MMed and DCH Lectures

Vaccines and vaccine preventable diseases

March 8, 2021

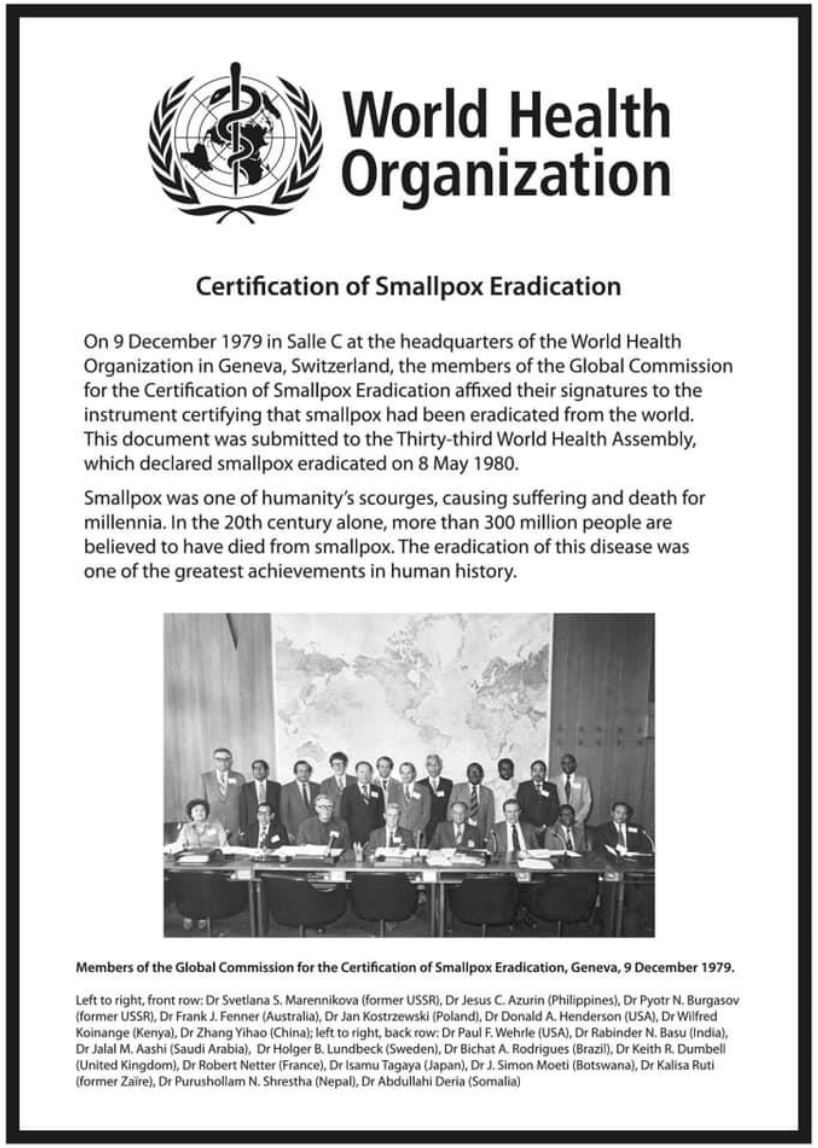
Prof Trevor Duke

Everything you need to know about vaccines

- History of Expanded Programme for Immunisation (EPI)
- Vaccines in PNG, diseases, recent changes and current schedule
- Understanding different vaccines types –
  - Live attenuated
  - Particle
  - Conjugate
- Update on new vaccines

Smallpox, World Health Organization

- Smallpox caused epidemics since 10,000 BC,
  - Decline of the Roman Empire
  - Devastating epidemics all over Europe
  - Crusades took smallpox to the New World (South America)
- Variolation – injection of small amount of smallpox under skin (outcomes: immunity, death, blood borne viruses, sepsis). Widely practiced in 18th century
- In 1796 a milkmaid, Sarah Nelmes, came to Edward Jenner (English physician) with cowpox
- Jenner passed on the disease to James Phipps - his gardener's son - by scratching his skin with infected matter
- When James had recovered from the cowpox, Jenner tried to give him smallpox. James did not develop smallpox disease.



World Health Organization

Certification of Smallpox Eradication

On 9 December 1979 in Salle C at the headquarters of the World Health Organization in Geneva, Switzerland, the members of the Global Commission for the Certification of Smallpox Eradication affixed their signatures to the instrument certifying that smallpox had been eradicated from the world. This document was submitted to the Thirty-third World Health Assembly, which declared smallpox eradicated on 8 May 1980.

Smallpox was one of humanity's scourges, causing suffering and death for millennia. In the 20th century alone, more than 300 million people are believed to have died from smallpox. The eradication of this disease was one of the greatest achievements in human history.

- Smallpox vaccination in PNG 1960-1976
- World declared smallpox free in December 1979

