Meningococcal Vaccination

Foundation Merieux

Asian Pacific Vaccinology Conference

December 2015

Prof Robert Booy

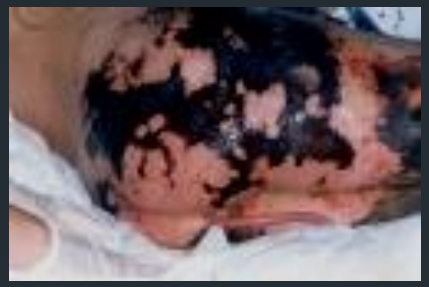
University of Sydney

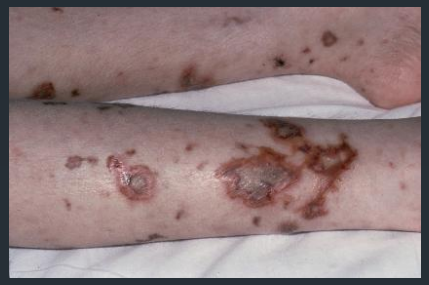
National Centre for Immunisation Research and Surveillance

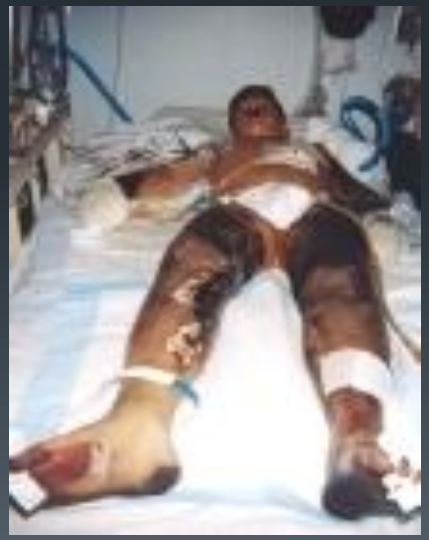
Marie Bashir Institute

Children's Hospital at Westmead

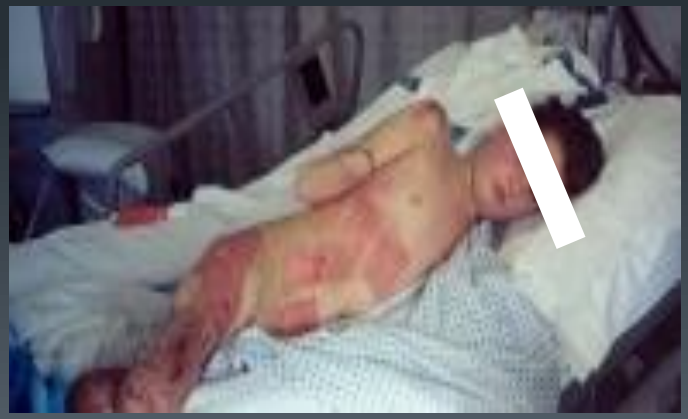
Meningococcal disease







- **5 Serogroups cause most disease**
  - **A, B, C, W135, and Y[1]**
- **Asymptomatic carriage common (~10%)[2]**
- **Transmission[1]**
  - **Contact with respiratory secretions**
  - **Coughing, kissing**
- **Incubation period: 2 – 10 days[3]**



1. Granoff D, et al. Meningococcal vaccines. In: Plotkin SA, Orenstein WA, Offit PA, eds. Vaccines. 5th ed. Philadelphia, PA: WB Saunders; 2008:399-434;
2. Cartwright N, et al. *Epidemiol Infect.* 1987;99:591-601; 3. WHO Meningococcal meningitis. Fact Sheet Nº141, November 2012. www.who.int/mediacentre/factsheets/fs141/en/

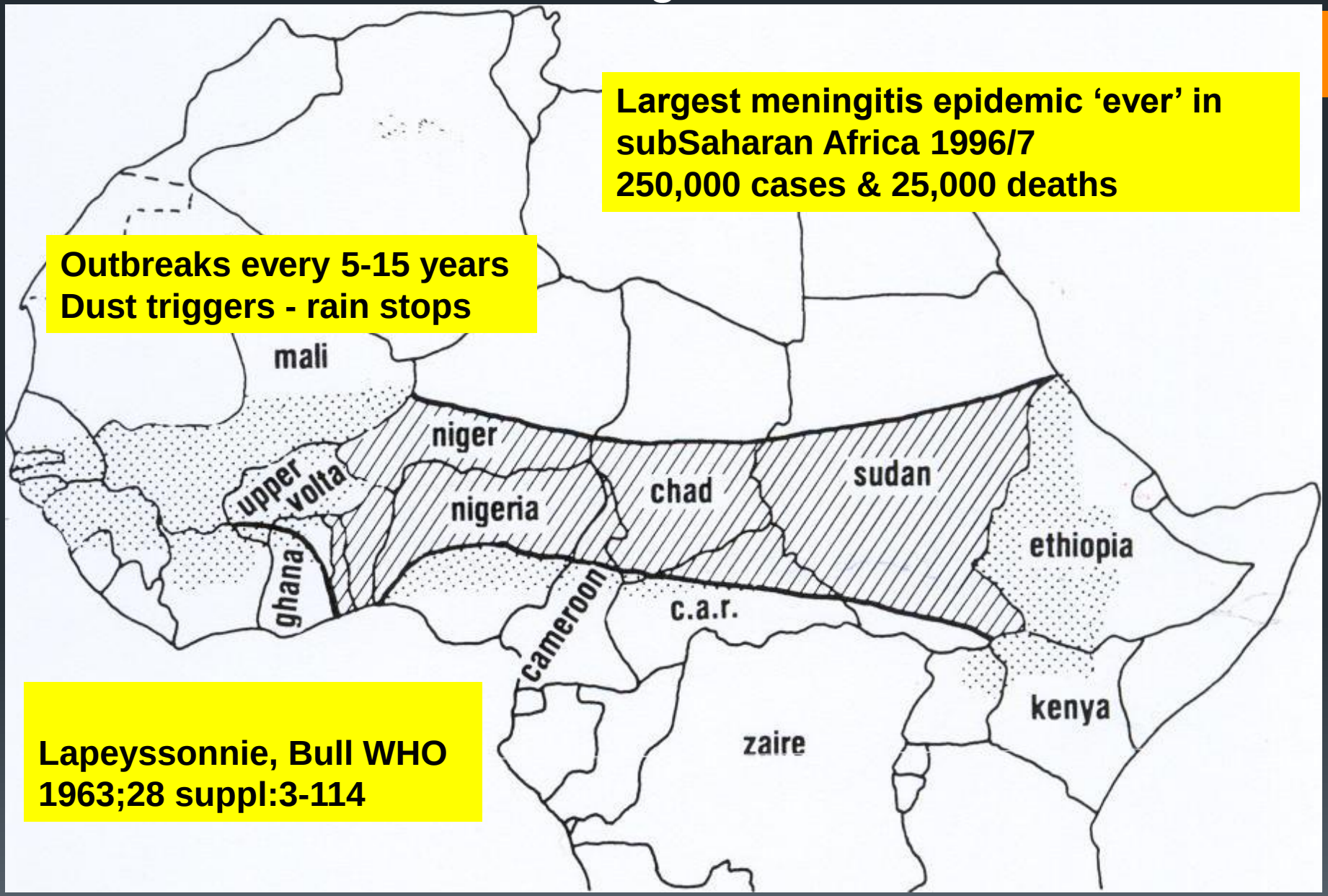
SUPPLÉMENT AU VOL. 28 DU *BULLETIN DE L'ORGANISATION MONDIALE DE LA SANTÉ*

LA MÉNINGITE CÉRÉBRO-SPINALE EN AFRIQUE

L. Lapeyssonnie

ORGANISATION MONDIALE D
GENÈVE
1963

African Meningitis Belt



Control of epidemic meningitis

- **Quarantine**
- **Chemoprophylaxis**
- **Vaccination (plain polysaccharide)**

- **Which is the most effective??**
- **Reactive vaccination often tardy**
- ***Improved socio-economic status – where has Men A gone in developed countries?***

Could universal vaccination eradicate the disease?

