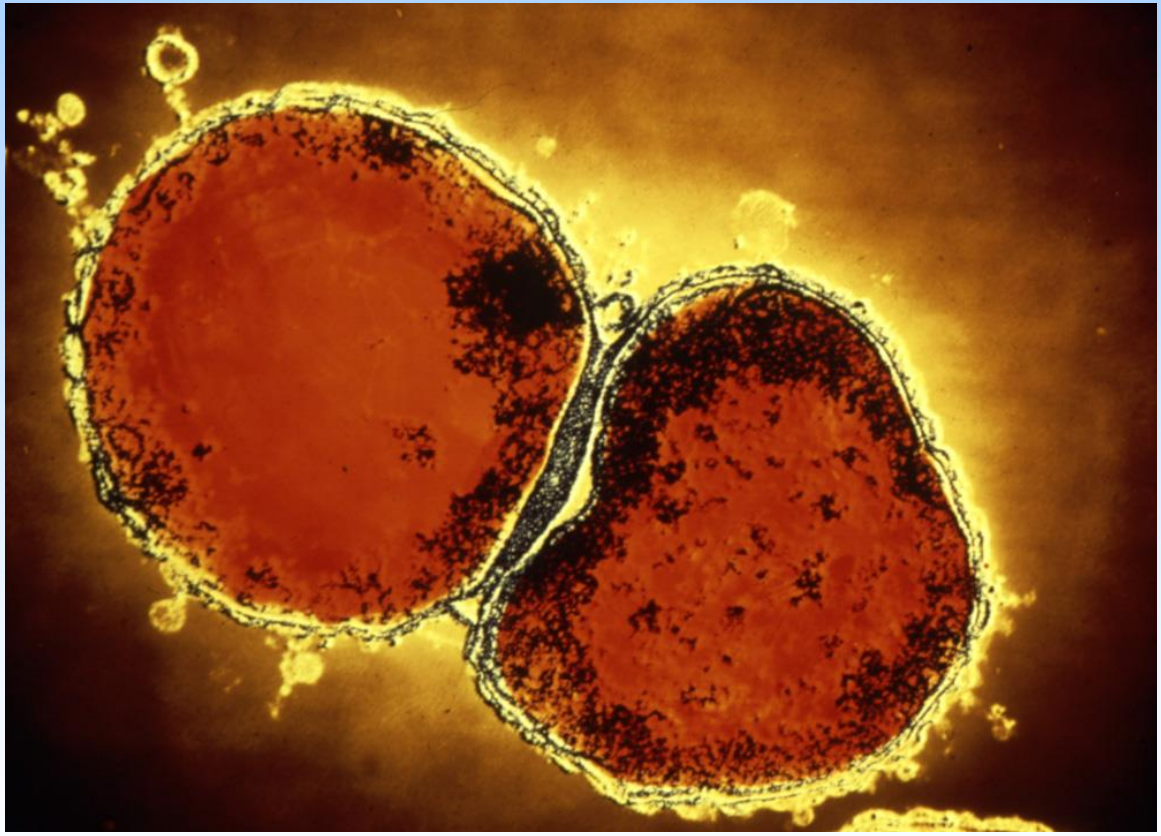
Typical rash of meningococcal septicemia



CDC/Mr. Gust

In this picture, confluent purpuric areas have formed with blistering and necrosis

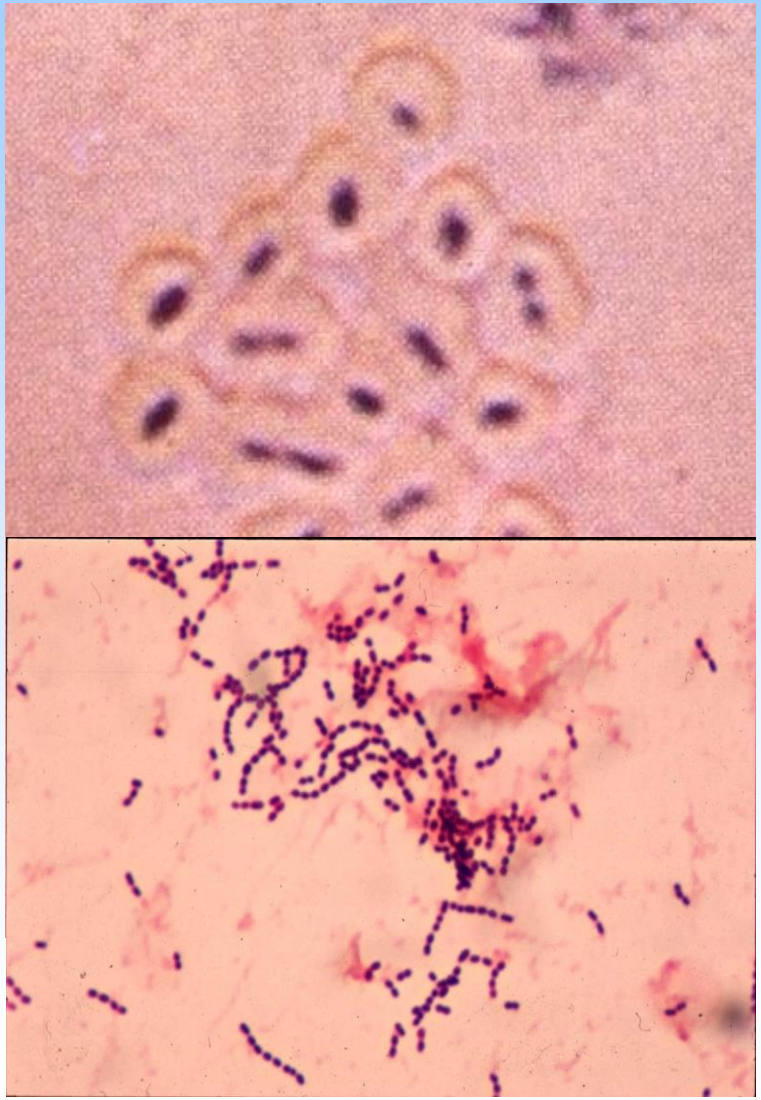
N. meningitidis[63]



Custom Medical Stock Photo, 2003

Streptococcus pneumoniae

- Gram-positive, facultative, encapsulated
- Capsular polysaccharides form the basis of serogroup and serotype classifications
- 90 serotypes
- Leading cause of vaccine-preventable bacterial disease in children
- The most common bacterial cause of
  - Community-acquired pneumonia (17-28%)
  - AOM (２５－５０%)
  - Sinusitis



Pediatr Infect Dis J 1992;11:S7--11

S. pneumoniae Disease Classification

Mucosal Disease	Invasive Disease
Pneumonia	Pneumonia*
Acute otitis media (AOM)	Bacteremia/sepsis
Sinusitis	Meningitis
Conjunctivitis	Other focal, sterile-site infections from hematogenous dissemination

***S. pneumoniae* disease may be classified as mucosal or invasive**

*Pneumonia may be classified as mucosal or invasive disease.
It is invasive if accompanied by bacteremia, pleural effusion, or other invasive complication.

CDC. *Morb Mortal Wkly Rep.* 1997;46(RR-8):1-24.

Impact of Pneumococcal Disease on Children

- Pneumococcal disease can result in[1-5]:
  - Death
  - Paralysis
  - Mental retardation
  - Seizures
  - Learning disabilities
  - Hearing loss
  - Other sequalae

1. Kornelisse RF, et al. *Clin Infect Dis*. 1995;21:1390-1397.
2. CDC. *Morb Mortal Wkly Rep*. 1997;46(RR-8):1-24.
3. Klein JO, et al. *Textbook of Pediatric Infectious Diseases.* 5th ed.; 2004:215-235.
4. Pikis A, et al. *Clin Pediatr (Phila).* 1996;35:72-78.
5. Dodge PR, et al. *N Engl J Med.* 1984;311:869-874.