Six vaccines chosen for start of the EPI in 1977

1. BCG (tuberculosis)
2. Sabin Oral Polio Vaccine (OPV)
3. Diphtheria
4. Tetanus
5. Pertussis
6. Measles

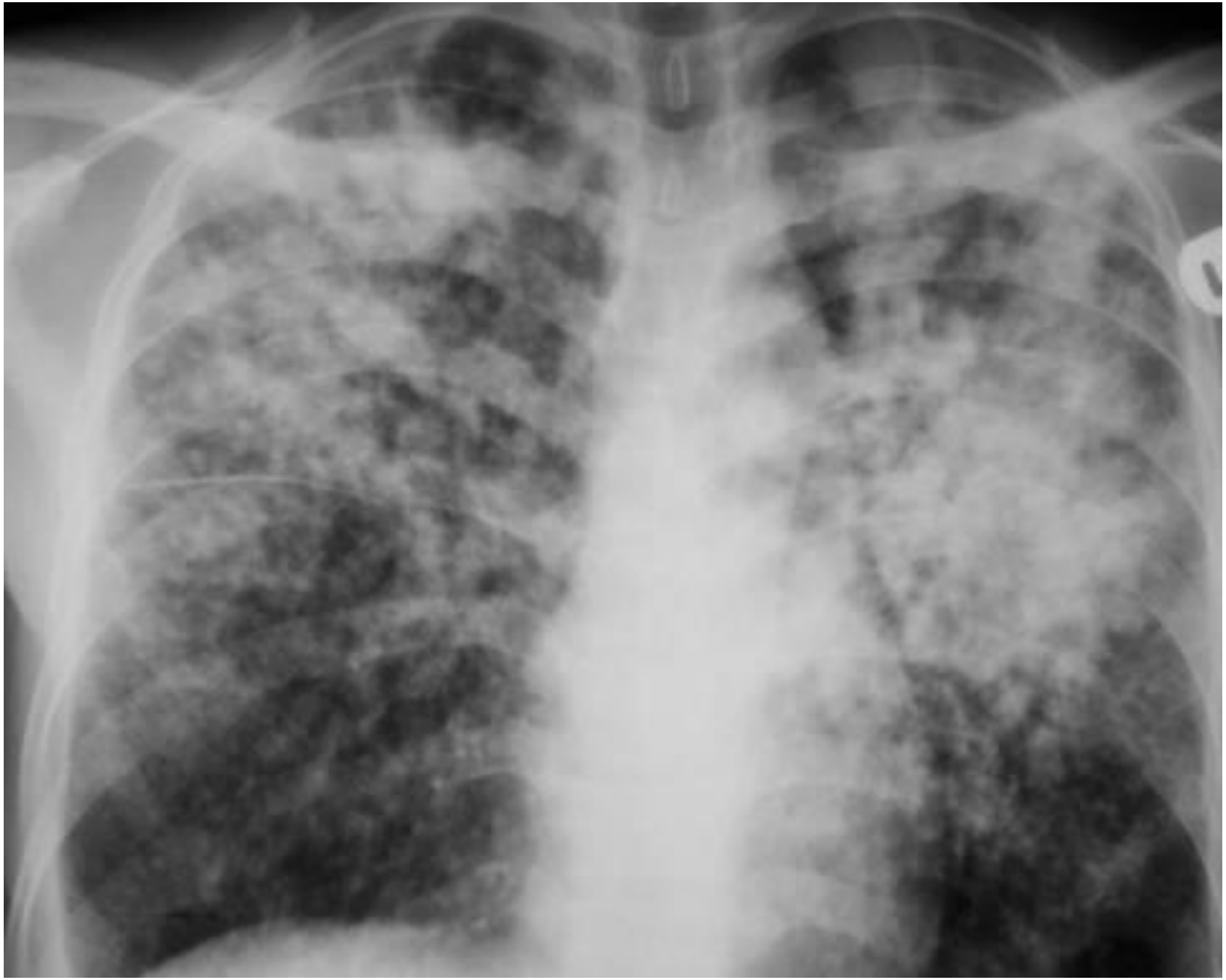
DTP = Triple Antigen

- Added since 1990s
  - Hepatitis B
  - Haemophilus influenza type b
  - Streptococcus pneumoniae
  - Rubella

Why these 6 vaccines?

- Disease with high morbidity / mortality
- Low cost
- Effective
- Safe

Vaccine	Age Group	Dose	Route	Disease Protects
BCG	Birth	0.05 ml (one dose)	Intradermal L upper arm	Tuberculosis
Hepatitis B	Birth	0.5 ml	Intramuscular R thigh	Hepatitis B
OPV	Infants (1, 2, 3 months)	2 drops (1, 2, 3 months)	Oral	Poliomyelitis
IPV (inactivated polio vaccine)	At 3 *and* 9 months	0.5 ml (with 3rd dose of OPV) 0.5ml at 9 months	Intramuscular R thigh	Poliomyelitis
Pentavalent	Infants (1, 2, 3 months)	0.5ml	Intramuscular R thigh	Diphtheria, whooping cough, pneumonia and meningitis (Hib), tetanus, hepatitis B
PCV-13	Infants (1, 2, 3 months)	0.5ml	Intramuscular L thigh	Streptococcus pneumoniae
Measles, Rubella (MR)	6, 9 and 18 months)	0.5ml	Subcutaneous R upper arm	Measles and Rubella, CRS
Tetanus Toxoid (Td)	Pregnant Mother, School Entry. School Leaving	0.5ml (2 doses one month apart)	Intramuscular L upper arm	Tetanus
Vitamin A	6 months to 2 years	3 doses (6, 9 months blue capsule 100,000 IU and 18 months red capsules 200,000 IU)	Oral	Protects from night blindness



BCG

- Live attenuated strain of *M. bovis*
- Developed in 1921 (100 years old!)
- Many different strains of BCG (Denmark, Japan, Serbia, Russia – all with different efficacy)
- Most effective if given at birth
- Most effective against disseminated TB *disease*
- *Disease vs infection*
  - Less effective again pulmonary TB or TB *infection (but some protection against infection)*

BCG effectiveness

- **Neonatal BCG vaccination:** up to 90% protection against severe types of disseminated TB: miliary TB and tuberculous meningitis, to which infants and young children are susceptible
- Good protection against pulmonary TB up to 10 years and moderate protection for 20 years
- Also protects against leprosy (*M. leprae*) and Buruli ulcer (*M. ulcerans*)
- Delaying BCG vaccination increases risk of TB
- Co-administration of BCG and hepatitis B at birth is safe and optimal

BCG contraindications

- Children with impaired congenital (SCID) or acquired immunity (HIV), leukaemia, lymphoma
- **In HIV**: if stable on anti-retroviral therapy, clinically well and immunologically stable (CD4% >25% for children <5 years, or CD4 count ≥200 if >5 years), BCG can be given