The meningococcus only survives in humans and conjugate vaccines can “clear it”

Vaccination prevents acquisition and thereby prevents transmission

DEVELOPMENT of Serogroup A CONJUGATE VACCINE in AFRICA

- **1992/3 A + C conjugate vaccine (Biocine/Sclavo) Gambia**
- **1996/7 A + C conjugate (Pasteur Merieux) Niger**
- ***2000 WHO Cairo meeting* African Gov’ts, KOLs – PATH & Industry partners**

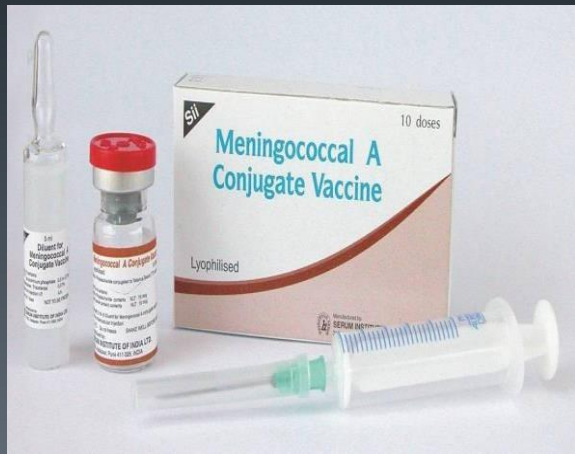
Meningitis Vaccine Project

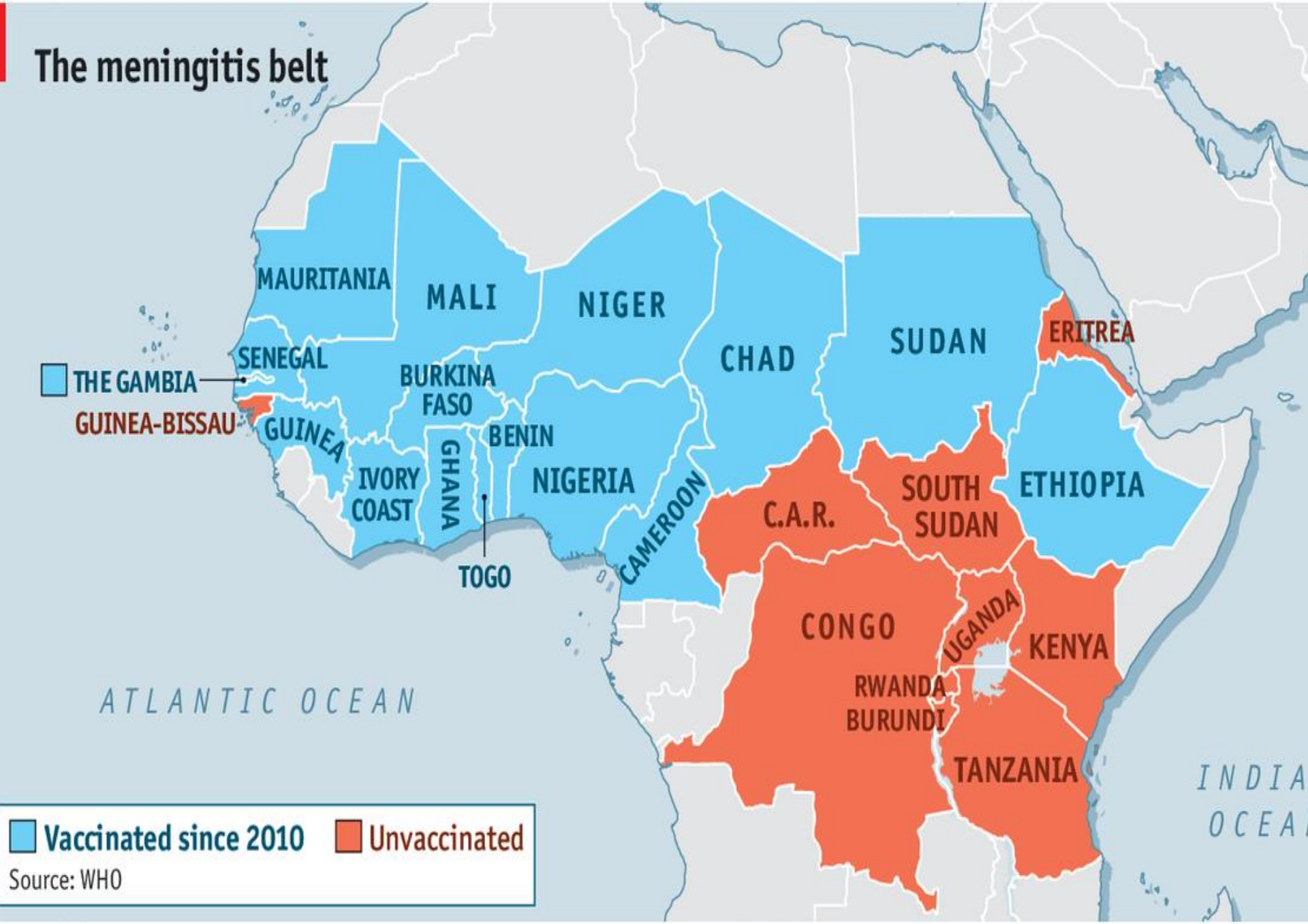
An affordable, serogroup A meningococcal conjugate vaccine for use in Africa
Established 2001, support from Bill & Melinda Gates Foundation $70 million

Men AfriVac: Achievements in just 10 years!

- ***Improved surveillance in 12 countries***
- **Efficient conjugation**
- **Technology transfer – Serum Institute India**
- **Vaccine made for <$0.50/dose**
- **Phase 2 trials: safe and immunogenic**
- **Licensed 2009** – no phase 3 efficacy trial
- ***Prequalified by WHO in 2010***
- ***Mass use Burkina Faso, Mali & Niger***

age 2 – 29 years from 2010




The meningitis belt
MAURITANIA
MALI
NIGER
CHAD
SUDAN
ERITREA
SENEGAL
THE GAMBIA
GUINEA-BISSAU
GUINEA
BURKINA FASO
BENIN
IVORY COAST
GHANA
NIGERIA
CAMEROON
TOGO
C.A.R.
SOUTH SUDAN
ETHIOPIA
CONGO
UGANDA
KENYA
RWANDA
BURUNDI
TANZANIA
ATLANTIC OCEAN
INDIA
OCEA
Vaccinated since 2010
Unvaccinated
Source: WHO

Meningococcal Meningitis Surveillance in the African Meningitis Belt, 2004–2013

- The incidence rate of NmA meningitis fell >10-fold,

from 0.27 per 100 000 in 2004-10

to 0.02/100 000 in 2011–13 ($P < .0001$)

Countries reporting consistently from 2004 through 2013 (Benin, Burkina Faso, Chad, Democratic Republic of Congo, Ghana, Côte d'Ivoire, Mali, Niger, Nigeria, Togo)

Clin Infect Dis. (2015) 61 (suppl 5): S410-S415

Example: Big impacts on Disease & Carriage in Chad!