Risk Factors for IPD

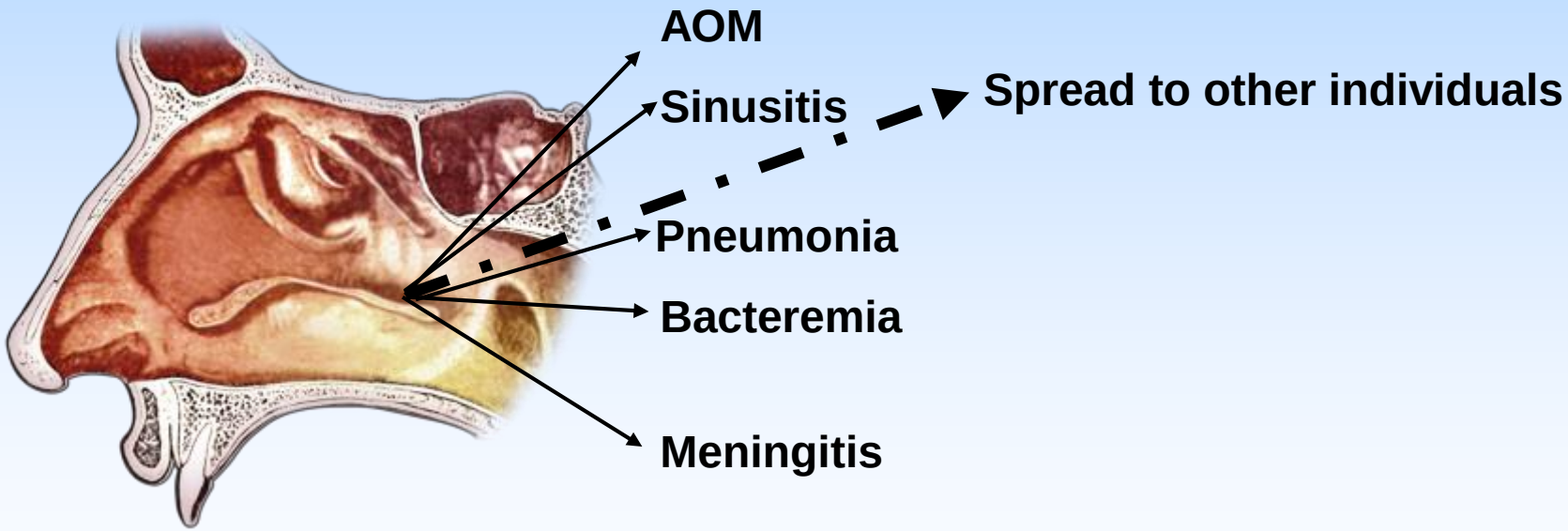
Age[1]	Underlying Medical Conditions[2,3]	Demographic Features[3,4]
• Children ≤2 years of age • Adults ≥65 years of age	• Congenital or acquired immunodeficiency • Sickle cell disease, asplenia, HIV • Pulmonary disease • Chronic heart disease • Chronic renal insufficiency, nephrotic syndrome • Diabetes • Cerebrospinal fistula • Existing or cochlear implants	• Day care attendance • Ethnicity

- **Age is the most important risk factor for pneumococcal disease[1]**

1. CDC. *Morb Mortal Wkly Rep*. 1997;46(RR-8):1-24.
2. Pickering LK. *Red Book.* 26th ed; 2003.
3. CDC. *Morb Mortal Wkly Rep*. 2000;49(RR-9):1-35.
4. Levine OS, et al. *Pediatrics.* 1999;103:1-5.

Nasopharyngeal Colonization

- ***S. pneumoniae*** **can be a normal inhabitant of the nasopharynx[1]**
- **Global nasopharyngeal (NP) colonization/carriage ranges:**
  - **10% to 85% in children <5 years of age[2,3]**
  - **4% to 45% in adults[2-4]**

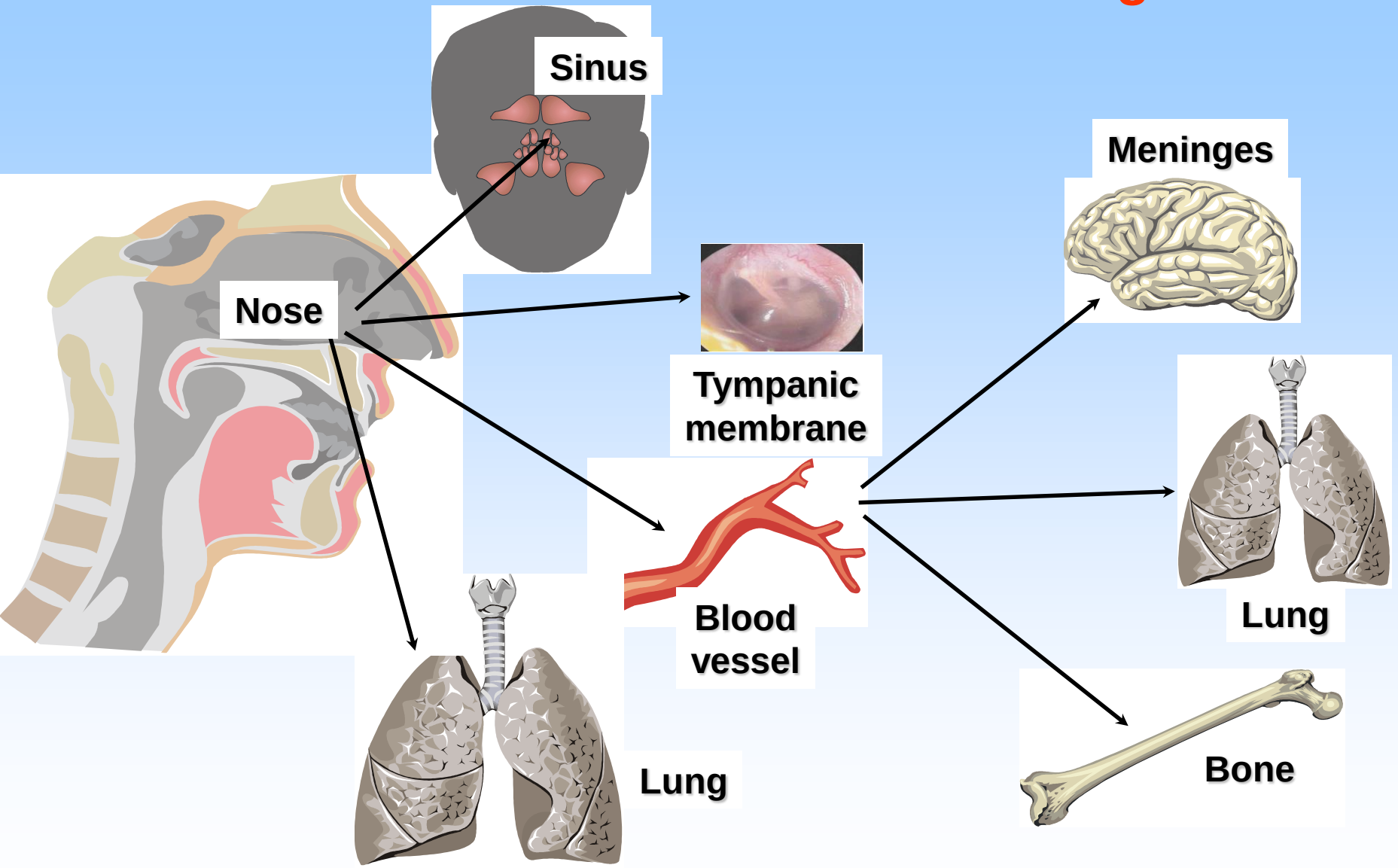


NP colonization is generally a prerequisite for mucosal and invasive pneumococcal disease[2,4]

Image adapted from: http://www.1911encyclopedia.org/images/f/f4/Olfactorysystem-2.jpg.

1. Hull MW, et al. *Infect Dis Clin North Am*. 2007;21:265-282.
2. Cardozo DM, et al. *Braz J Infect Dis*. 2006;10:293-303.
3. Regev-Yochay G, et al. *Clin Infect Dis*. 2004;38:632-639.
4.Chi DH, et al. *Am J Rhinol*. 2003;17:209-214.

Infection Pathogenesis



Invasive Pneumococcal Diseases among Malaysian Children

Tan Kah Kee MD
Pediatric Infectious Disease Consultant
Hospital Tuanku Ja'afar
70300 Seremban