✓HIV exposed but well infants, **if mother on ART** – BCG

X HIV exposed and clinical signs of HIV, or mother not on ART – No BCG

X Pregnancy – No BCG

✓Lactating mothers - BCG

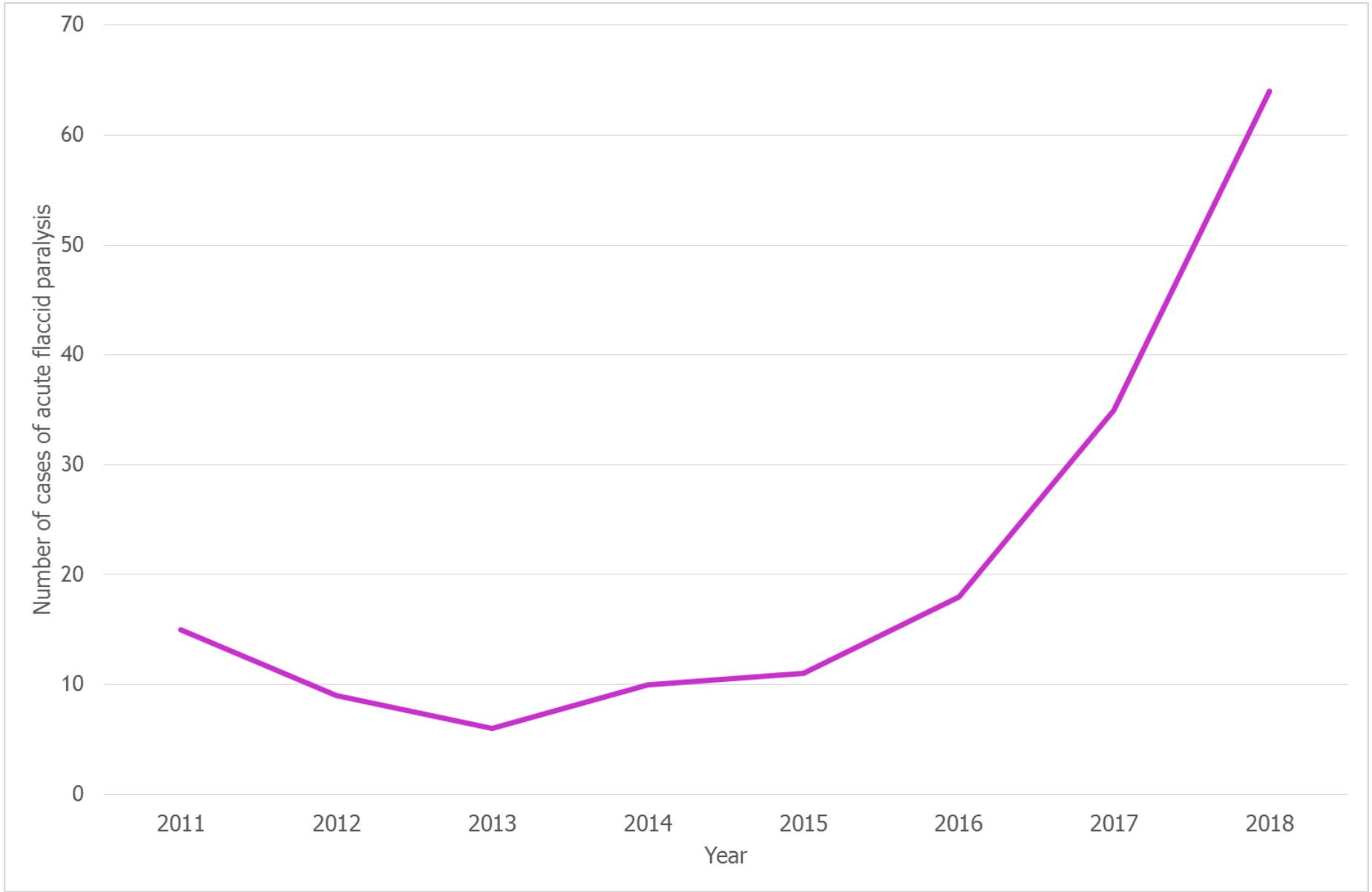
✓Preterm or LBW – give BCG at birth

Dr Winnie Sadua with 6 year old Gafo, first polio patient

https://polioeradication.org/news-post/everyday-heroes-for-polio-eradication/

Polio vaccination in PNG

- Last case of wild-type polio in 1999, declared polio free 2016
- Global eradication of polio virus type 2 and type 3
- 2016: Switch from Trivalent OPV (polio types 1,2,3) to Bivalent OPV (polio 1,3)
- Addition of IPV (Trivalent) because it is inactivated and cannot cause vaccine-derived polio
- A booster dose of IPV at 3 months reduces viral shedding of OPV, so that’s why OPV x 3 doses, then IPV with dose #3



Annual Child Morbidity and Mortality Report 2019

Vaccine derived poliovirus

- May 2018: case of acute flaccid paralysis in Lae, MP: vaccine-derived poliovirus type 1 (cVDPV1)
- June 2018: NDoH confirmed an outbreak of poliomyelitis
- Occurred because of low vaccination coverage, and poor sanitation and hygiene
- June 2018-2019
  - 5-6 rounds of mass polio vaccination campaigns, enhanced surveillance including environmental surveillance
  - 26 cases in total: EHP (6), Enga (5), ESP (4); Morobe (3); Madang (3); Jiwaka (2); SHP (1), NCD (1), Gulf (1) – one death
  - By the end of 2018, 97% of children <15 years of age had been vaccinated, no new cases found in 2019

How does “vaccine derived polio” occur?

- OPV = live attenuated poliovirus, replicates in GI tract → immune response
- Where sanitation is poor, excreted virus can circulate for long periods, and *allow genetic change to virulent strain*
- Estimated incidence 1:17 million
- Democratic Republic of the Congo, Indonesia, Mozambique, Niger, Nigeria, Somalia, Syria, PNG

Polio vaccination in PNG – July 2021

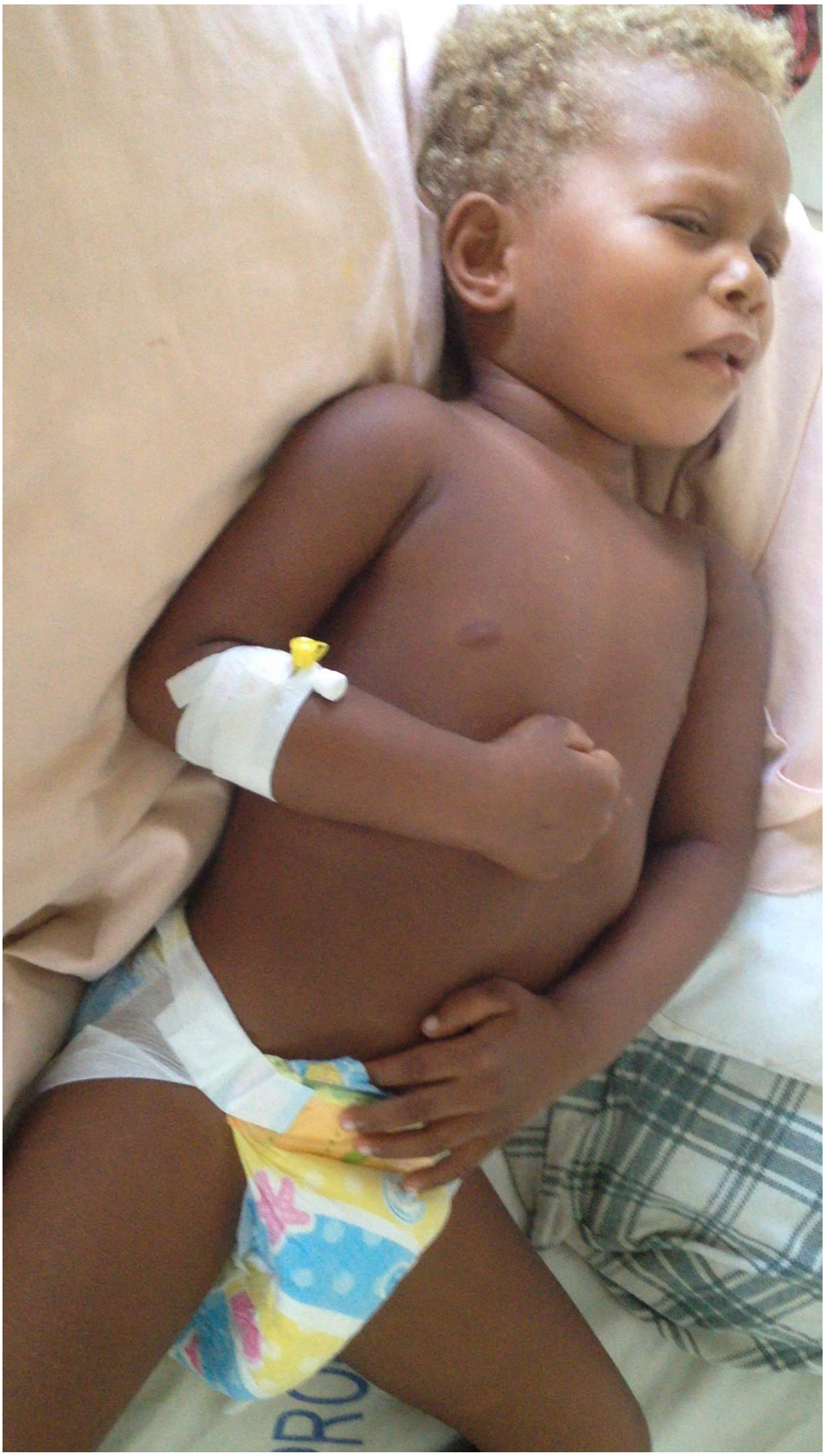
- Addition of 2nd IPV dose (9 months)
- Recommended by WHO / SAGE
- Further boost against all 3 serotypes of poliovirus
- IPV protects against type 2 polio virus, a source of vaccine derived virus in many countries
- Eventually complete switch to IPV as in other countries