1.8 million aged 1 - 29 years single dose vaccine, in rural area near capital in Dec 2011 ***(in context of an epidemic)***

Disease incidence rate ratio 0.096 (0.05,0.20)

No cases detected in vaccinated areas, even in those too young or too old to be vaccinated – suggests carriage impact

Carriage adjusted OR 0.019 (0.002, 0.14)

32 carriers in 4278 age-stratified individuals,
about 3 months before vaccination,
1 carrier in 5001 people 4–6 months after vaccination

Even tho' fewer young kids & more school-aged children, young adults

Daugla, Lancet 2014; 383:40-47

History of Men A vaccination in Chad

Chad was one of the first countries in Africa to attempt to prevent meningococcal disease by vaccination

In 1936, a serogroup A whole cell vaccine was produced at Sarh (formerly Fort Archambault) and widely distributed throughout Chad with apparent success, although no clinical trial was done

Polysaccharide vaccines first used extensively 1988 epidemic – but epidemics continued despite much use of polysaccharide vaccines in reactive campaigns

Unique research opportunity in Chad

Studies done before and after vaccination provide some evidence for an effect but can be confounded by temporal changes in disease (or carriage) incidence that are independent of any intervention

This constraint applies especially to infections that tend to be epidemic such as meningococcal infection

The fact that only part of Chad was vaccinated, provided a unique opportunity to measure the effect of PsA–TT on meningococcal A disease incidence in vaccinated and unvaccinated areas at the same time **(sadly, carriage study not done in control areas)**

Clinical Infectious Diseases
Nov 2015 - supplement

No cases in 16 countries after MenAfriVac campaigns!

WHO analysis of routine vaccination in Burkina Faso: taking pre-emptive approach is cheaper than waiting for an outbreak and then vaccinating en masse (Colombini et al)

Mathematical model predicts return of epidemics in 15 years unless *MenAfriVac* made routine - assuming 10 years' average vaccine protection **(Karachaliou et al)**

Neonatal tetanus fell 25%! *(Borrow et al)*

Tetanus immunity rose, 20% to 59% in Mali (Basta et al)

"Knockout jab"

The Economist

MenAfriVac Nov 14th 2015

- *All of this makes **MenAfriVac** one of the brightest public-health stars around*
- *..if countries in the meningitis belt follow the prescription these studies suggest, they should be able, quickly, to put the lid on two scourges for the price of one*

WHO approved MenAfriVac for routine use 2015 – Ghana first

Preziosi expects 8–10 meningitis-belt countries to introduce routine MenAfriVac in 2016 - *Complacency or Competing health priorities, such as roll-out of IPV could slow introduction*

Using TT as a carrier protein

An attractive option for 3 reasons:

- Conjugate vaccines using TT as a carrier protein had been successfully developed
- Neonatal and non-neonatal tetanus are public health problems in sub-Saharan Africa
- conjugate vaccines that were made with TT had shown an ant-itetanus serologic response when tested

But risk of *carrier induced epitopic suppression,* in regard to the polysaccharide part of the conjugate vaccine, in teenage & adult studies of Men and Pneumo conjugates

Infants and adolescents

		Immune response to polysaccharide of	conjugate vaccine	Reference
HibV	Infant	DTP → HibV-TT	↑	[3-9]†
		TT → HibV-TT	↑	[10, 11]*
		DTP → HibV-DT	↑	[12]
		Passive maternally acquired TT→ HibV-TT	↓	[13, 14]†
	Neonate	TT → HibV-TT	No difference	[15]*
PCV	Infants	DTwP → PCV11-DT	↑	[16]*
		DTwP → PCV11-TT	↑	
		DTaP → PCV13-CRM_{197}	↑	[17]*
		DTaP → PCV7-CRM_{197}	Variable according to serotype	[18]*
		DTaP → PCV7-CRM_{197}	No difference	[19]*
MenCV	Adolescents (11–18 years)	Td → MenCV4-DT	↓	[20]*
		Tdap → MenCV4-DT	No difference	[21]*
		Tdap → MenCV4-CRM_{197}	No difference	[22]*
		TT → MenCV-TT	↓	[23]*

MenAfrivac: Issues

- **SEROGROUP A**

  How long will protection last?

  at personal and population levels

- **OTHER SEROGROUPS - replacement? *outbreaks?***

  serogroup X outbreak Niger 2005/6

  serogroup W Burkina Faso 2002

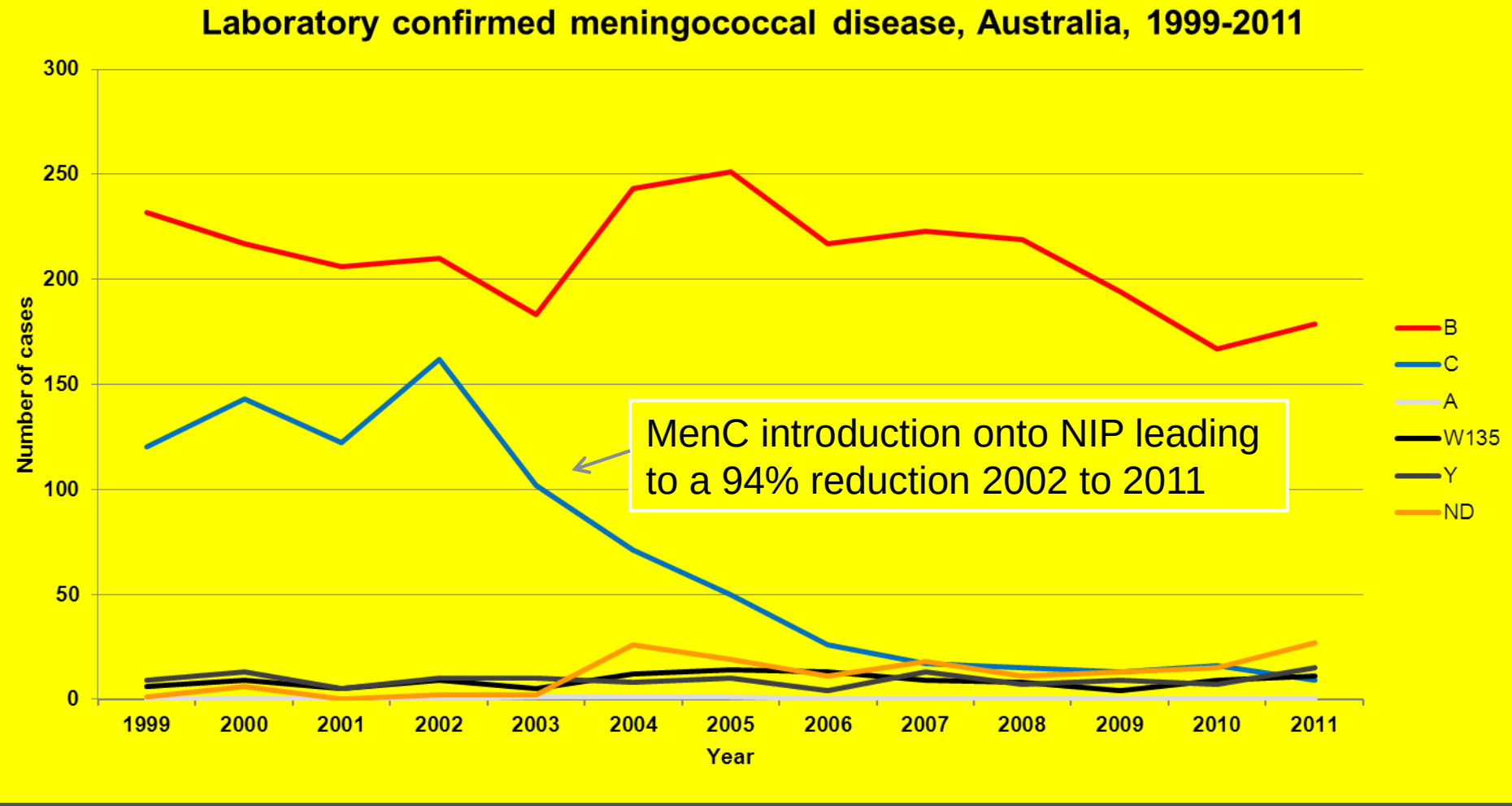
  serogroup C since the 1970s;