Presented at National Pneumococcal workshop 28 March 2015

Pneumococcal Infections

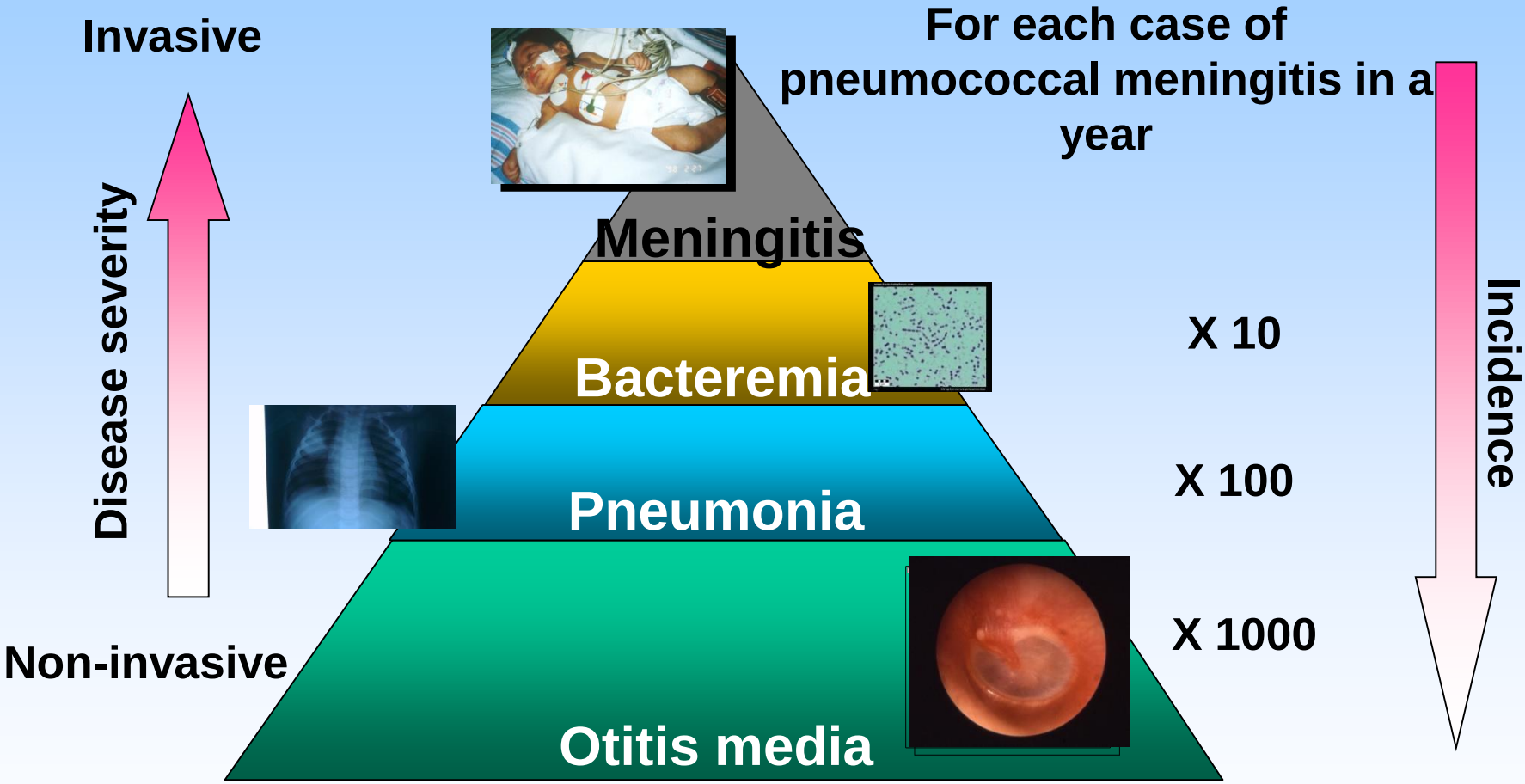
- Burden of disease highest in youngest & oldest sections of population
- Annual deaths : 1 million < 5 years old
- High case fatality rates in meningitis(20-50%)
- 30-60 % of survivors with long-term sequalae
- Treatment complicated by worldwide emergence of penicillin-resistance (IMR 2011: 36.9% penicillin-nonsusceptible)

Streptococcus Pneumoniae

- Common inhabitants of respiratory tract
- > 90 known serotypes
- 6-11 most common serotypes account for >70% of invasive disease worldwide.
- Polysaccharide capsule important virulence factor
- Type-specific antibody is protective

Weekly Epidemiol Record 2012 ; 87:129-144
Johnson HL et al;PLoS Med 2010

S. pneumoniae Disease Burden in Children



Annual incidence of invasive pneumococcal disease in <2 year olds ~150/100,00, United States

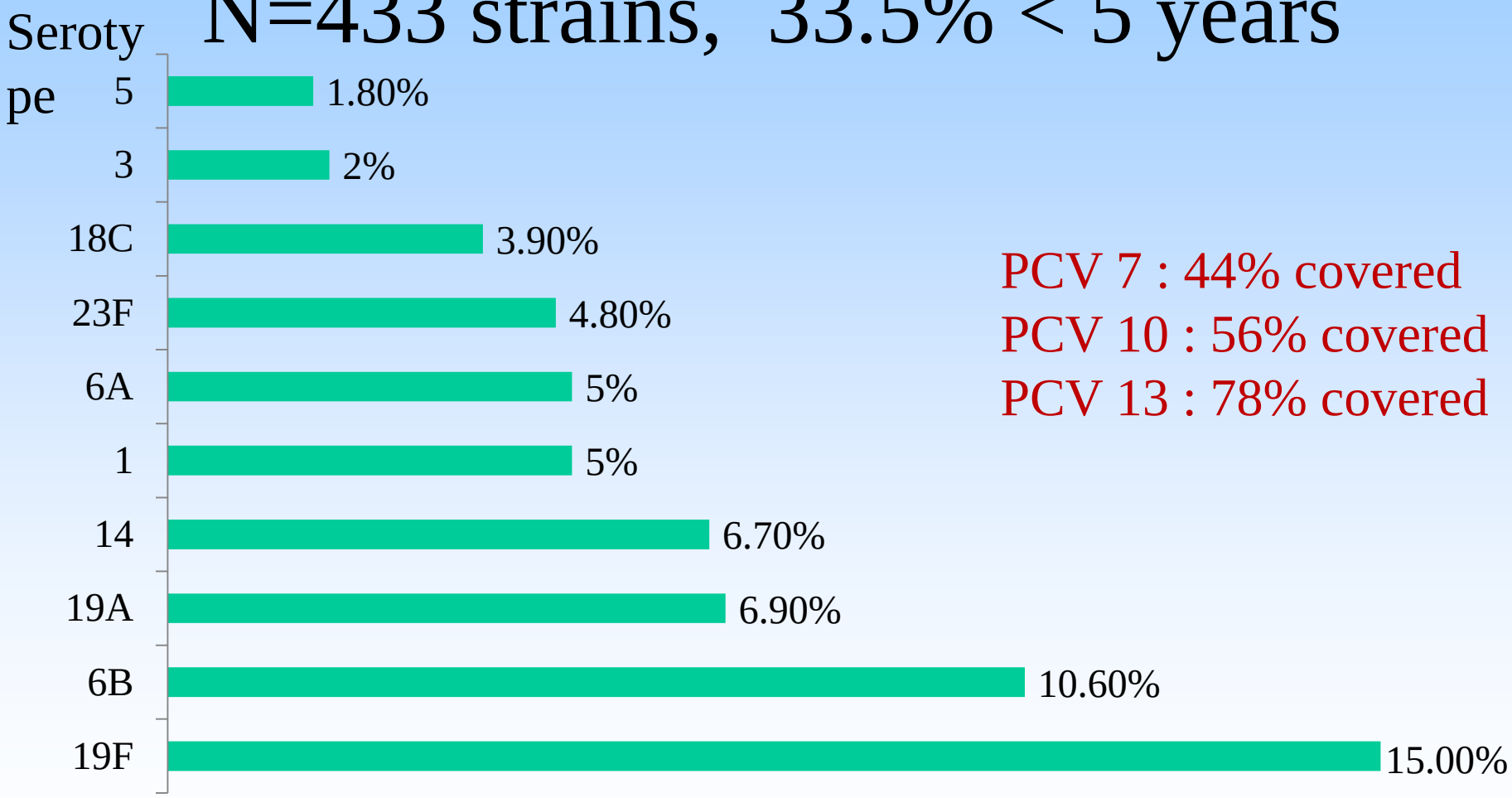
Pediatrics. 2000;106:367-376 & MMWR. 1997;46:1-24

Invasive Pneumococcal Disease Syndromes

- Bacteremia
- Meningitis
- Pneumonia
- Septic arthritis
- Hemolytic uremic syndrome

Copelovitch L et al;Pediatrics 2010 ; 125

Pneumococcal serotypes in Malaysia N=433 strains, 33.5% < 5 years



PCV 7 : 44% covered
PCV 10 : 56% covered
PCV 13 : 78% covered

Yasin MR et al;Vaccine 2011;34

Invasive Pneumococcal Disease in Hospitalised Malaysian Children

- Children with IPD & isolation of Strept. Pneumo. in sterile sites recruited (blood,CSF,pleural fluid, joint,peritoneal & pericardial) between 1 Jan 2007-31 Dec 2009
- 13 participating hospitals nationwide
- Pneumococcal isolates send to IMR for serotyping.
- Quellung reaction for serotyping

Dr Tan Kah Kee, Paediatric Infectious Disease Specialist (used with permission)

Participating Hospitals (N=13)

- HKL
- HIP
- HPP
- HKB
- HTJ
- UMMC
- HKT
- HTAA
- HTAR
- HSB Alor Setar
- HSelayang
- HUS Kuching
- HLikas KK

Dr Tan Kah Kee, Paediatric Infectious Disease Specialist (used with permission)

Results (1) - Demographics

- Total patients with IPD =164 (2008:88 ; 2009:76)
- Gender distribution : Males 56.7%(N=93) ; Females 43.3%(N=71)(M:F = 1.3 : 1)
- Racial distribution : Malays 66.7% , Chinese 7.3% , Indians 1.8% , Ibans 1.8% , Bidayuh(0.6%) , Kadazan 0.6% , Others 21.2%

