NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

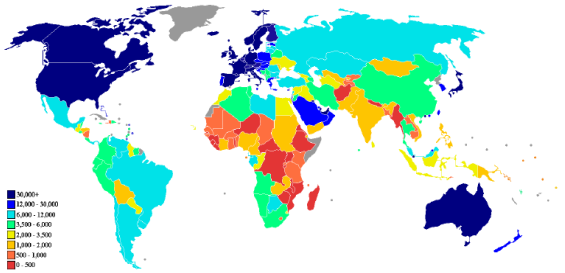
Enteric Vaccines

Dr KH Keddy
Centre for Enteric Diseases
National Institute for Communicable Diseases
National Health Laboratory Service

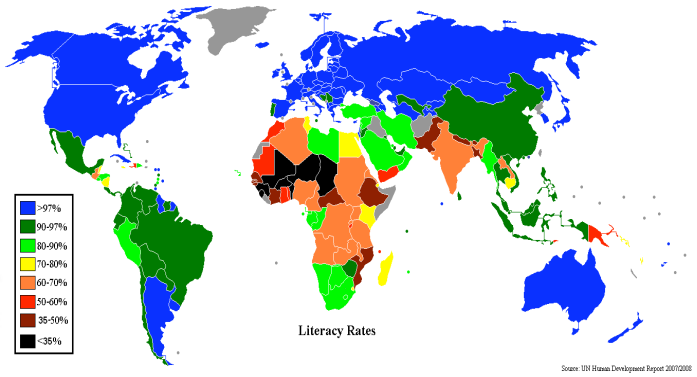
NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