  - 2015 Nigeria and Niger 12,000 cases, 800 deaths

- ***Develop a pentavalent (A+C+W+X+Y) conjugate – trials 2016***

  OR a conserved ***protein vaccine?? BOTH EXPENSIVE!!***

Successful introduction of MenC vaccination into Australia's National Immunisation Program



Ongoing routine vaccination of 1 yr olds (carriage remains "very low") antibody protection became low and minimal "replacement" disease

Data source: Australian
Communicable Diseases

Followed for 4 years after Men C conjugate vaccination at 12 months of age;

1 year later: substantial fall in protection

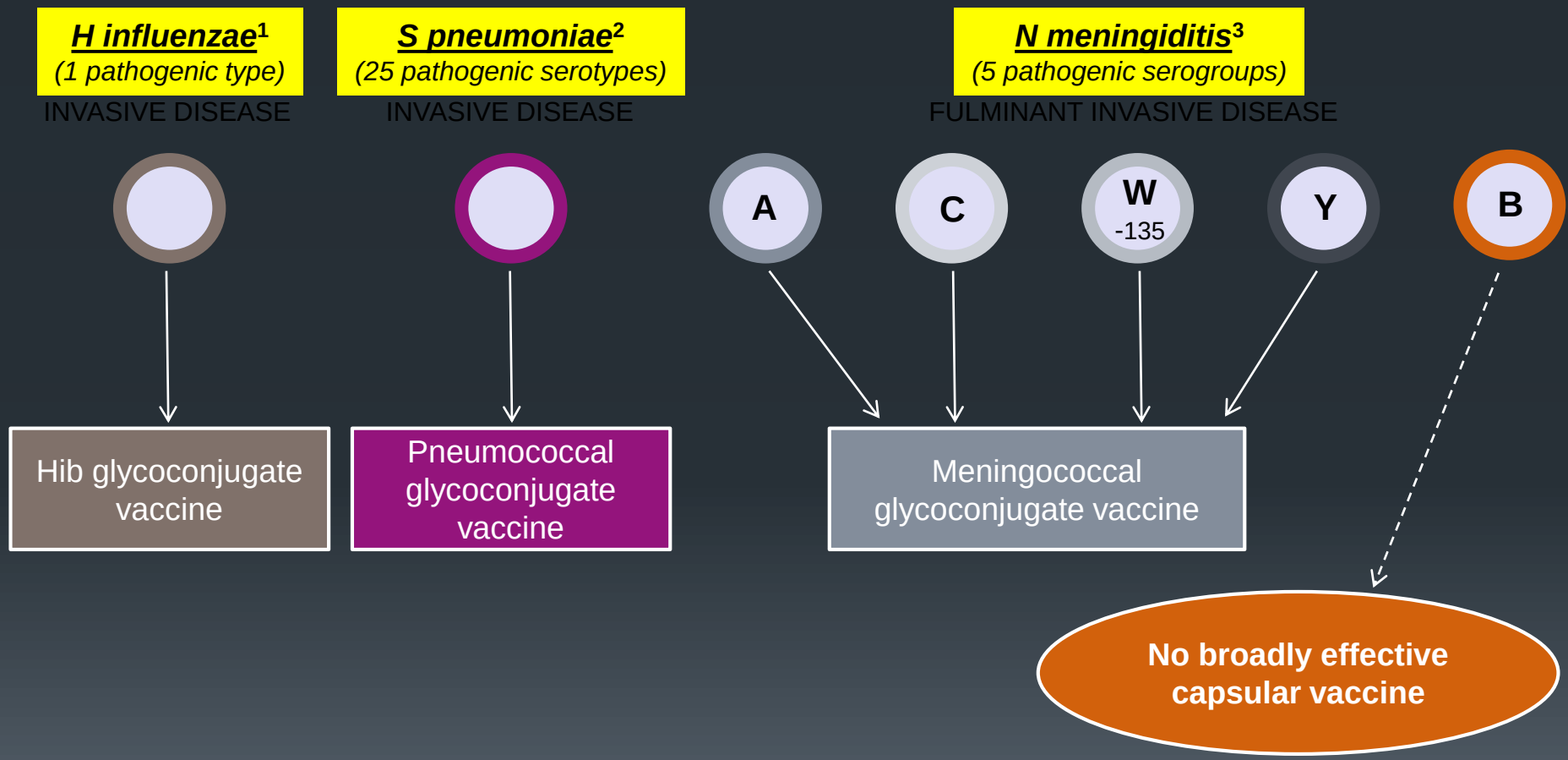
About 25% had a natural boost in 4 years F/U!!

Does this indicate community transmission of men C??

Meningococcal B epidemiology: middle and high income countries

- Highest incidence in babies
- New epidemic strain hits teens first
- Up to 2:100,000/year in developed countries
- maritime influence?
- uncommon in Asia, or not well measured

Conjugate Vaccines Against Meningitis-Causing Pathogens Have Been Successful Using the Polysaccharide (PS) Capsule



1. Watt JP, et al. *J Pediatr*. 2003;143(suppl 6):S163–S187; 2. Black S, et al. *Pediatr Infect Dis J*. 2007;26:771–777.
3. Häyrinen J, et al. *J Infect Dis*. 1995;171:1481–1490.

Meningococcal B vaccines

Novartis/Chiron
MeNZB™ licensed in
New Zealand, 2004

- Previously highly strain specific
  - outbreaks (NZ, Cuba, Norway)
  - Outer membrane vesicle vaccines
  - All seemed successful – **ceased except Cuba**
  - **Didn't come back in NZ…**
- Need antigens conserved in most prevalent types
- Need to immunise early in infancy (disease epi)
- 2 vaccine candidates
  - 4 component
  - Human factor H binding protein – 2 variants