Dr Tan Kah Kee, Paediatric Infectious Disease Specialist (used with permission)

Results(2) - Demographics

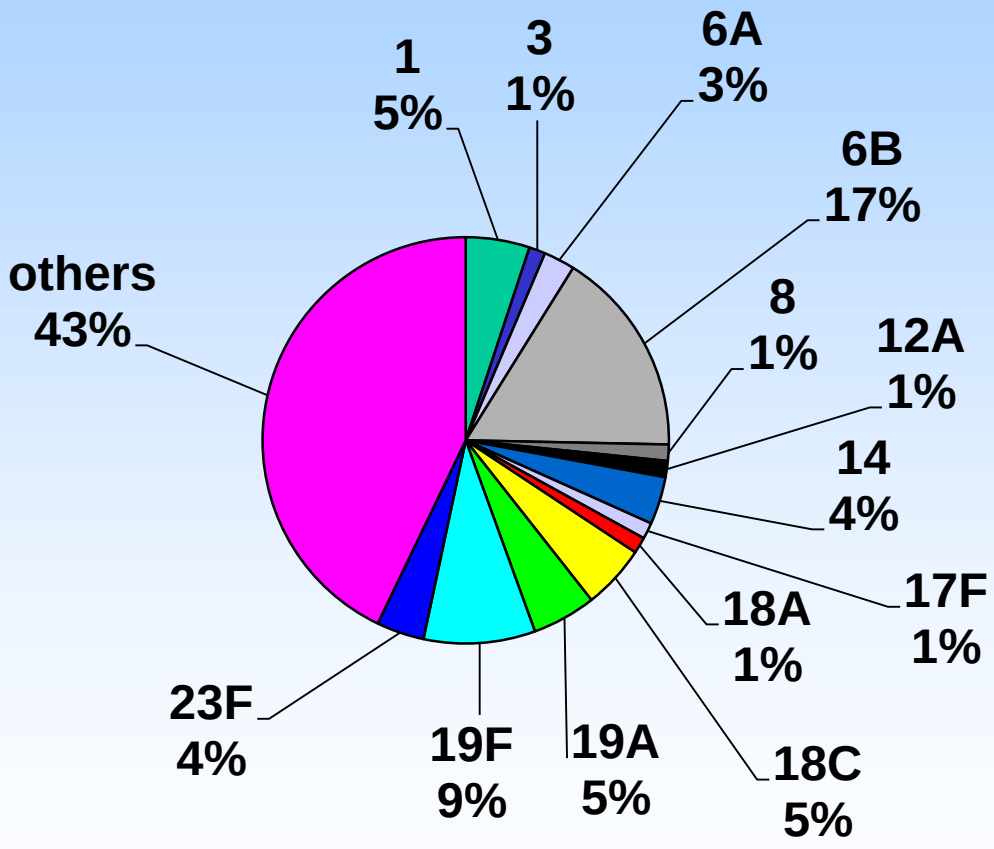
- Mean age = 25.7 mths
- Median age = 15.0 months
- Range = 0-144 months
- Age < 2 yrs = 68.3% (N=112)
- Age < 5 yrs = 86.6%(N=142)

Results(3) – Blood , CSF , Pleural fluid

- Blood culture +ve = 85.6% (N=160)
- CSF culture +ve = 39.6% (N=56)
- CSF antigen +ve(latex) = 55.6%(N=20)
- Pleural fluid culture +ve = 64.3%(N=28)

Dr Tan Kah Kee, Paediatric Infectious Disease Specialist (used with permission)

Results(4)- Pneumococcal Serotypes (N=79)



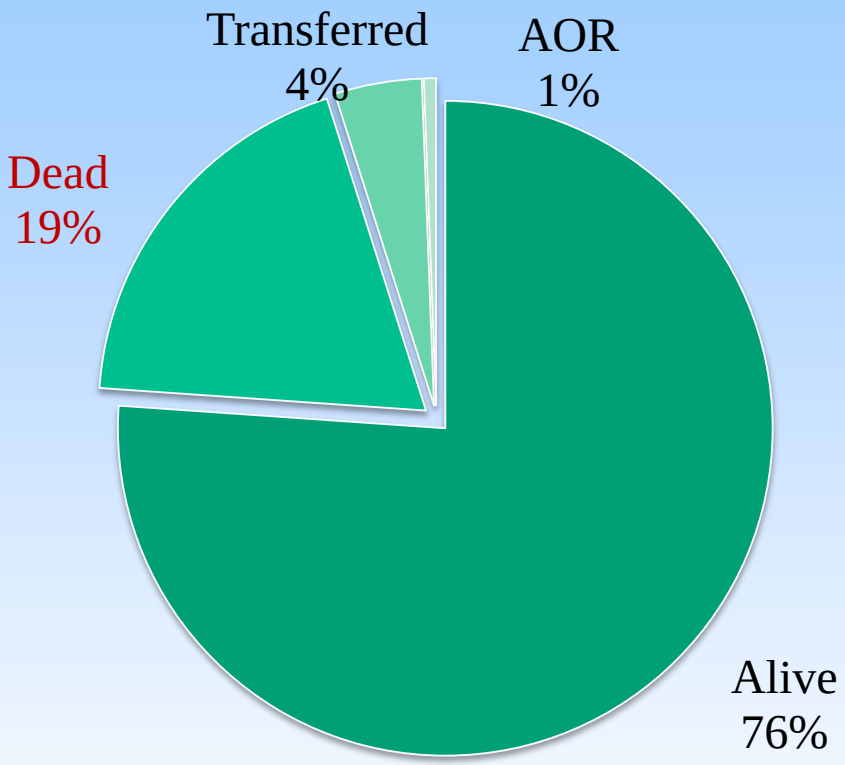
Dr Tan Kah Kee, Paediatric Infectious Disease Specialist (used with permission)

Serotypic Coverage

- 7-valent = 37.9% (30/79)
- 10-valent = 43.0% (34/79)
- 13-valent = 51.8% (41/79)

Dr Tan Kah Kee, Paediatric Infectious Disease Specialist (used with permission)

Outcome



13%(N=21) has neurological sequalae at discharge

Dr Tan Kah Kee, Paediatric Infectious Disease Specialist (used with permission)

Ventilatory Support

- 44%(N=72) required ventilatory support
- Median duration = 4 days
- Range = 1-43 days

Dr Tan Kah Kee, Paediatric Infectious Disease Specialist (used with permission)

Penicillin Susceptibility

- Blood isolates : S 84.5% I 2.3% R 13.2%
- CSF isolates : S 89.5% I 10.5% R 0%

Dr Tan Kah Kee, Paediatric Infectious Disease Specialist (used with permission)

Study Limitations

- Mild cases may not be captured
- Private hospital cases not included
- Culture method limited by prior antibiotics
- Molecular methods during study not available

Dr Tan Kah Kee, Paediatric Infectious Disease Specialist (used with permission)

Summary of findings

- IPD is severe in Malaysian children
- Significant mortality
- Serotypic coverage moderate
- Penicillin resistance moderate

Dr Tan Kah Kee, Paediatric Infectious Disease Specialist (used with permission)

Conclusions

- Invasive pneumococcal disease is a serious cause of morbidity & mortality in Malaysian children
- Different spectrum of pneumococcal infection seen
- Mortality does occur in spite of appropriate therapy
- Penicillin resistance moderate
- Preventive measure by vaccination needs urgent consideration

Dr Tan Kah Kee, Paediatric Infectious Disease Specialist (used with permission)

Perubahan Jadual Imunisasi MMR

Jadual Lama :

IMUNISASI	Umur (Bulan)										(Tahun)		
	0	1	2	3	5	6	9	12	18	21	7	13	15
BCG	Dos 1										Tiada parut		
Hepatitis B	Dos 1	Dos 2				Dos 3							
DTaP			Dos 1	Dos 2	Dos 3				Booster				
Hib			Dos 1	Dos 2	Dos 3				Booster				
Polio (IPV)			Dos 1	Dos 2	Dos 3				Booster				
Measles						Sabah sahaja							
MMR								Dos 1					
MR											Booster		
DT											Booster		
OPV													
HPV												Perempuan sahaja	
Tetanus													Booster

Jadual Baru :

IMUNISASI	Umur (Bulan)										(Tahun)		
	0	1	2	3	5	6	9	12	18	21	7	13	15
BCG	Dos 1												
Hepatitis B	Dos 1	Dos 2				Dos 3							
DTaP			Dos 1	Dos 2	Dos 3				Booster				
Hib			Dos 1	Dos 2	Dos 3				Booster				
Polio (IPV)			Dos 1	Dos 2	Dos 3				Booster				
Measles						Sabah sahaja							
MMR							Dos 1	Dos 2					
MR											Booster		
DT											Booster		
OPV													
HPV												Perempuan sahaja	
Tetanus													Booster
JE (Sarawak)							Dos 1			Dos 2			