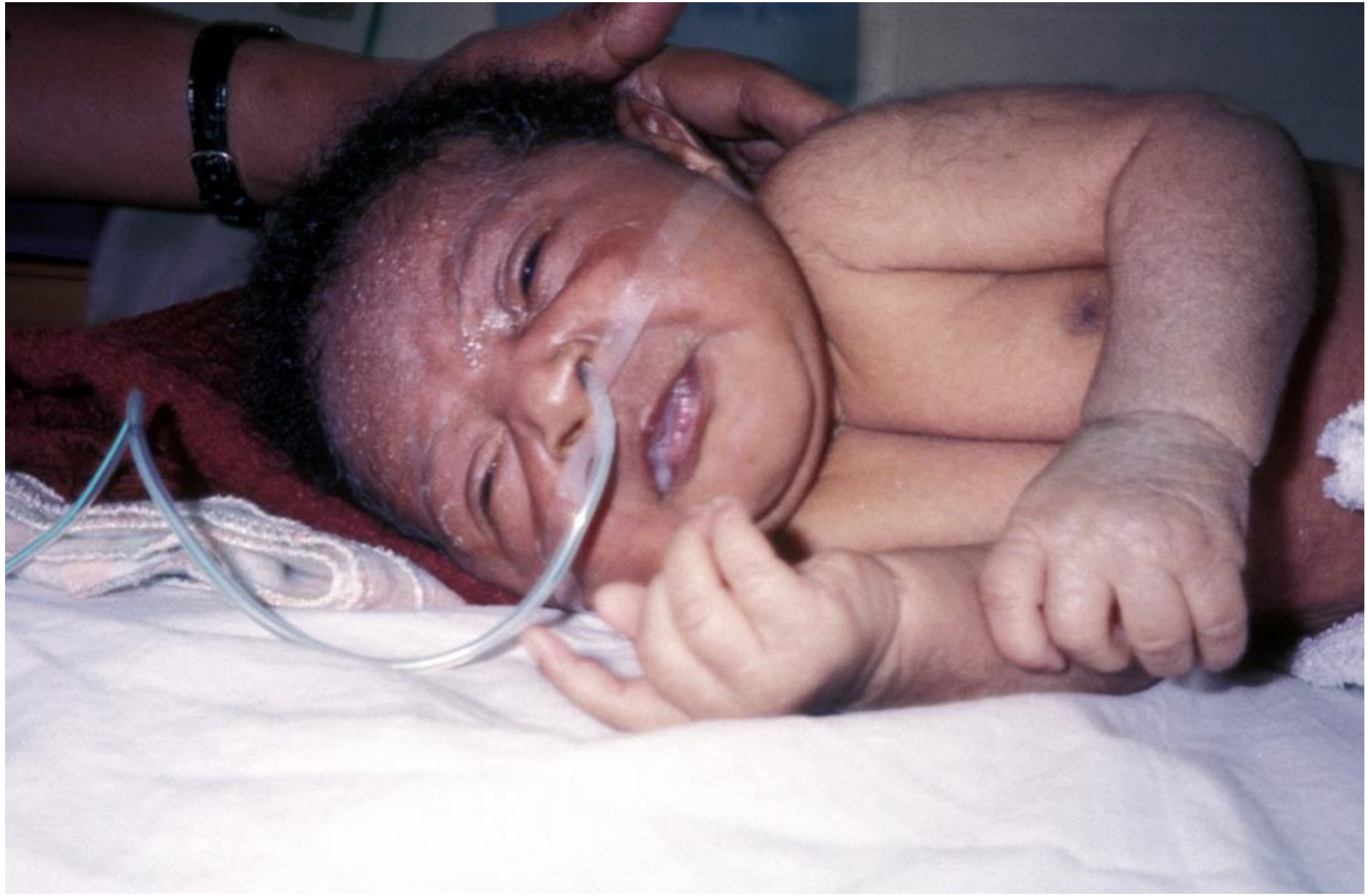
Understanding the schedule

OPV (bivalent 1, 3)	Infants (1, 2, 3 months)	2 drops (1, 2, 3 months)	Oral
IPV (inactivated Polio vaccine, trivalent)	At 3 months and 9 months	0.5 ml (with 3rd dose of OPV) and (2021): 0.5ml at 9 months	Intramuscular R thigh

AFP

- Polio
- Guillain Barre syndrome
- Transverse myelitis
- Spinal cord compression
- SMA



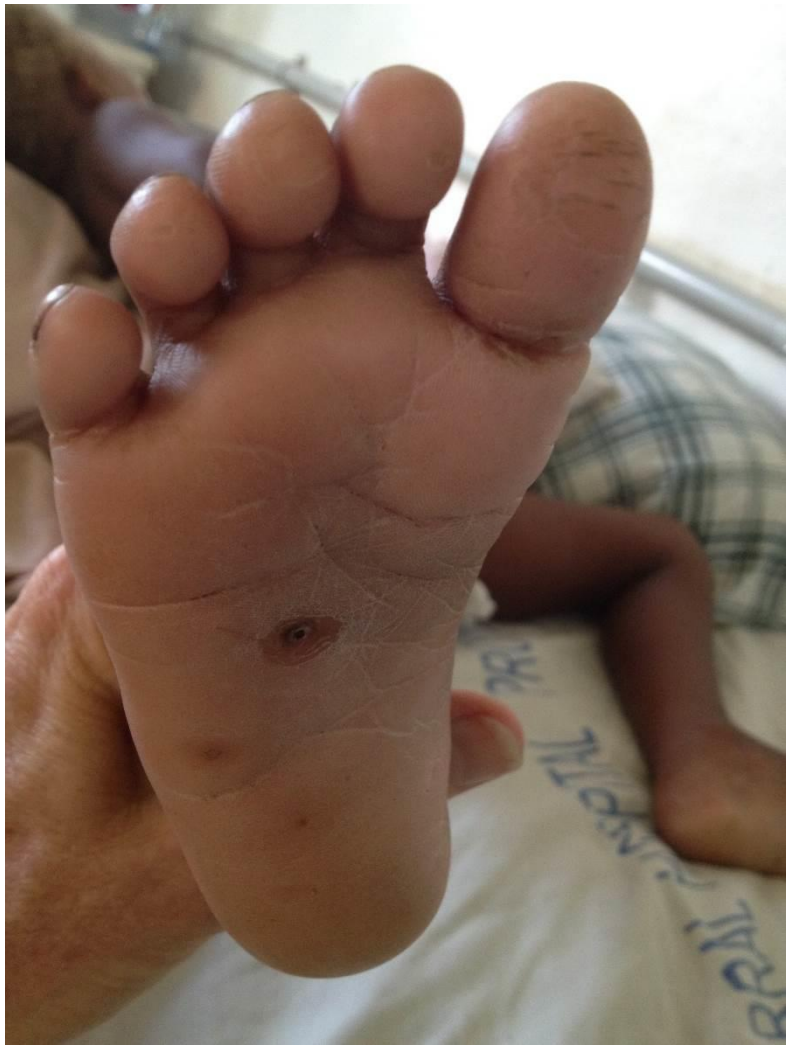


Tetanus

- Part of pentavalent vaccine (DTP-Hib-Hep B)
- Tetanus toxin inactivated by formaldehyde = tetanus “toxoid”
- An “adjuvant” added = to increase immunogenicity (increase the antibody response) – when combined with B. pertussis this adds to the immune response
- Being tetanus immune does not stop *Clostridium tetani* growing in a wound, it just neutralizes the toxin, so proper wound care essential
- Booster needed after if no vaccine for 10 years
- If partially vaccinated