Reverse Vaccinology Allowed the Identification of Novel MenB Antigens

Genomic-based approach to vaccine development

Complete *N. meningitidis* genome sequence

2158

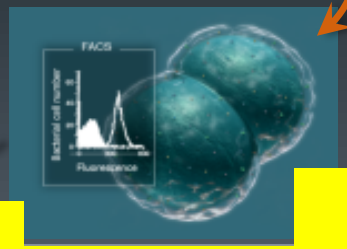
Bioinformatic analysis

570

Protein expression in *E. coli*

350

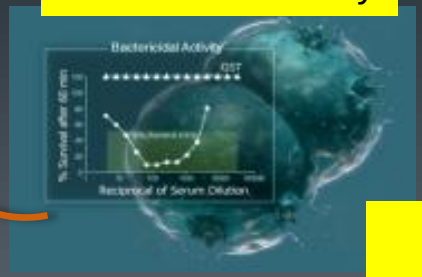
Protein purification and immunization



91

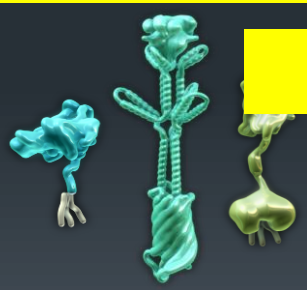
Confirmation of surface exposure

28



Confirmation of bactericidal activity

3



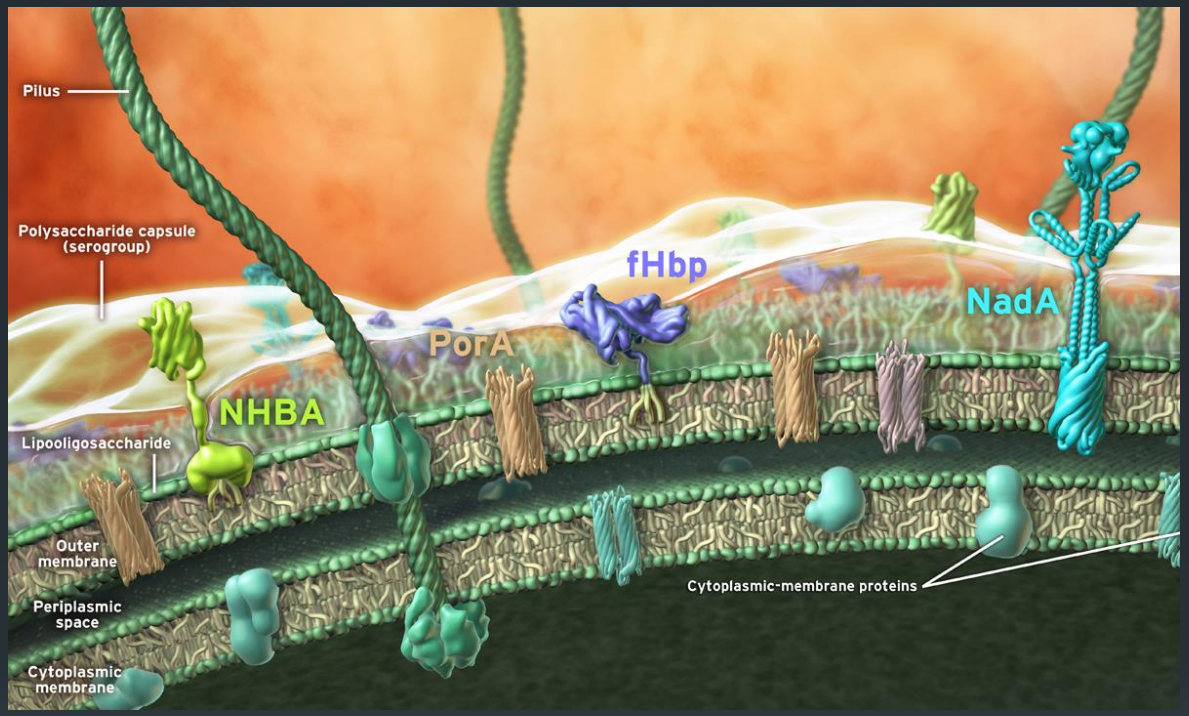
Final candidates selected for vaccine development

1. Tettelin H, et al. *Science*. 2000;287:1809–1815; 2. Rappuoli R. *Vaccine*. 2001;19:2688–2691; 3. Pizza M, et al. *Science*. 2000;287:1816–1820.

Summary of Antigenic Components of BEXSERO

Important for meningococcal survival, function, or virulence

- **NadA: Neisserial adhesin A Protein**
  - **Promotes adherence to and invasion of human epithelial cells[1-3]**
- **fHBP: factor H Binding Protein**
  - **Binds factor H, which enables bacterial survival[4,5] in the blood**
- **NHBA: Neisseria Heparin-Binding Antigen Fusion Protein**
  - **Binds heparin, which may increase the serum resistance of bacteria[6-8]**
- **NZ PorA P1.4: porin A**
  - **Major outer membrane vesicle protein—induces strain-specific bactericidal response**



Combining antigens that target different steps of meningococcal pathogenesis is likely to optimize MenB vaccine effectiveness

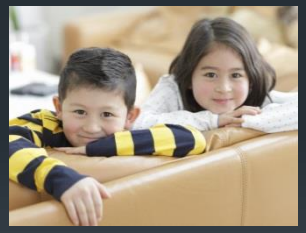
1. Comanducci M, et al. *J Exp Med*. 2002;195:1445–1454; 2. Capecchi B, et al. *Mol Microbiol*. 2005;55:687–698; 3. Mazzon C, et al. *J Immunol*. 2007;179:3904–3916; 4. Madico G, et al. *J Immunol*. 2006;177:501–510; Schneider MC, et al. *J Immunol*. 2006;176:7566–7575; 6. Semuto D, et al. *Proc Natl Acad Sci USA*. 2010;107:3770–3775; 7. Welsch JA, et al. *J Infect Dis*. 2003;188:1730–1740; 8. Plested JS, et al. *Clin Vaccine Immunol*. 2008;15:799–804.

BEXSERO® Has Been Studied in Large Clinical Studies Starting in Early Infants Through Adults

Approximately 7800 subjects (from 2 months of age) received at least 1 dose of the vaccine*

Infants and children 2 months to <2 years of age

- 5850 received at least 1 dose of BEXSERO
- 3285 received booster dose in second year of life



250 children 2 to 10 years of age

1703 adolescents and adults ≥11 years of age

*BEXSERO was evaluated in 13 studies, including 9 randomized controlled clinical trials.