Jadual baru Imunisasi MMR digunakan bermula tahun 2016

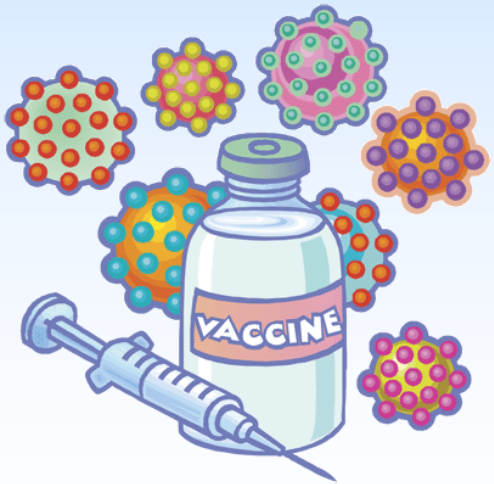
Diterbitkan oleh :
Bahagian Pendidikan Kesihatan
Kementerian Kesihatan Malaysia
www.infosihat.gov.my I www.myhealth.gov.my

Pneumococcal
Rotavirus
Chickenpox
Meningococcal

Some concerns of parents

Common questions about vaccines

- Do I need to vaccinate my child against diseases that aren't common anymore?[15]
- Are vaccines safe?[16]
- Do vaccines cause autism?[16]
- Are preservatives found in vaccines?[16]
- Can my child get a disease from a vaccine?[16]
- My child is allergic to eggs
- Are vaccines halal?



Ref 15: CDC, p 8

Ref 16: IOM, p 1, 4

Some vaccine side effects

- Common side effects[5]
  - Redness, swelling, and pain at injection site
  - Low-grade fever
- Uncommon, serious side effects[5]
  - Allergic reaction

Ref 5: AAP, p 38, 46

Advice on vaccination of those with egg allergy

- Influenza vaccines (containing <1 μg of ovalbumin per dose) can be given to most people with egg allergy, including anaphylaxis
  - Those with severe allergy should be vaccinated in settings where anaphylaxis can be recognised/treated
- MMR vaccines can be given to any egg allergic person

“Natural Immunity” (Getting Immunity By Getting Sick)

- What is it? Does it work? What are the costs?
- Some people believe that it’s better to get a disease naturally than to be vaccinated against it.
- One theory is that chickenpox, for example, helps mature the immune system.
- And a mature immune system should be better able to fight infection from diseases, right?
- What are the facts about natural immunity?

Choosing Natural Immunity Is Risky!

- Chickenpox kills children in the United States every year.
- Before a chickenpox vaccine was licensed, almost 7,000 children per year were hospitalized for serious complications of chickenpox like encephalitis, hepatitis, flesh eating-strep, and toxic shock syndrome.

Choosing Natural Immunity Can Be Risky To Others.

- A parent who is not immune to chickenpox can easily catch the disease from an infected child. 1 in 5 adults who get chickenpox develops pneumonia, which can be deadly.
- If a “routine” disease like chickenpox can have these results, natural immunity is a risky alternative to vaccination.

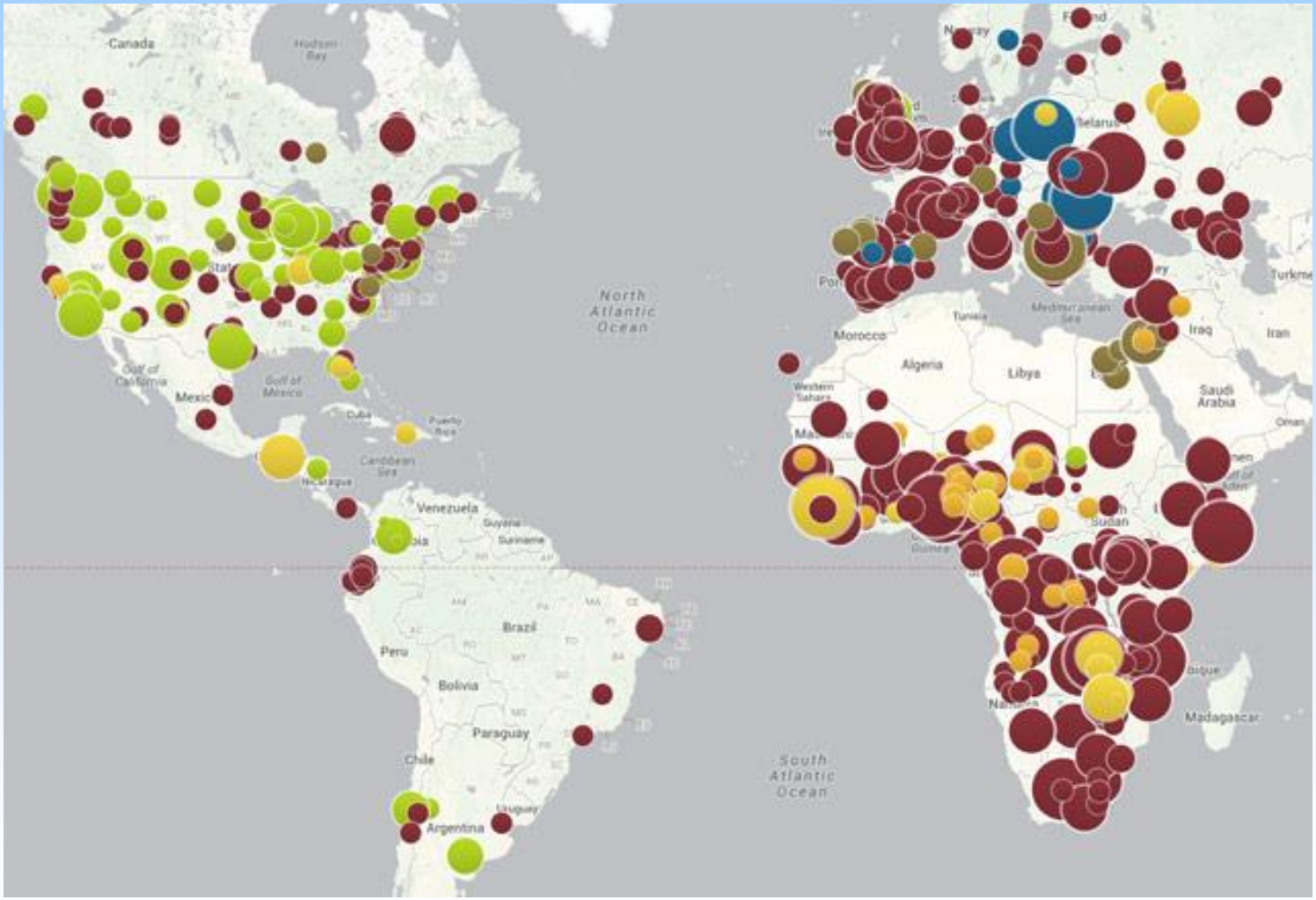
Childhood Diseases Carry Serious Risks.

- Hib or pneumococcal disease can cause bacterial meningitis, leading to brain damage or death.
- Pertussis (whooping cough) can cause coughing spells so bad that it is hard for infants to eat, drink, or breathe. These spells can last for weeks. Pertussis can lead to pneumonia, seizures, brain damage, and death.
- Polio may lead to paralysis and death. Polio used to be very common in the United States, killing and paralyzing thousands of people a year.
- Tetanus (lockjaw) infection can cause painful tightening of the muscles. It can lead to "locking" of the jaw so the victim cannot open his mouth or swallow. Tetanus results in death in about 10% of cases.

HERD IMMUNITY

- Children who are immunised are protected from the disease. They cannot get the disease and they cannot give the disease
- If enough children are vaccinated against a disease then the disease cannot spread into the community.
- This is called “herd immunity”

Anti Immunization Movement



Measles outbreaks (purple) worldwide and whooping cough (green) in the U.S. 2008-2014 (Council on Foreign Relations),

Accessed 23 Jan 2014. http://www.latimes.com/business/hiltzik/la-fi-mh-antivaccination-movement-20140120,0,5576371.story#ixzz2rHqM1Aec

New Straits Times

3 minute read

Johor baby dies of diphtheria, wasn't vaccinated

A 14-month-old baby girl has died, believed to be due to diphtheria, on Monday. (NSTP Archive)

By Ibrahim Isa - October 17, 2018 @ 10:53pm

JOHOR BAHRU: A 14-month-old baby girl has died, believed to be due to diphtheria, on Monday.

Health director-general Datuk Dr Noorhisham Abdullah in a statement said the baby did not receive diphtheria immunisation because the family had refused it.

"The child started out having fever and sore throat on Oct 4 and was taken to a private clinic by her mother for initial treatment on Oct 11. The next day, the child was taken to the emergency unit of a hospital after having breathing difficulties and loss of appetite.