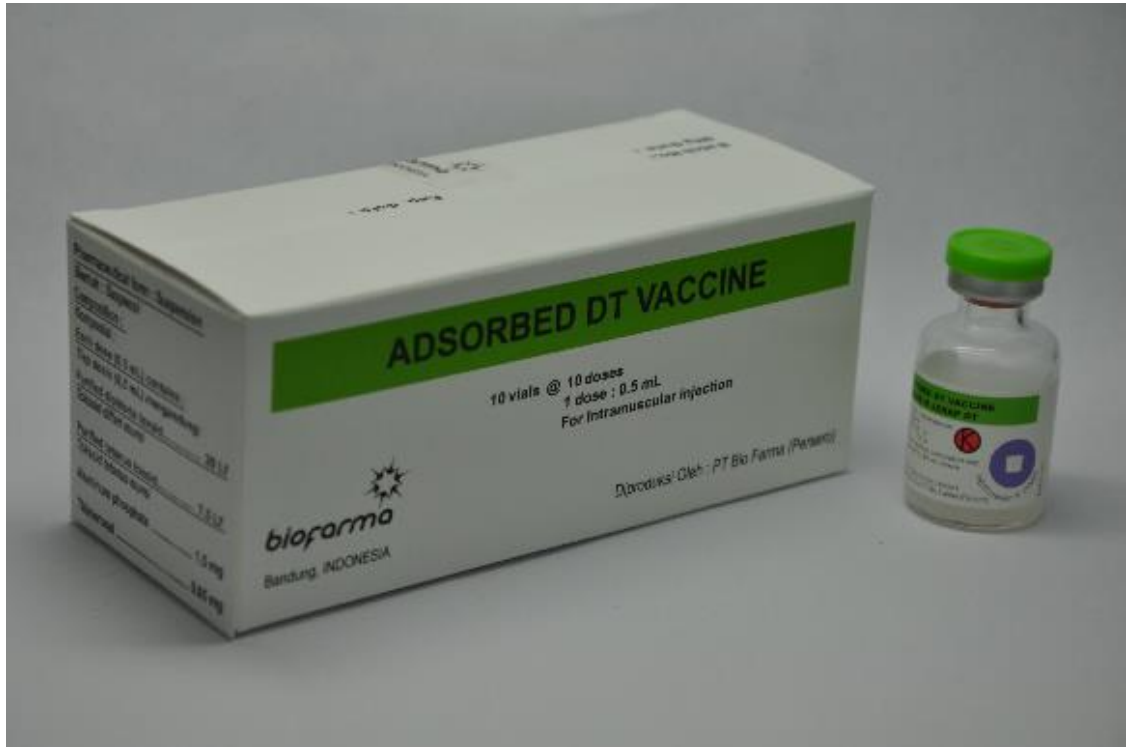
Tetanus prone wound

- Being tetanus immune does not stop *Clostridium tetani* growing in a wound, it just neutralizes the toxin, so proper wound care essential
- Incubation period 10 days (3-21 days)
- 3 doses in infancy + booster at school entry – protection into adulthood
- Booster needed after if no vaccine for 10 years
- If partially vaccinated (e.g. 2 doses, or unsure → revaccinate)

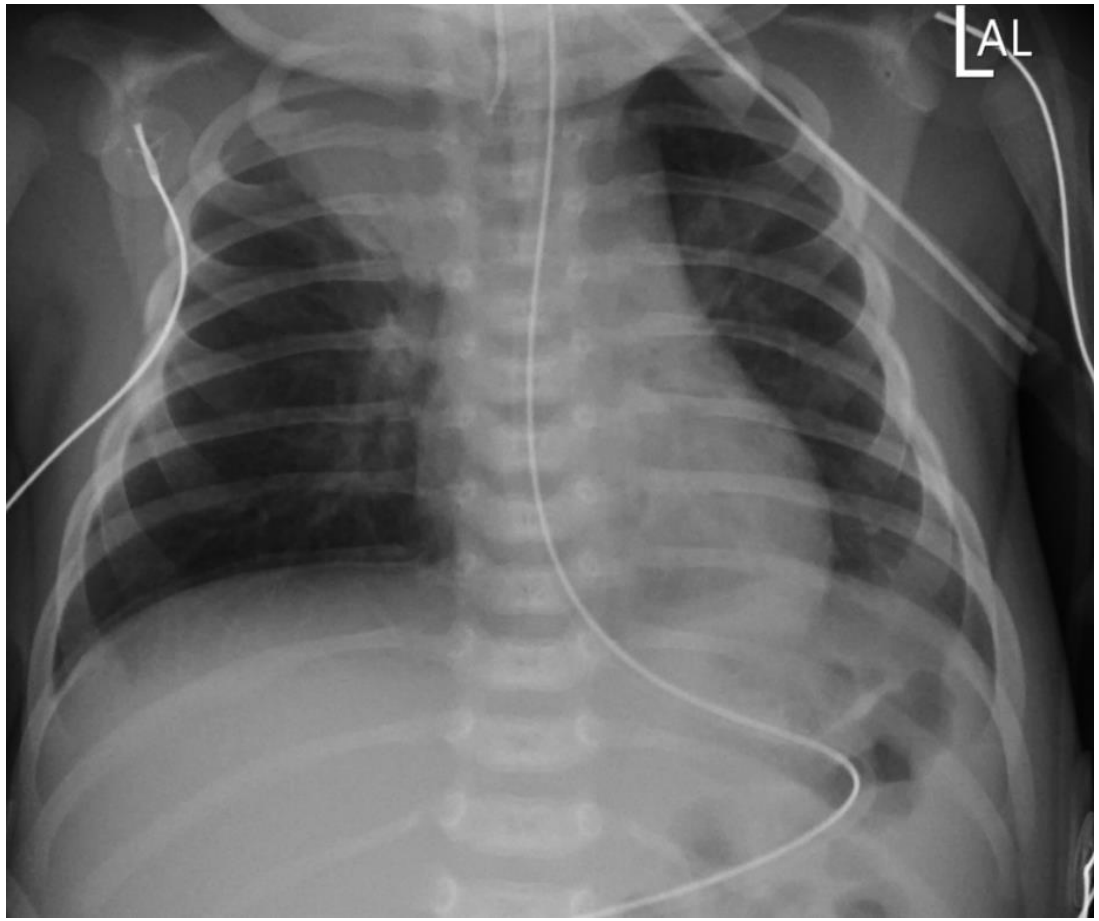


Changes to tetanus booster

- 2018: tetanus toxid (TT) replaced with Tetanus-diphtheria (Td), (because TT less manufactured)
- 10 dose vial
- Storage requirements same – keep 2-8 degrees, never freeze
- open vial may be used for 28 days provided cold chain / sterility conditions met