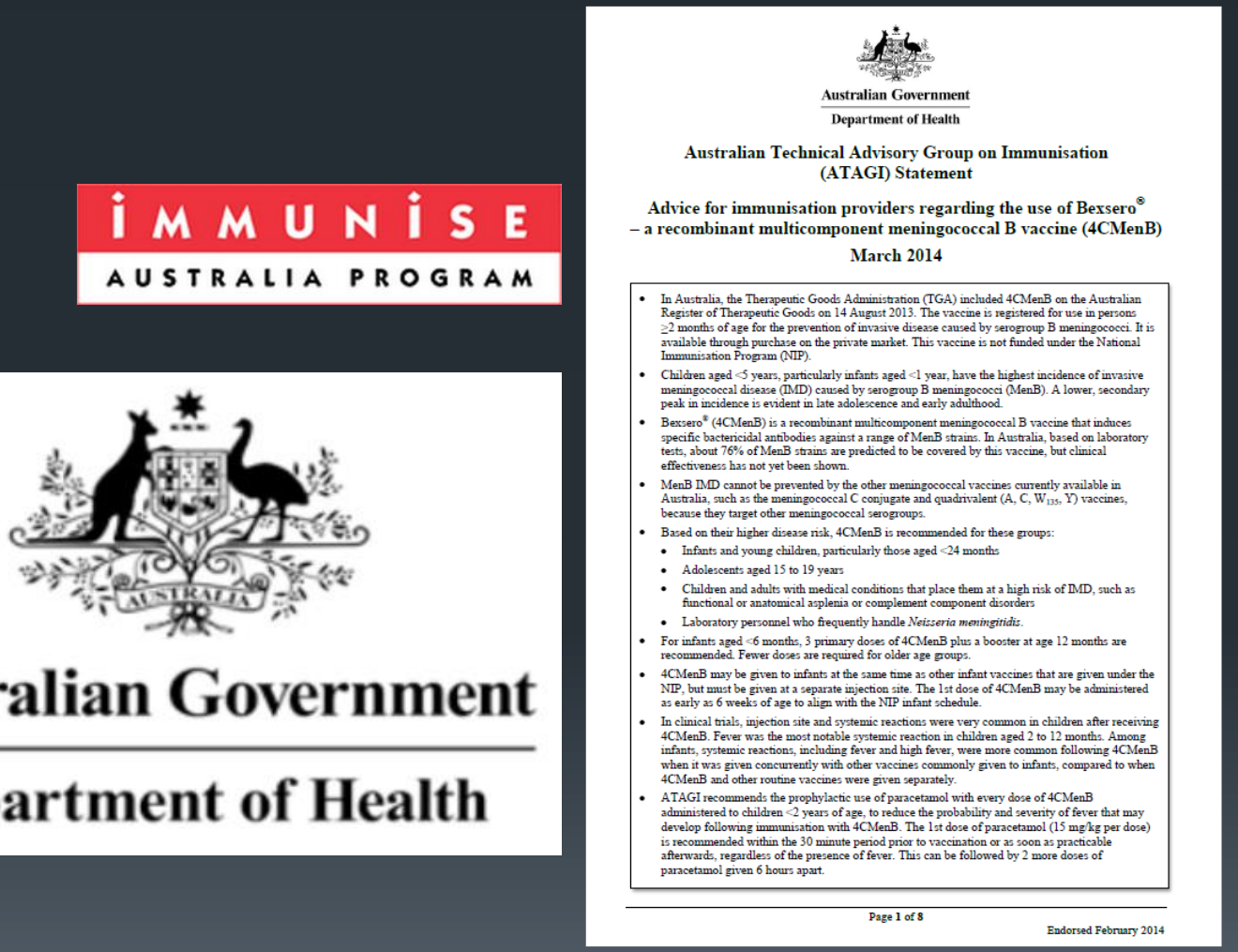
Data on file, Novartis Vaccines and Diagnostics.

In 2014, the Department of Health's Technical Advisory Group on Immunisation issued

'Advice for immunisation providers regarding the use of Bexsero®

IMMUNISE AUSTRALIA PROGRAM

Australian Government
Department of Health



Australian Government
Department of Health

Australian Technical Advisory Group on Immunisation (ATAGI) Statement

Advice for immunisation providers regarding the use of Bexsero® – a recombinant multicomponent meningococcal B vaccine (4CMenB)

March 2014

- In Australia, the Therapeutic Goods Administration (TGA) included 4CMenB on the Australian Register of Therapeutic Goods on 14 August 2013. The vaccine is registered for use in persons ≥2 months of age for the prevention of invasive disease caused by serogroup B meningococci. It is available through purchase on the private market. This vaccine is not funded under the National Immunisation Program (NIP).
- Children aged <5 years, particularly infants aged <1 year, have the highest incidence of invasive meningococcal disease (IMD) caused by serogroup B meningococci (MenB). A lower, secondary peak in incidence is evident in late adolescence and early adulthood.
- Bexsero® (4CMenB) is a recombinant multicomponent meningococcal B vaccine that induces specific bactericidal antibodies against a range of MenB strains. In Australia, based on laboratory tests, about 76% of MenB strains are predicted to be covered by this vaccine, but clinical effectiveness has not yet been shown.
- MenB IMD cannot be prevented by the other meningococcal vaccines currently available in Australia, such as the meningococcal C conjugate and quadrivalent (A, C, W_{135}, Y) vaccines, because they target other meningococcal serogroups.
- Based on their higher disease risk, 4CMenB is recommended for these groups:
  - Infants and young children, particularly those aged <24 months
  - Adolescents aged 15 to 19 years
  - Children and adults with medical conditions that place them at a high risk of IMD, such as functional or anatomical asplenia or complement component disorders
  - Laboratory personnel who frequently handle *Neisseria meningitidis*.
- For infants aged <6 months, 3 primary doses of 4CMenB plus a booster at age 12 months are recommended. Fewer doses are required for older age groups.
- 4CMenB may be given to infants at the same time as other infant vaccines that are given under the NIP, but must be given at a separate injection site. The 1st dose of 4CMenB may be administered as early as 6 weeks of age to align with the NIP infant schedule.
- In clinical trials, injection site and systemic reactions were very common in children after receiving 4CMenB. Fever was the most notable systemic reaction in children aged 2 to 12 months. Among infants, systemic reactions, including fever and high fever, were more common following 4CMenB when it was given concurrently with other vaccines commonly given to infants, compared to when 4CMenB and other routine vaccines were given separately.
- ATAGI recommends the prophylactic use of paracetamol with every dose of 4CMenB administered to children <2 years of age, to reduce the probability and severity of fever that may develop following immunisation with 4CMenB. The 1st dose of paracetamol (15 mg/kg per dose) is recommended within the 30 minute period prior to vaccination or as soon as practicable afterwards, regardless of the presence of fever. This can be followed by 2 more doses of paracetamol given 6 hours apart.

Page 1 of 8

Endorsed February 2014

http://www.immunise.health.gov.au/

Recommendations

Based on their higher disease risk, 4CMenB is recommended for:

- Infants and young children, particularly those aged <24 months
- Adolescents aged 15 to 19 years
- Children and adults with medical conditions that place them at a high risk of IMD, such as functional or anatomical asplenia or complement component disorders (see Chapter 4.10 of *The Australian Immunisation Handbook,* 10th edition1)
- Laboratory personnel who frequently handle *Neisseria meningitidis*

4CMenB is also recommended for all children and young adults who wish to reduce their risk of MenB disease

Only 30% uptake with an enthusiastic GP…

http

Advise patients that the prophylactic administration of paracetamol, at the time and closely after the jab, can reduce the incidence and intensity of post-vaccination febrile reactions