"The patient was then admitted into the paediatric ward and later the paediatric's intensive care unit on Oct 13 as she had become weaker and needed respiratory aid," Noorhisham said.

On Monday, the patient succumbed to severe diphtheria with multiorgan failure, he informed.

He added that test was done on a throat swab sample of the patient and it showed the presence of the corynebacterium diphtheriae bacteria and the ministry was now waiting for lab confirmation.

RECOMMENDED

#Showbiz: Mamat regains consciousness, partially

Two senior citizens die while waiting for free food coupons at ICC Pudu

Malaysia doesn't need a Constitutional Court, says minister

Malaysia doesn't need a Constitutional Court, says minister

New leads in stabbing of Maria Chin's

MMR and Autism

- The original paper (now RETRACTED) – Lancet, 1998

1. *Autism and measles, mumps, and rubella vaccine: no epidemiological evidence for a causal association* - Lancet, 1999
2. *Time trends in autism and in MMR immunization coverage in California* - JAMA, 2001
3. *A population-based study of measles, mumps, and rubella vaccination and autism* - NEJM, 2002
4. *Neurologic disorders after measles-mumps-rubella vaccination* - Pediatrics, 2002
5. *MMR vaccination and pervasive developmental disorders: a case-control study* - Lancet, 2004
6. *Age at first measles-mumps-rubella vaccination in children with autism and school-matched control subjects: a population-based study in metropolitan Atlanta* - Pediatrics, 2004
7. *Vaccines for measles, mumps and rubella in children* - Cochrane Collaboration, 2005
8. *Vaccines for measles, mumps and rubella in children* - Cochrane Collaboration, 2012
9. *How the case against the MMR vaccine was fixed by Brian Deer*, BMJ, 2011
10. *Wakefield's article linking MMR vaccine and autism was fraudulent* - BMJ Editorial, 2011

The case for vaccines

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

THE LANCET

The NEW ENGLAND JOURNAL of MEDICINE

厚生労働省 EUPHA

NHS

MINISTRY OF HEALTH

ncirs

THE COCHRANE COLLABORATION®

NIH

World Health Organization

VS

The case against

Every government, every major health agency of every country around the world, the consensus of respectable, peer-reviewed medical journals, medical doctors, researchers and scientists

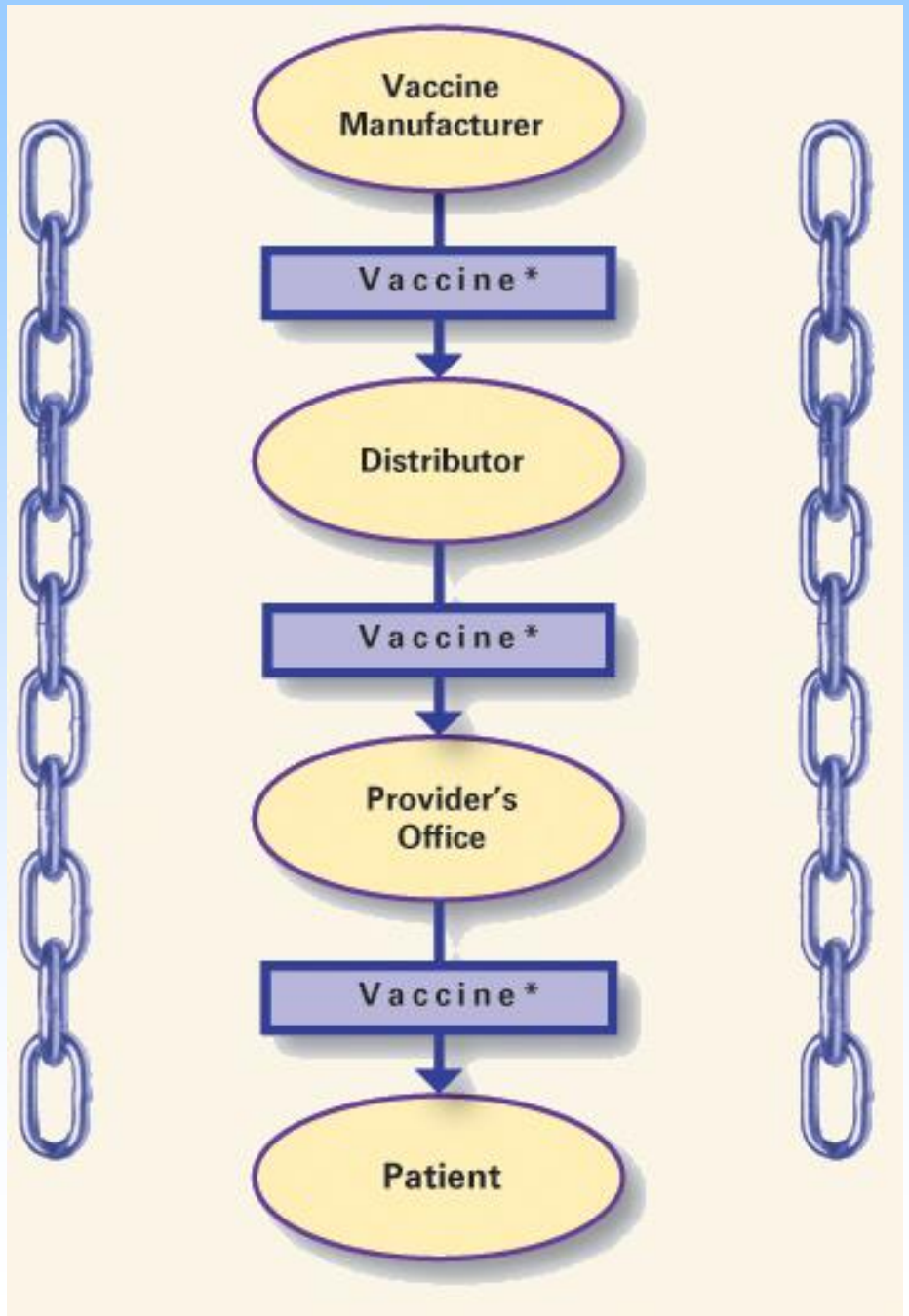
VS

a handful of pseudoscientific paperbacks and self-published bunk

Refutations to Anti-Vaccine Memes

The Vaccine Meme Machine

The Cold Chain


Vaccine Manufacturer
Vaccine*
Distributor
Vaccine*
Provider's Office
Vaccine*
Patient


VACCINE


091AM
4JUL09


091AM
4JUL09


Store in Freezer
5°F (-15°C) or colder
MMRV*
Varicella*
Zoster*
MMR*,+
Store in Refrigerator
35°F–46°F (2°–8°C)
MMR*,+
Inactivated Combination Vaccines
Vaccines containing Diphtheria, Tetanus, and/or acellular Pertussis
Hepatitis A
Hepatitis B
Hib
HPV*
Influenza (LAIV & TIV)
IPV
Meningococcal (MCV & MPSV)
Pneumococcal (PCV & PPV)
Rotavirus
* Do not expose to light.
+ Unreconstituted lyophilized (freeze-dried) MMR may be frozen or refrigerated.

Dengvaxia (Sanofi)

Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia: a phase 3, randomised, observer-masked, placebo-controlled trial

*Maria Rosario Capeding, Ngoc Huu Tran, Sri Rezeki S Hadinegoro, Hussain Imam HJ Muhammad Ismail, Tawee Chotpitayasunondh, Mary Noreen Chua, Chan Quang Luong, Kusnandi Rusmil, Dewa Nyoman Wirawan, Revathy Nallusamy, Punnee Pitisuttithum, Usa Thisyakorn, In-Kyu Yoon, Diane van der Vliet, Edith Langevin, Thelma Laot, Yanee Hutagalung, Carina Frago, Mark Boaz, T Anh Wartel, Nadia G Tornieporth, Melanie Saville, Alain Bouckenooghe, and the CYD14 Study Group**

Lancet 2014; 384: 1358–65
Published Online
July 11, 2014
http://dx.doi.org/10.1016/

Summary

Background An estimated 100 million people have symptomatic dengue infection every year. This is the first report of a phase 3 vaccine efficacy trial of a candidate dengue vaccine. We aimed to assess the efficacy of the CYD dengue vaccine against symptomatic, virologically confirmed dengue in children.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy and Long-Term Safety of a Dengue Vaccine in Regions of Endemic Disease

S.R. Hadinegoro, J.L. Arredondo-García, M.R. Capeding, C. Deseda, T. Chotpitayasunondh, R. Dietze, H.I. Hj Muhammad Ismail, H. Reynales, K. Limkittikul, D.M. Rivera-Medina, H.N. Tran, A. Bouckenooghe, D. Chansinghakul, M. Cortés, K. Fanouillere, R. Forrat, C. Frago, S. Gailhardou, N. Jackson, F. Noriega, E. Plennevaux, T.A. Wartel, B. Zambrano, and M. Saville, for the CYD-TDV Dengue Vaccine Working Group*

ABSTRACT

BACKGROUND

A candidate tetravalent dengue vaccine is being assessed in three clinical trials involving more than 35,000 children between the ages of 2 and 16 years in Asian–Pacific and Latin American countries. We report the results of long-term follow-up interim analyses and integrated efficacy analyses.