A child with cough and cyanosis



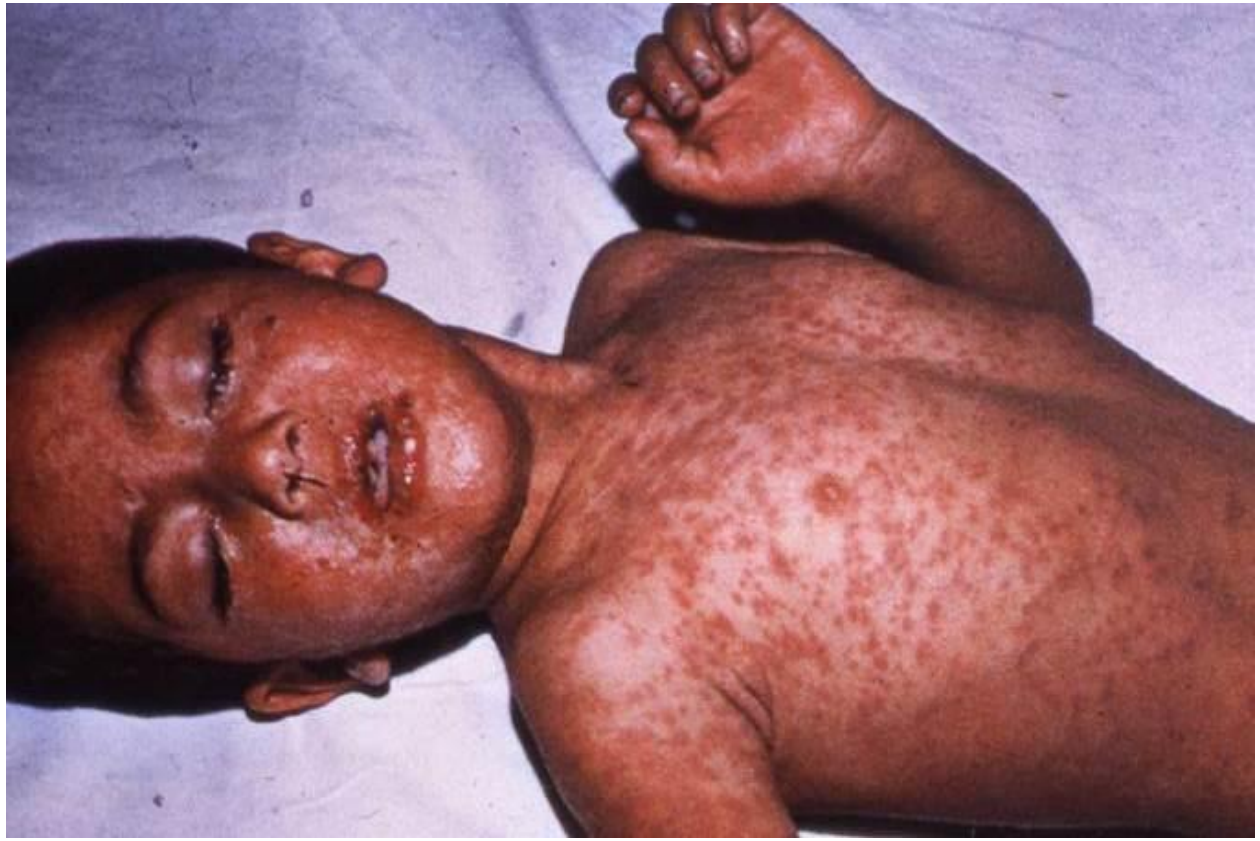
Pertussis

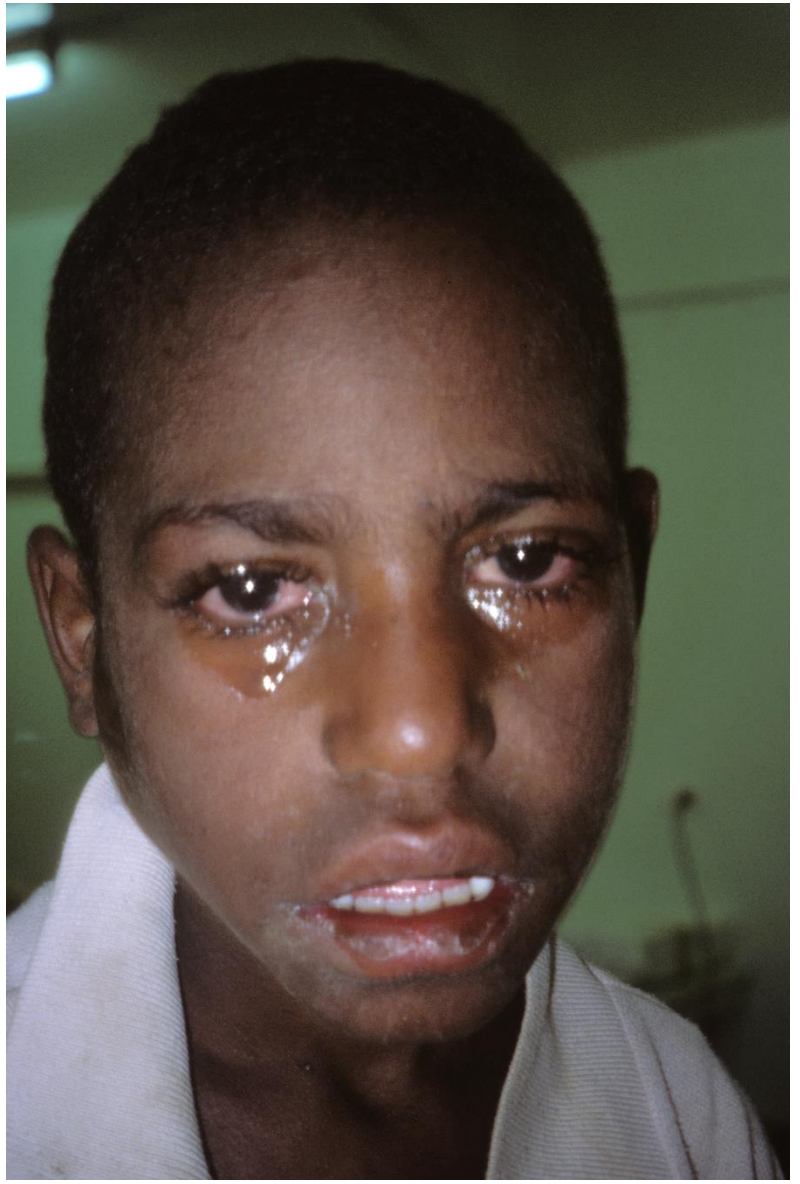
- Highly prevalent, and highly infectious (90% of non-immune contacts will acquire the infection)
- Outbreaks frequent (Goilala 2011, Finchaffen 2018)
- *B. pertussis*: Gram negative bacilli (pleomorphic)
- Maximum risk to young infants (before the 2nd dose, which is protective)
- Adults and adolescents are reservoir (waning immunity by age 18, even if vaccinated).

Datta S et al. Pertussis outbreak in Papua New Guinea: the challenges of response in a remote geo-topographical setting. Western Pacific Surveillance and Response Journal, 2012, 3(4):3-6.

Pertussis

- Treatment:
  - Reduces the period of infectivity, but may not reduce the duration of coughing
  - Azithromycin
  - Treat family contacts, and immunise
  - Admit to hospital if hypoxic, apnoea, not feeding well, seizures, emergency signs
  - May last months (“100 day cough”)





Measles vaccine

- Since 1982
- Aim >90% coverage from 9 months, with 2nd opportunity for MV_2
- 6 months dose: because risk of severe measles in young infants in PNG, however much lower seroconversion if MV_1 given at 6 months (70% vs 90% at 6 months).
- Low seroconversion rates in <6 months because of maternal antibodies – in PNG 69% of infants at 6 months had residual maternal antibodies

Immune response to measles vaccine in 6 month old infants in Papua New Guinea

Jonah Kurubi[1], John Vince[1], Paulus Ripa[1], Nakapi Tefuarani[1], Michaela Riddell[2] and Trevor Duke[1,3]

- After vaccination at 6 months
  - 35.7%: measles antibodies consistent with protection (IgG >330 IU/ml)
  - 17.7%: measles antibody response (IgG 150–330 IU/ml) that is likely to afford some protection
  - 46.8%: no detectable antibody response (IgG <150 IU/ml)