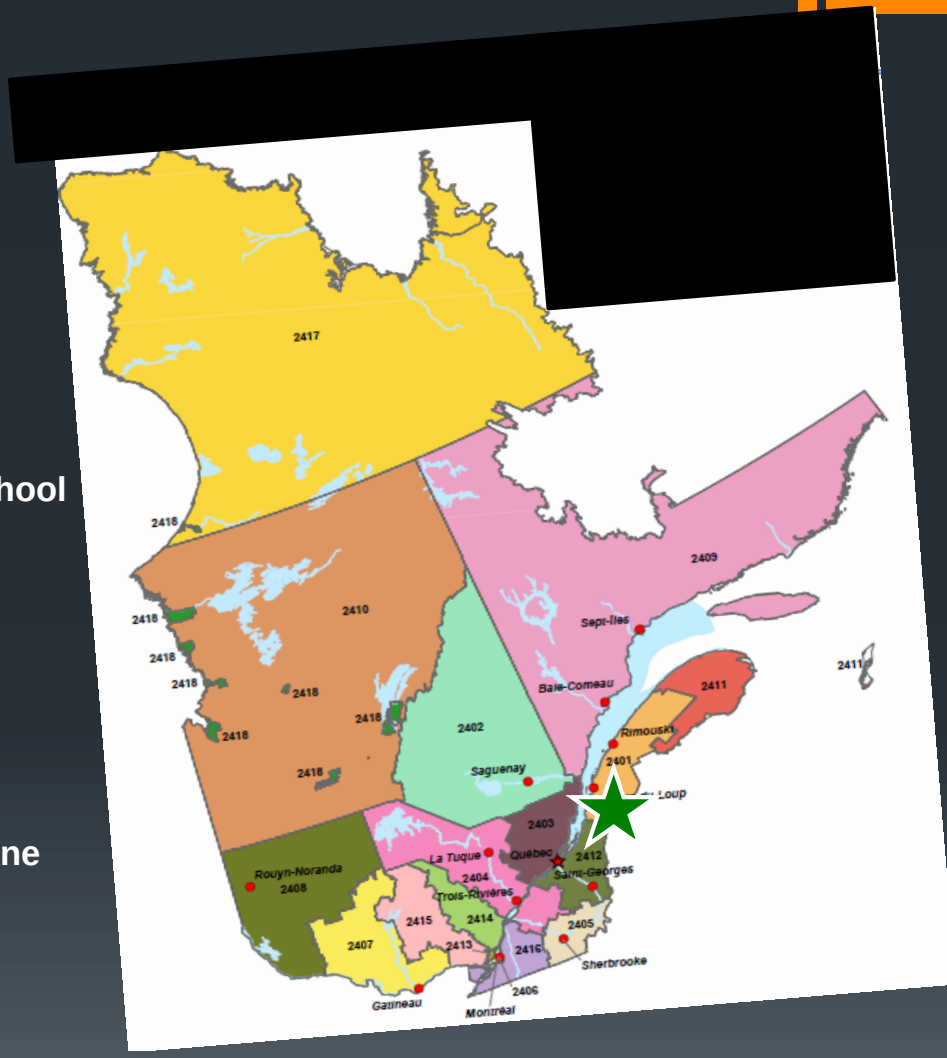
Background of ‘Fluvax’ febrile convulsion scare in Australia during 2010

So far, so good with implementation in the UK since Sept 2015

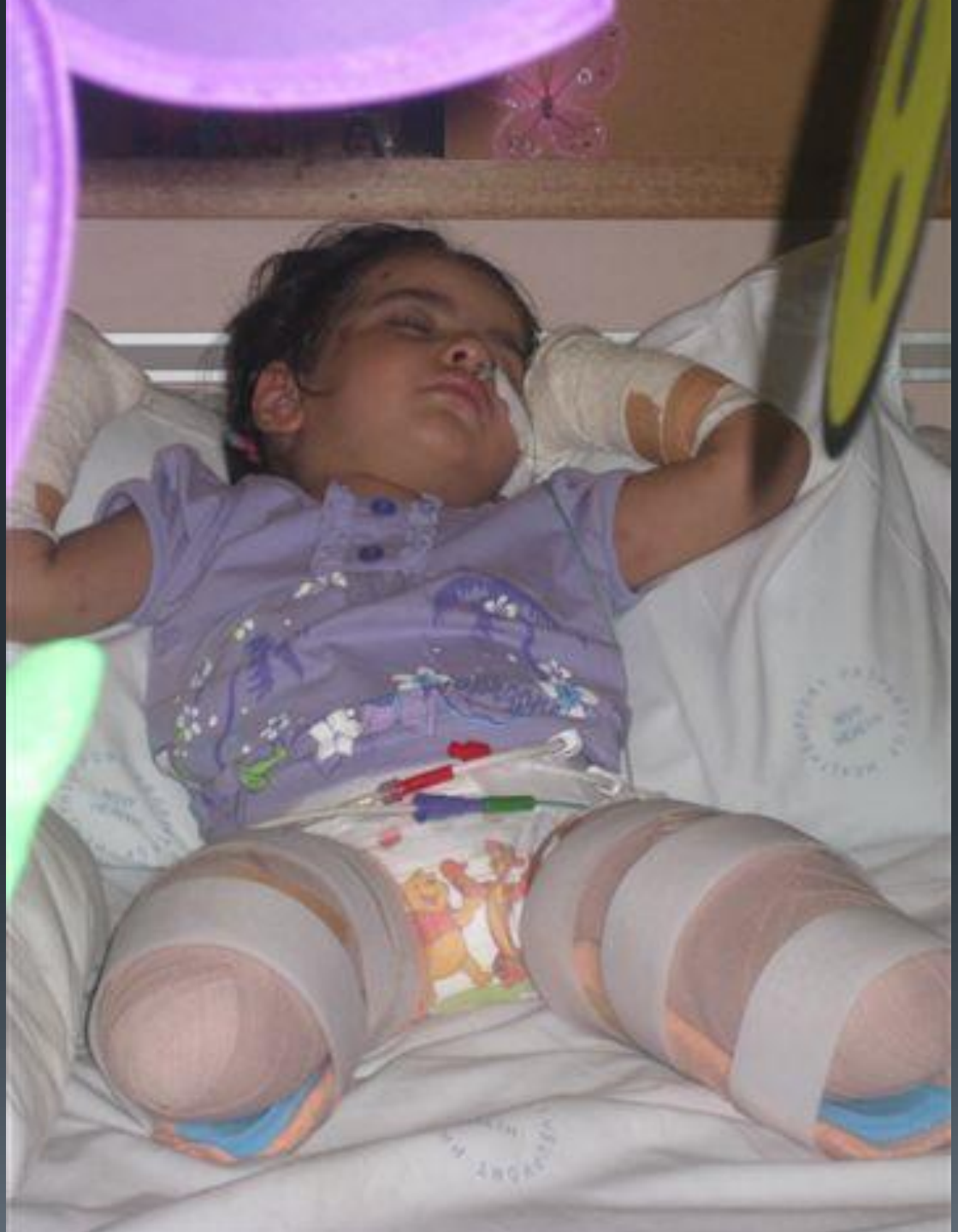
Bexsero Regional Program in Québec

Post-marketing studies started May 2014

- **Saguenay – Lac St. Jean region**
- **Program:**
  - **all persons aged 2months to <20 years of age**
  - **Between May 5 and June 17, 43,740 persons received their first dose**
- **Safety study:**
  - **Online safety survey of 12,332 vaccinees**
  - **Diary cards to assess fever, paracetamol use, school absenteeism, etc.**
  - **Within 8 days and 6 months after vaccination**
  - **Antipyretic use high (93% 2years old & under)**
  - **No signal of concern to date**
- **Effectiveness study, incl. vaccine registry:**
  - **Routine surveillance monitors for potential vaccine**




Governments need convincing to use Men B vaccines
There are obvious *and hidden* complication in the limbs and elsewhere



Uncertainties around effectiveness, carriage and transmission impact & cost-effectiveness

Bexsero Men B vaccine licensed in Australia

Today: Happy but new issues with school progress

Will the vaccine be recommended for routine use?