METHODS

We are assessing the incidence of hospitalization for virologically confirmed dengue as a surrogate safety end point during follow-up in years 3 to 6 of two phase 3 trials, CYD14 and CYD15, and a phase 2b trial, CYD23/57. We estimated vaccine efficacy using pooled data from the first 25 months of CYD14 and CYD15.

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Saville at Sanofi Pasteur, 2 Ave. Pont Pasteur, 69367 Lyon CEDEX 07, France, or at melanie.saville@sanofipasteur.com.

*A complete list of investigators in the CYD-TDV Dengue Vaccine Working Group is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on July 27, 2015, at NEJM.org.

Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia: a phase 3, randomised, observer-masked, placebo-controlled trial

*Maria Rosario Capeding, Ngoc Huu Tran, Sri Rezeki S Hadinegoro, Hussain Imam HJ Muhammad Ismail, Tawee Chotpitayasunondh, Mary Noreen Chua, Chan Quang Luong, Kusnandi Rusmil, Dewa Nyoman Wirawan, Revathy Nallusamy, Punnee Pitisuttithum, Usa Thisyakorn, In-Kyu Yoon, Diane van der Vliet, Edith Langevin, Thelma Laot, Yanee Hutagalung, Carina Frago, Mark Boaz, T Anh Wartel, Nadia G Tornieporth, Melanie Saville, Alain Bouckenooghe, and the CYD14 Study Group**

Lancet 2014; 384: 1358–65
Published Online July 11, 2014 http://dx.doi.org/10.1016/S0140-6736(14)61060-6

See Comment page 1327

*Members listed at end of paper

Research Institute for Tropical Medicine, Alabang, Muntinlupa City, Philippines (M R Capeding MD); Pasteur Institute Ho Chi Minh City, Ho Chi Minh City, Vietnam (Prof N H Tran MD, C Q Luong MD); Department of Child Health, Medical School, University of Indonesia, Cipto Mangunkusumo Hospital,

Summary

Background An estimated 100 million people have symptomatic dengue infection every year. This is the first report of a phase 3 vaccine efficacy trial of a candidate dengue vaccine. We aimed to assess the efficacy of the CYD dengue vaccine against symptomatic, virologically confirmed dengue in children.

Methods We did an observer-masked, randomised controlled, multicentre, phase 3 trial in five countries in the Asia-Pacific region. Between June 3, and Dec 1, 2011, healthy children aged 2–14 years were randomly assigned (2:1), by computer-generated permuted blocks of six with an interactive voice or web response system, to receive three injections of a recombinant, live, attenuated, tetravalent dengue vaccine (CYD-TDV), or placebo, at months 0, 6, and 12. Randomisation was stratified by age and site. Participants were followed up until month 25. Trial staff responsible for the preparation and administration of injections were unmasked to group allocation, but were not included in the follow-up of the participants; allocation was concealed from the study sponsor, investigators, and parents and guardians. Our primary objective was to assess protective efficacy against symptomatic, virologically confirmed dengue, irrespective of disease severity or serotype, that took place more than 28 days after the third injection. The primary endpoint was for the lower bound of the 95% CI of vaccine efficacy to be greater than 25%. Analysis was by intention to treat and per procotol. This trial is registered with ClinicalTrials.gov, number NCT01373281.

STUDY DESIGN

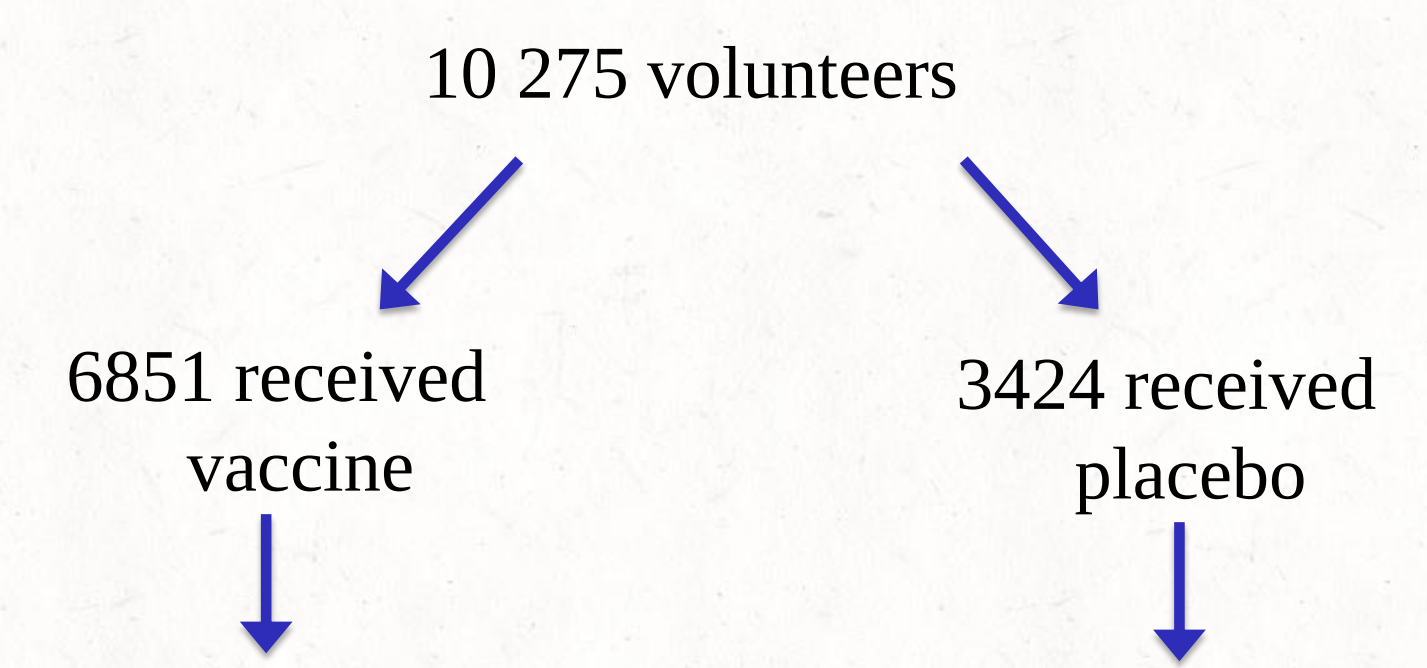
- Multi-centred, observer-masked RCT
- Participants are healthy children aged 2-14 years
- Involves 5 Asia Pacific countries (12 centres)
- Randomisation stratified by site & age

OUTCOME INVESTIGATED?

Incidence of virologically confirmed dengue[1]

Secondary outcomes: hospitalisation, severity

STUDY DESIGN



RESULTS

	Vaccine group (N=6848)			Control group (N=3424)			Vaccine efficacy (% [95% CI])
	Cases* (n)	Person-years at risk†	Incidence density‡ (95% CI)	Cases (n)	Person-years at risk	Incidence density (95% CI)	
Primary analysis (per-protocol)§	117	6526	1·8 (1·5–2·1)	133	3227	4·1 (3·5–4·9)	56·5% (43·8–66·4)
Intention-to-treat analysis¶	286	13571	2·1 (1·9–2·4)	309	6623	4·7 (4·2–5·2)	54·8% (46·8–61·7)

Defined as a first episode of virologically confirmed dengue by either dengue non-structural protein 1 antigen ELISA, dengue screen PCR, or a serotype-specific PCR. †The cumulative time (in years) until the participant was diagnosed with virologically confirmed dengue or until the end of the active follow-up period, whichever came first. The person-years at risk presented in the tables is the sum of individual units of time for which the participants contributed to the analyses. ‡Calculated as the number of cases divided by the cumulative person-years at risk. §Per-protocol efficacy population included participants who received three injections, according to protocol, and did not present with any of the criteria in a pre-specified list (appendix); virologically confirmed dengue occurring at least 28 days after the third injection. ¶Intention-to-treat efficacy population included all participants who received at least one injection, and participants were analysed in the group to which they were randomised, irrespective of per-protocol criteria; virologically confirmed dengue occurring from baseline.