  - Aim >90% coverage from 9 months, with 2nd opportunity for MV_2

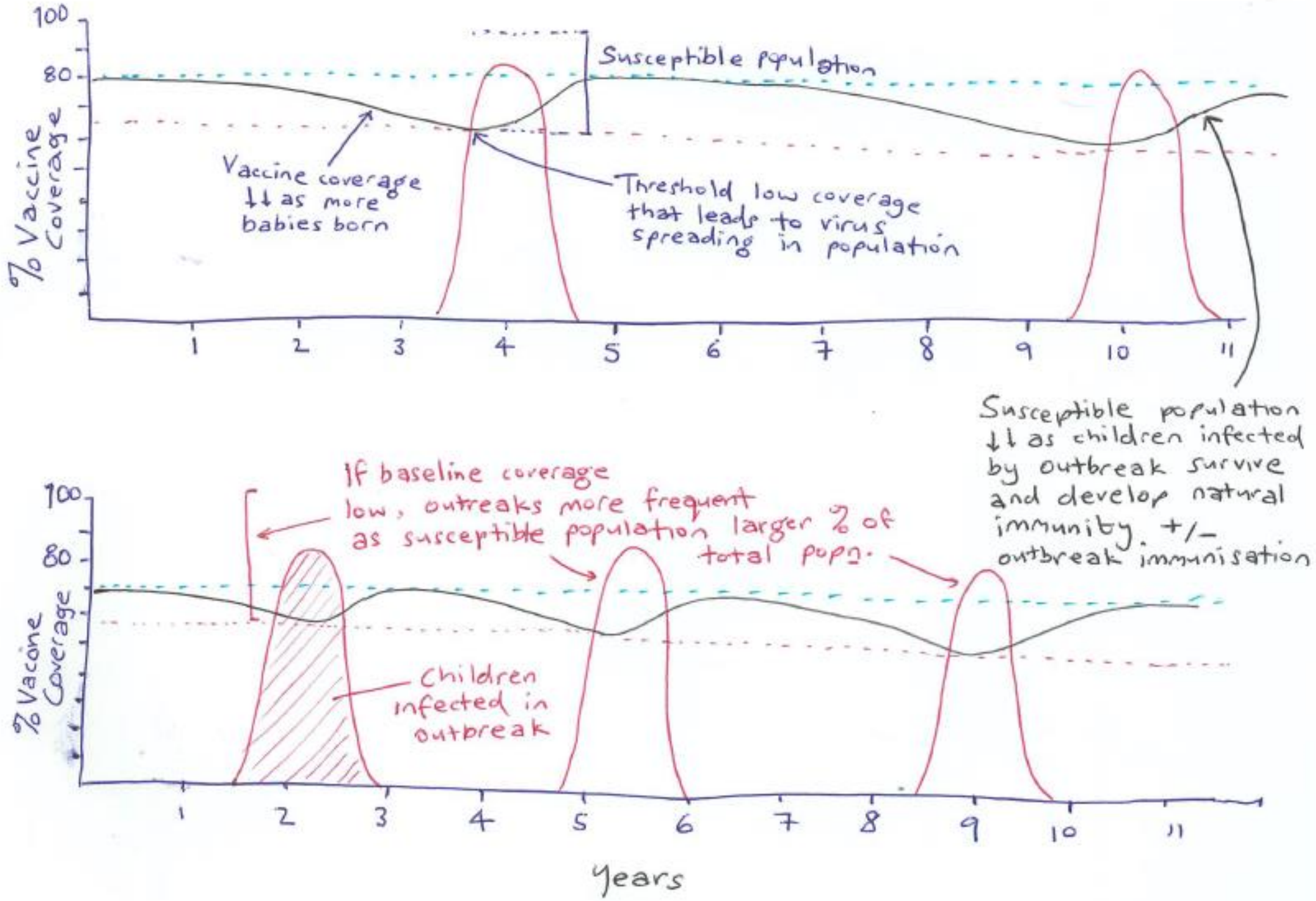
Tropical Medicine and International Health

VOLUME 14 NO 2 PP 167–173 FEBRUARY 2009

Why do measles outbreaks occur?

- If coverage only 80%, then 20+% susceptible…over time the susceptible population increases because of all the new babies born…above 20% susceptible population, virus

- With coverage greater than 80%, the interval between outbreaks typically lengthens – from 2–4 years to 4–8 years

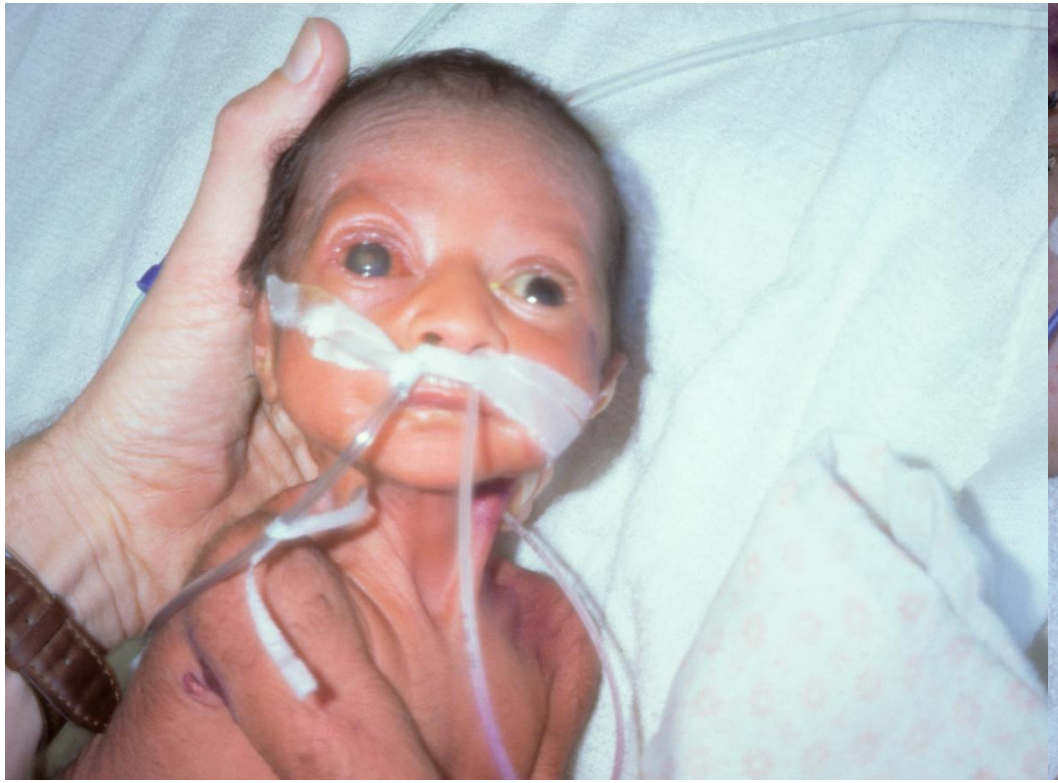

100
80
% Vaccine Coverage
Susceptible population
Vaccine coverage ↓↓ as more babies born
Threshold low coverage that leads to virus spreading in population
1
2
3
4
5
6
7
8
9
10
11
Susceptible population ↓↓ as children infected by outbreak survive and develop natural immunity. +/- outbreak immunisation
If baseline coverage low, outreaks more frequent as susceptible population larger % of total popn.
Children infected in outbreak
Years