UK University Study: preventing acquisition of meningococcal carriage

Read, Lancet 2014

2954 participants randomly assigned

987 assigned to control , 979 4CMenB , 988 MenACWY

33% of 4CMenB group, 34% MenACWY group & 31% controls were carriers at study entry

By 1 month, there was no difference in carriage between controls and 4CMenB (odds ratio 1·2, 95% CI 0·8–1·7) or MenACWY-CRM (0·9, [0·6–1·3]) groups

From 3 months after dose two, 4CMenB vaccination resulted in significantly lower carriage of

any meningococcal strain (**18·2%** [95% CI 3·4–30·8]),

capsular groups BCWY (**26·6%** [10·5–39·9]) &

capsular groups CWY (**29·6%** [8·1–46·0]

compared with control vaccination

Further work in teens and travellers indicated - RCT & observational

Complications of serogroup B meningococcal disease in survivors

Infect Disord Drug Targets. 2014;14:205-12

Dastouri F, Hosseini AM, Haworth E, Khandaker G, Rashid H, **Booy R**

National Centre for Immunisation Research and Surveillance,

This systematic review evaluated the prevalence of long-term complications of serogroup B meningococcal disease (MD)

- Only 12 appropriate studies were identified by searching databases from 1946 to 2014

Systematic review

The average prevalence of hearing impairment was 4.2% among serogroup B MD survivors;
2.3% suffered amputation, 2.3% seizures

Compared with complications due to non-meningococcal B bacterial meningitis, *physical impairment and seizures were more common in survivors of meningococcal B disease*

Few studies quantified less frequent/obvious complications such as *cognitive dysfunction*
More comprehensive reporting of complications and costs of serogroup B MD in survivors and their families is needed to inform vaccination policy

Outcomes of invasive meningococcal serogroup B disease in 245 children & adolescents (MOSAIC): a case-control study

Viner RM Booy R et al Lancet Neurol 2012; 11:774-83

Serogroup B meningococcal disease is commonest cause of meningitis & septicaemia in children in high-income countries

Assessment of new serogroup B meningococcal vaccines is hampered by lack of data on burden of disease in survivors

Of 537 UK children who had serogroup B meningococcal disease over 2 years, 245 were assessed

328 controls were also recruited

Complications

- Children who had serogroup B meningococcal disease were more likely than controls to have:
- bilateral sensorineural hearing loss of 40 dB or more
- lower full-scale IQ

  mean 99·5 for children with MD, 107·2 controls
- psychological disorders 61 (26%) of 235 children with MD vs 33 (10%) of 322 controls
- ***Children with MD also more likely to have deficits in executive function and multiple aspects of memory***

Complications

- 10% have major disabling deficits and
- >30% have one or more deficits in physical, cognitive, and psychological functioning, with the additional burden of memory deficits and executive function problems
- *All survivors of serogroup B meningococcal disease should be screened for psychological disorders and cognitive deficits*

What this large study lacked?

- ***There were no physical examinations done by the researchers – relied only on the medical notes***
- **Long-term complications - 3 or more years after disease were not captured**
- Special attention was not given to the severe cases that required intensive care
- An economic analysis has not been published

Extra costs and impacts
A case I saw recently

11 yr old boy from regional NSW, Australia
Age at diagnosis: 7 months
Complications of meningococcal disease

- Skin necrosis: many patches requiring split skin grafts

- **Extra issues**

  Mother did not work for 1 year $35,000 plus benefits
  2 years “burns suits” changed every 6 weeks = $700 each
  Travel & accommodation costs from regional NSW $450/trip
  Father’s time off work
  Mental disturbance - It took mother “12 months to stop crying”
  Grandparents (both sets) heavily involved in support/childcare

Bone growth plate damage right radius (elbow) and right tibia at ankle: *detected 10 years later*

Surgical correction of right tibia

Local Lions club provided $18,000 to help with the many expenses associated with recovery

– but ran out by 6 months post-operation

Money covered new wide bed, bed cradle, wheel chair, shower chair, crutches, dressings, sundry medications, special clothing e.g. pants split to accommodate external fixation, travel by family peri-operatively & accommodation

Additional costs

Mother took another 4 months off work as child was in constant pain post-surgery

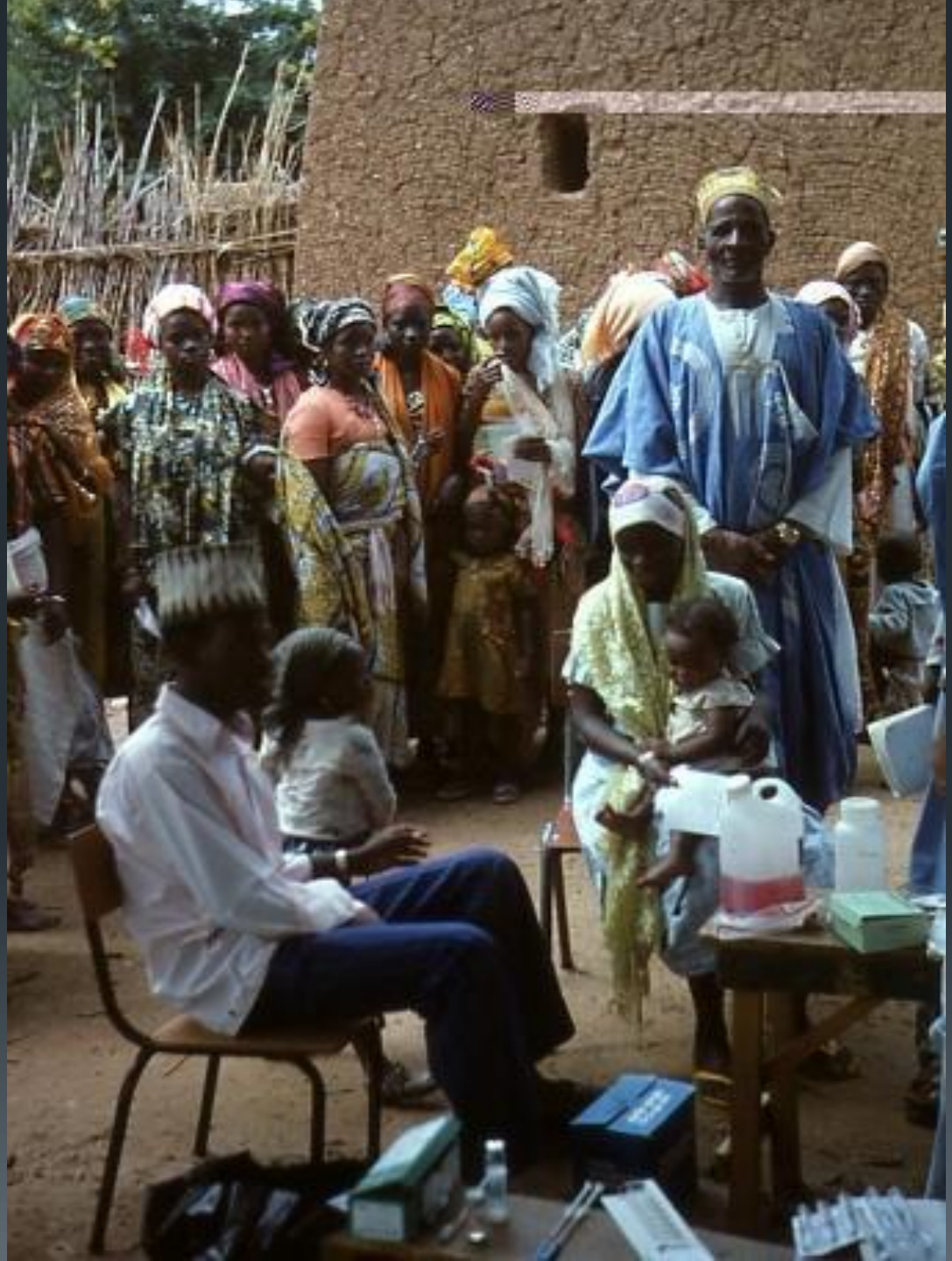
She then suffered exacerbations of Crohn's disease causing two hospital admissions for herself

Weekly private physiotherapy continuing: $80 each

Additional travel costs not covered above $500/trip plus parent time off work – 1 trip so far

Robust shoes to assist with residual gait

Mental disturbance: Disturbed sleep, mental anguish,



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Giribaldi family &
Eliza Ault-Connell,
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‘Doctoring Little Mermaid’ tells the story Of Eliza: triumph of resilience over adversity