***Table 2*: Efficacy of CYD-TDV vaccination against symptomatic, virologically-confirmed dengue due to any serotype**

- Incidence density significantly lower in vaccine group compared to control (1.8 vs 2.1)
- **Vaccine efficacy = 56.5%** (CI 43.8-66.4)[1]

RESULTS

Interesting points:

- Efficacy is **higher in participants with pre-existing dengue neutralising antibodies** than in those who were seronegative[1]

- Vaccine is **most effective for serotype 3** and least effective for serotype 1

- 54 (1%) participants in the vaccine group and 33 (1%) of those in the control group had serious **adverse events** within 28 days of vaccination[1]

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 24, 2015 VOL. 373 NO. 13

Efficacy and Long-Term Safety of a Dengue Vaccine in Regions of Endemic Disease

S.R. Hadinegoro, J.L. Arredondo-García, M.R. Capeding, C. Deseda, T. Chotpitayasunondh, R. Dietze, H.I. Hj Muhammad Ismail, H. Reynales, K. Limkittikul, D.M. Rivera-Medina, H.N. Tran, A. Bouckenooghe, D. Chansinghakul, M. Cortés, K. Fanouillere, R. Forrat, C. Frago, S. Gailhardou, N. Jackson, F. Noriega, E. Plennevaux, T.A. Wartel, B. Zambrano, and M. Saville, for the CYD-TDV Dengue Vaccine Working Group*

ABSTRACT

BACKGROUND

A candidate tetravalent dengue vaccine is being assessed in three clinical trials involving more than 35,000 children between the ages of 2 and 16 years in Asian–Pacific and Latin American countries. We report the results of long-term follow-up interim analyses and integrated efficacy analyses.

METHODS

We are assessing the incidence of hospitalization for virologically confirmed dengue as a surrogate safety end point during follow-up in years 3 to 6 of two phase 3 trials, CYD14 and CYD15, and a phase 2b trial, CYD23/57. We estimated vaccine efficacy using pooled data from the first 25 months of CYD14 and CYD15.

RESULTS

Follow-up data were available for 10,165 of 10,275 participants (99%) in CYD14 and 19,898 of 20,869 participants (95%) in CYD15. Data were available for 3203 of the 4002 participants (80%) in the CYD23 trial included in CYD57. During year 3 in

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Saville at Sanofi Pasteur, 2 Ave. Pont Pasteur, 69367 Lyon CEDEX 07, France, or at melanie.saville@sanofipasteur.com.

*A complete list of investigators in the CYD-TDV Dengue Vaccine Working Group is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on July 27, 2015, at NEJM.org.

N Engl J Med 2015;373:1195-206.
DOI: 10.1056/NEJMoa1506223

STUDY DESIGN

- A long-term safety analyses based on data collected during year 3 of phase 3 trials in:
- Five Asian–Pacific countries (CYD14)
- Latin American countries (CYD15)
- CYD23 extension study (CYD57) in Thailand

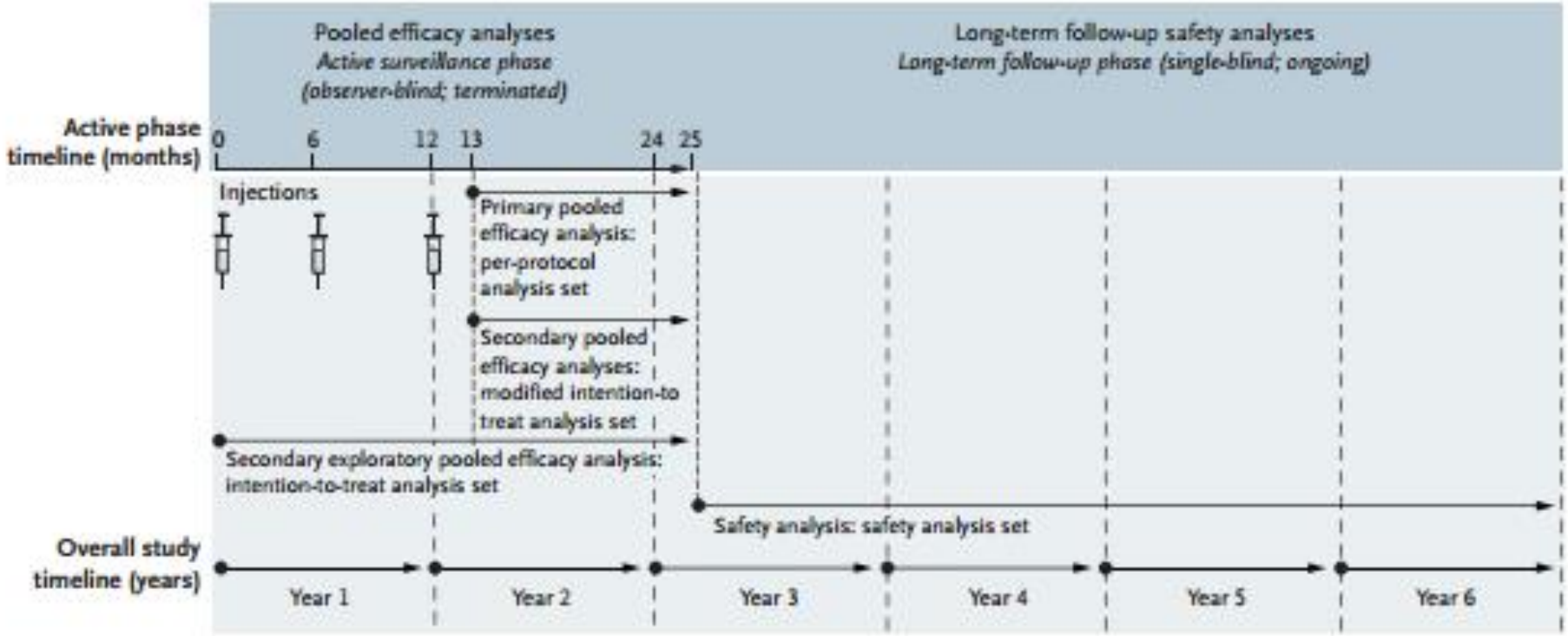


Figure 1. Overview of the Surveillance Phase and Long-Term Follow-up Phase of the CYD-TDV Candidate Vaccine Trials.

CYD-TDV is a candidate recombinant, live, attenuated, tetravalent dengue vaccine that has been assessed in two phase 3 randomized efficacy studies (called CYD14 and CYD15) involving a total of more than 31,000 participants between the ages of 2 and 16 years in Asian–Pacific and Latin American countries. In addition, 3203 of 4002 participants (80%) who were between the ages of 4 and 11 at initial enrollment in the phase 2b CYD23 trial in Thailand are being followed in the CYD57 trial. The trials had similar designs. According to the study designs, the long-term follow-up phase will continue for a total of 6 years after enrollment.

RESULTS

- During year 3, **severe dengue** was reported in 18 of 22,177 participants in the vaccine group and in 6 of 11,089 in the control group[2]

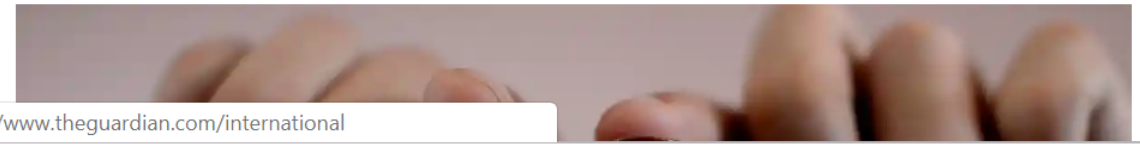
- The pooled **relative risk of hospitalization** for virologically confirmed dengue in the vaccine group for the three trials was **0.84**[2]

- Pooled **vaccine efficacy** against dengue of any severity and any serotype among children aged >9 years was **65.6%**[2]

Philippines

Suspended dengue vaccine was given to 730,000 children, Philippines says

Sanofi's Dengvaxia immunisation could worsen disease in some patients not previously exposed to virus



Tue 5 Dec 2017 03.46 GMT

1,730

The Philippines has ordered an investigation into the immunisation of more than 730,000 children with a dengue vaccine that has been suspended following an announcement by French drug company Sanofi that it could worsen the disease in some cases.

The World Health Organisation said it hoped by the end of the year to conduct a full review of data on the vaccine, commercially known as Dengvaxia. In the meantime, the WHO recommended it be used only in people who had a prior infection with dengue.

Last week, the Philippines department of health halted the use of Dengvaxia. Brazil, where dengue is a significant health challenge, had already recommended restricted use of the vaccine.

> Outbreaks like Zika distract us from other medical emergencies
> *Gary Finnegan*
>
> Read more

Dengue is a mosquito-borne tropical disease, killing about 20,000 people a year and infecting hundreds of millions.

Sanofi explained its "new findings" at a news conference in Manila but did not say why action was not taken after a WHO report in mid-2016 that identified the risk.

While Sanofi's Dengvaxia is the first approved vaccine for dengue, scientists already recognised it did not protect equally against the four different types of the virus.

most viewed


Russians leaked Mueller investigation evidence online, prosecutors say


Ariana Grande mocked for Japanese tattoo typo: 'Leave me and my grill alone'