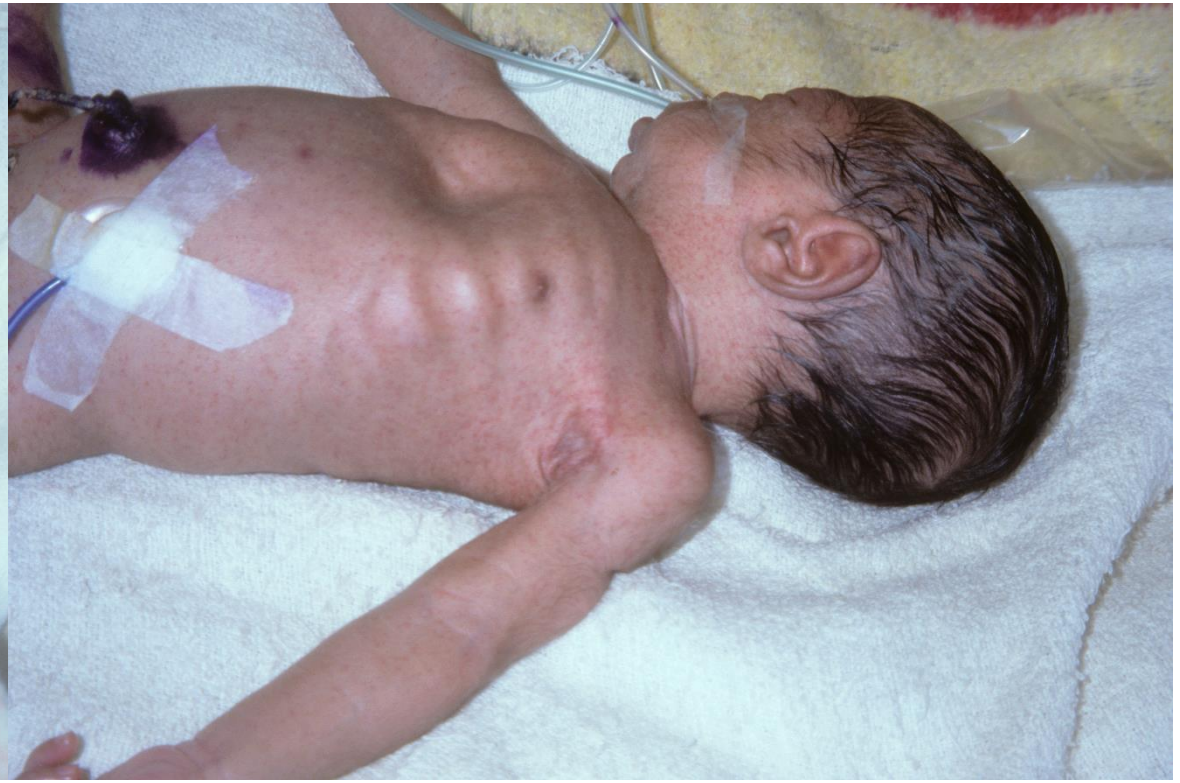
To successfully control measles

1. Routine immunisation
2. Supplemental immunisation activities – mass campaigns every 3-4 years to achieve coverage >90%
3. 2 doses, one after 18 months (or school years)
4. Effective case finding and disease surveillance

Every child who is vaccinated helps

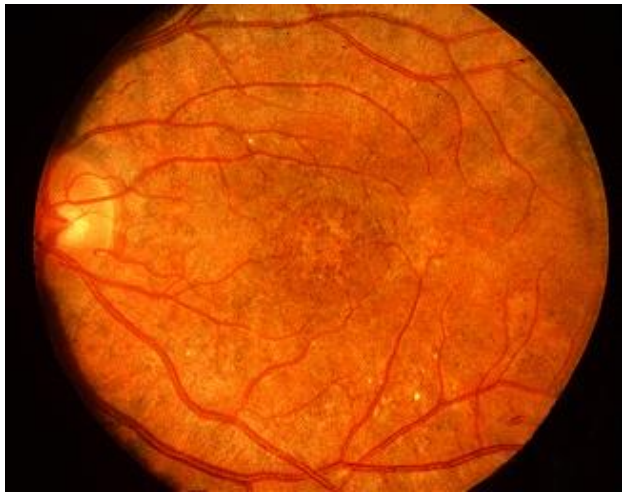
- Outbreaks that arise despite high vaccine coverage associated with very low case fatality.
- Vaccinated children who develop measles have a much lower rate of dying and complications, and a lower rate of passing on measles





Congenital rubella syndrome

- Microcephaly, hearing loss (60%)
- Eyes – cataract, glaucoma (raised intraocular pressure), squint, nystagmus
- Cardiac – PDA, PS
- Petechiae, hepatomegaly, splenomegaly



“Salt & pepper” retinopathy: CDC retinal photograph

“MR” vaccine (R=rubella)

- First vaccine to prevent congenital malformations
- Introduced in 2015
- Importance of surveillance for CRS:
  - We do not know the incidence of CRS
  - 90% of women >15 in PNG are immune to Rubella
  - The vaccine can reduce wild-type circulation of Rubella virus, and young mothers may be *less* protected if MR coverage is low
- Key is to maintain high MR coverage

Rubella control in Papua New Guinea: Age-specific immunity informs strategies for introduction of rubella vaccine

Vaccine 30 (2012) 7506–7512

AFR surveillance (acute fever and rash)

- Measles
- Rubella
- Parvovirus (Fifth disease, erythema infectiosum)
- HHV-6 (Roseola infantum)
- Scrub typhus
- Enterovirus (hand-foot-and-mouth disease)

- *plus* Congenital Rubella Syndrome (CRS) Surveillance

Hepatitis b vaccine

- Introduced in 1990s – different, a childhood vaccine to prevent adult diseases
- The first “recombinant” vaccine (1986) – insertion of DNA into cells which then produce protein to initiate an immune response
- Prevention of vertical transmission of HBV
- Prevention of chronic carrier status, chronic hepatitis, cirrhosis
- First vaccine to prevent cancer – hepatocellular carcinoma
- Inactivated vaccine
- Given ideally in first 24 hours…then 3 doses

2000s: new vaccines against pneumonia and meningitis

- Not part of original EPI in 1977, introduced 2008 and 2014 in PNG
- Both infections in top 5 causes of admissions and deaths each year
- Bacterial meningitis
  - Culture positive 12%
    - 40% S. pneumococcus
    - 40% Hib 40%
    - 20% other (N. meningitides)
- Pneumonia
  - 20% S. pneumoniae
  - 15-20% Haemophilus influenza type b

Haemophilus influenzae type b

- Introduced in 2008 in PNG
- Part of Pentavalent (5) – DTP-Hib-hepatitis b
- Highly effective against *Haemophilus influenzae* type b meningitis, and invasive Hib disease (severe pneumonia, bacteraemia)

Conjugate pneumococcal vaccines

- Introduced in PNG in 2013-14
- Infants cannot generate strong memory antibody response to polysaccharide (sugar), but they can to a protein, e.g. tetanus toxoid
- Capsular polysaccharide of pneumococcus linked to protein
- Polysaccharide antigens linked to protein
  - Like Hib vaccine, except Hib only one polysaccharide antigen and PCV 13!

Pneumococcal conjugate vaccine

- 80% of infants in PNG have nasopharyngeal carriage of multiple serotypes of *S. pneumoniae*
- >90% different serotypes
- 13 in PCV13, most pathogenic serotypes
- Vaccine prevents **invasive infection** (meningitis, bacteraemia)
- Limited effect on NP carriage
- Serotype replacement post-vaccine

PNG common disease causing serotypes (Infect, Immunity 1994)	**13-valent vaccine (PCV 13)**
	1
2	
	3
	4
5	5
	6A
6B	6B
7F	7F
	9V
14	14
	18C
	19A
19F	19F
23F	23F

Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind, placebo-controlled trial

F T Cutts, S M A Zaman, G Enwere, S Jaffar, O S Levine, J B Okoko, C Oluwalana, A Vaughan, S K Obaro, A Leach, K P McAdam, E Biney, M Saaka, U Onwuchekwa, F Yallop, N F Pierce, B M Greenwood, R A Adegbola, for the Gambian Pneumococcal Vaccine Trial Group*

Lancet 2005; 365: 1139–46

See Comment page 1113

- 16,000 children, 3 doses of 9-valent from 6 weeks of age, >25 days apart
- Efficacy against radiological pneumonia: 333 / 8189 vs 513 / 8151: 37% (27-45%)
- Efficacy against clinical pneumonia: 7-12%
- Reduced admissions: 15% (7-21%)
- Very high efficacy against pneumococcal meningitis – rarely seen in well immunized populations post PCV13

Vaccines in the near (?) future

- SARS CoV-2
- Human Papilloma Virus
- Rotavirus vaccine

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