Challenges in Africa

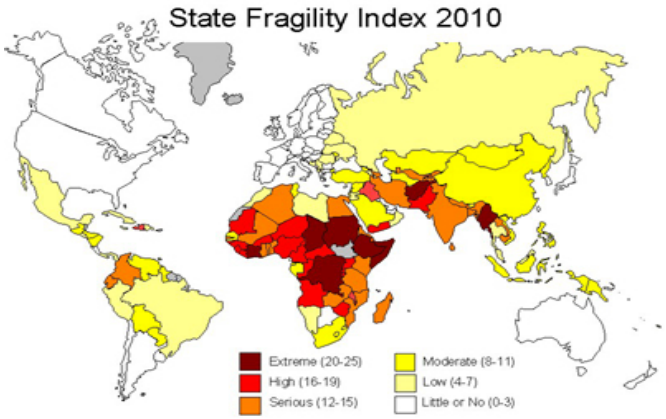
International GDP



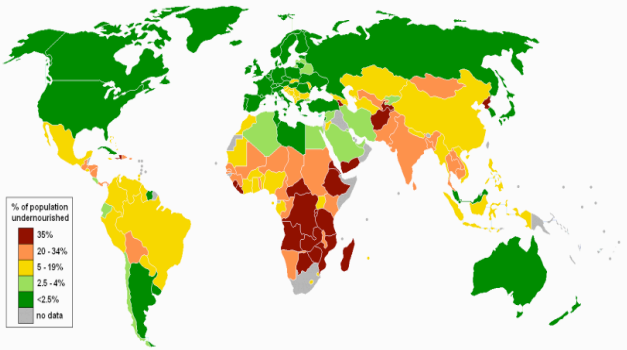
International Literacy Levels



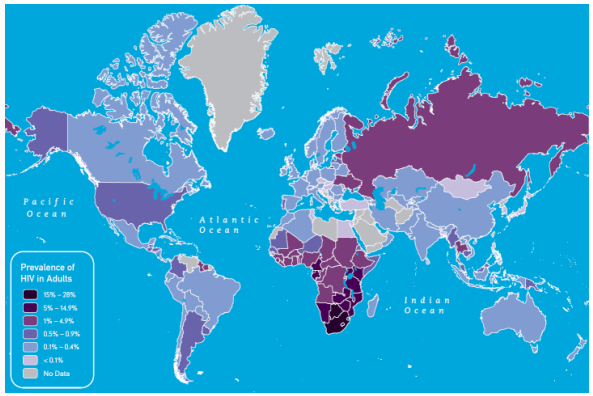
State Fragility Index 2010

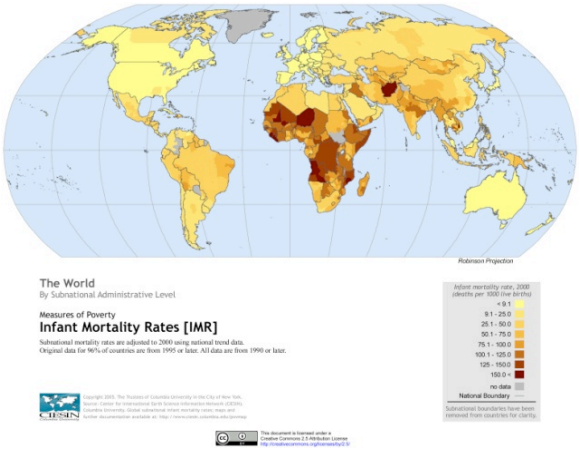


International Undernourishment Levels



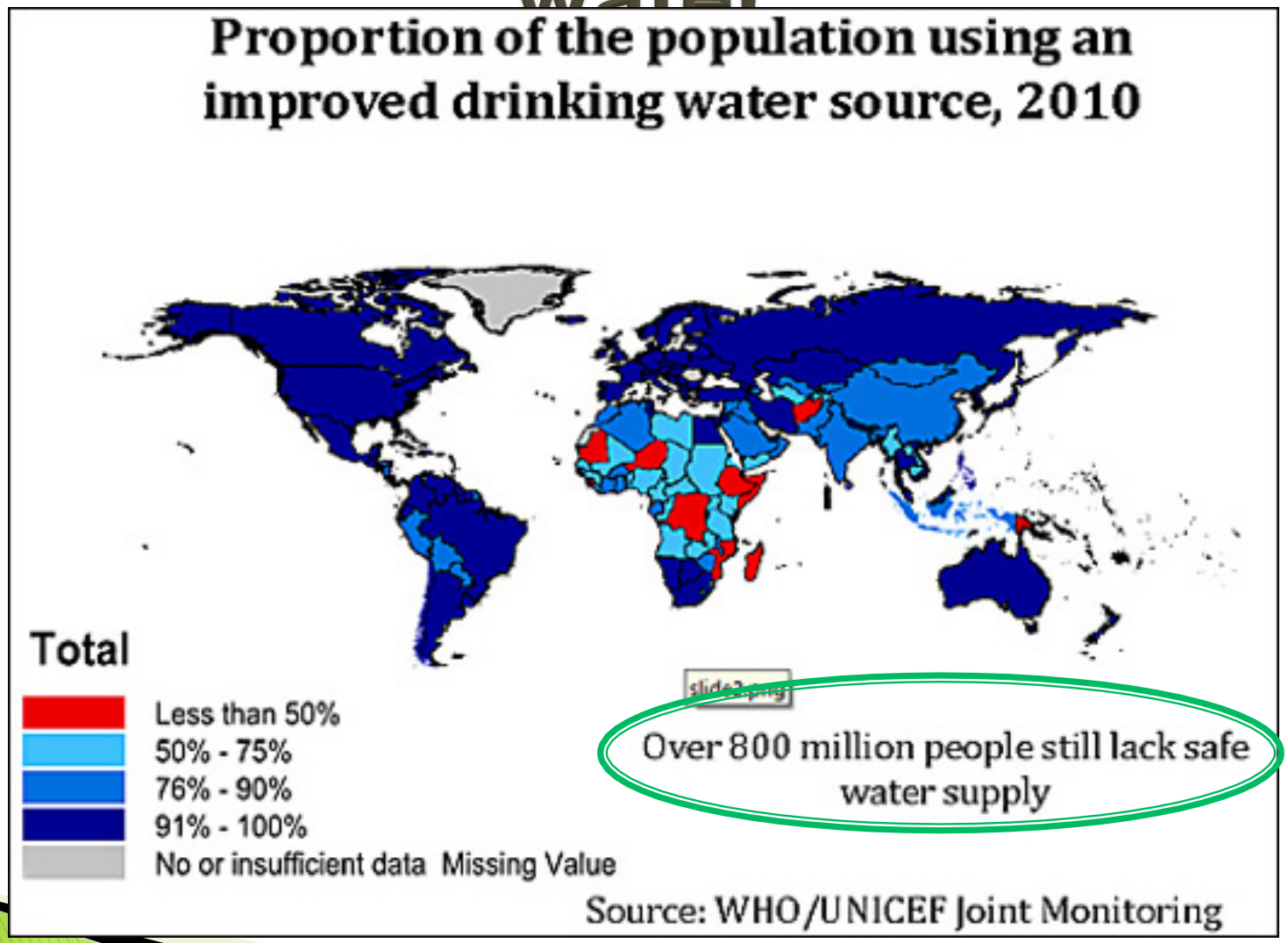
International HIV





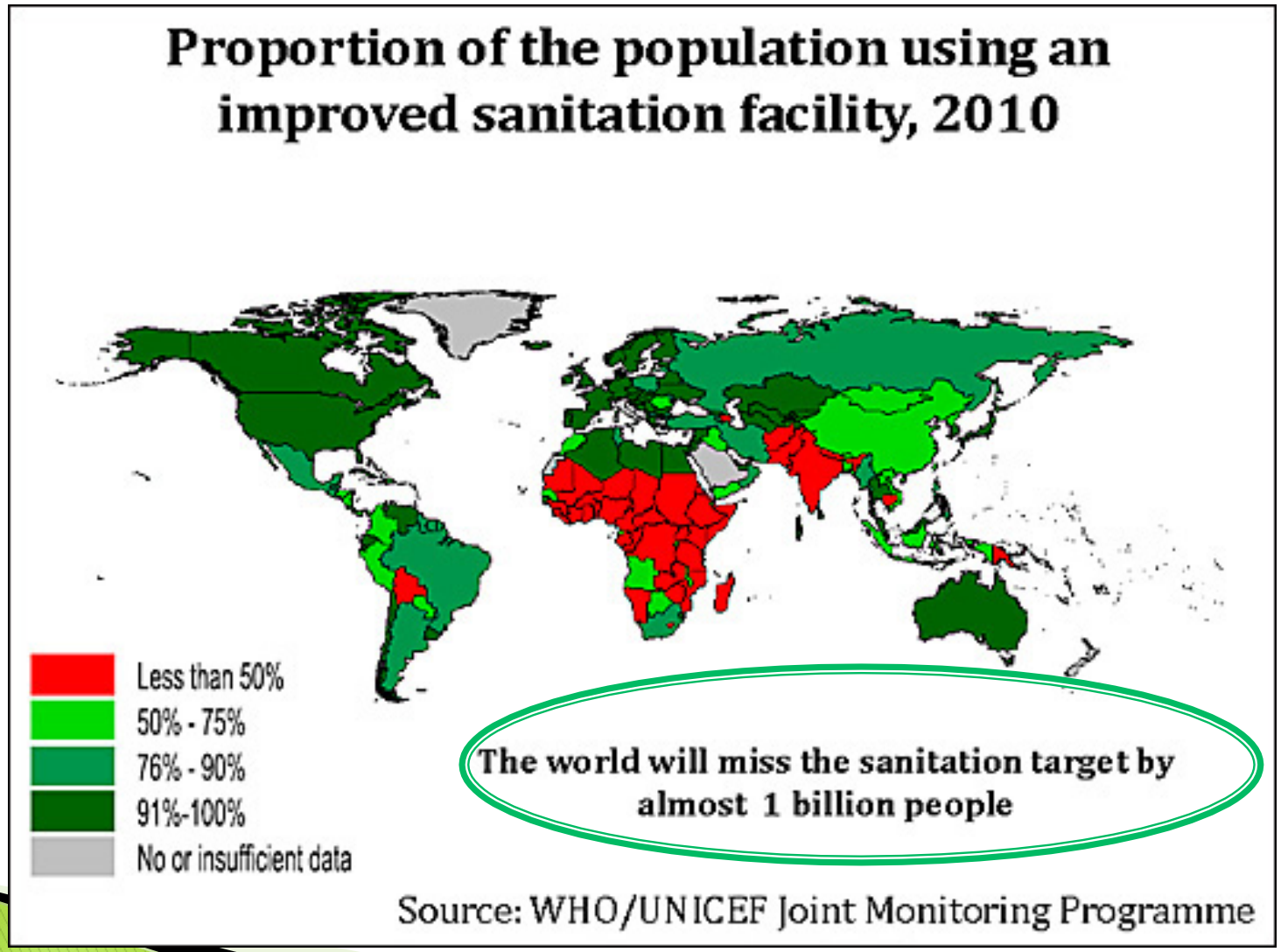
NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division in the National Health Laboratory Service

Access to improved drinking water



NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division in the National Health Laboratory Service

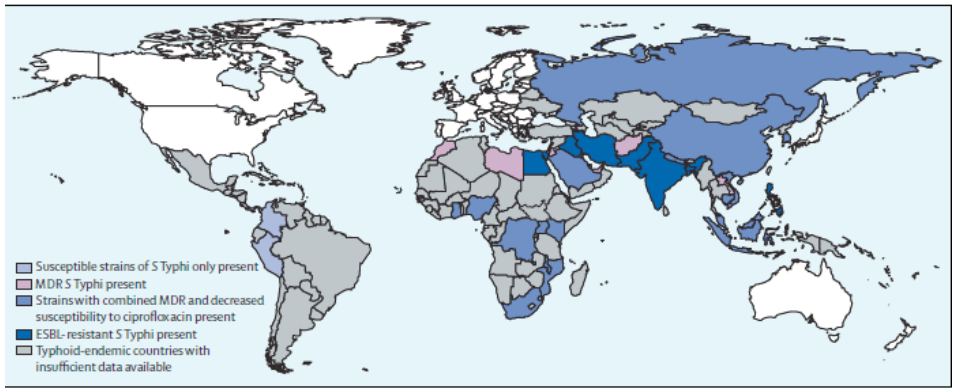
Access to improved sanitation



NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

History of enteric vaccines

- Typhoid fever vaccine: developed 1890s - used in Boer War 1899-1902.
- Inactivated whole cell vaccine, – heat killed, then later heat-phenol inactivated.
- Three doses required.
- Severe systemic and local reactions – caused poor compliance.
- Outbreaks of chloramphenicol resistant typhoid fever in Mexico & Vietnam 1970s.
- Incentive - alternative antibiotics and vaccines developed.



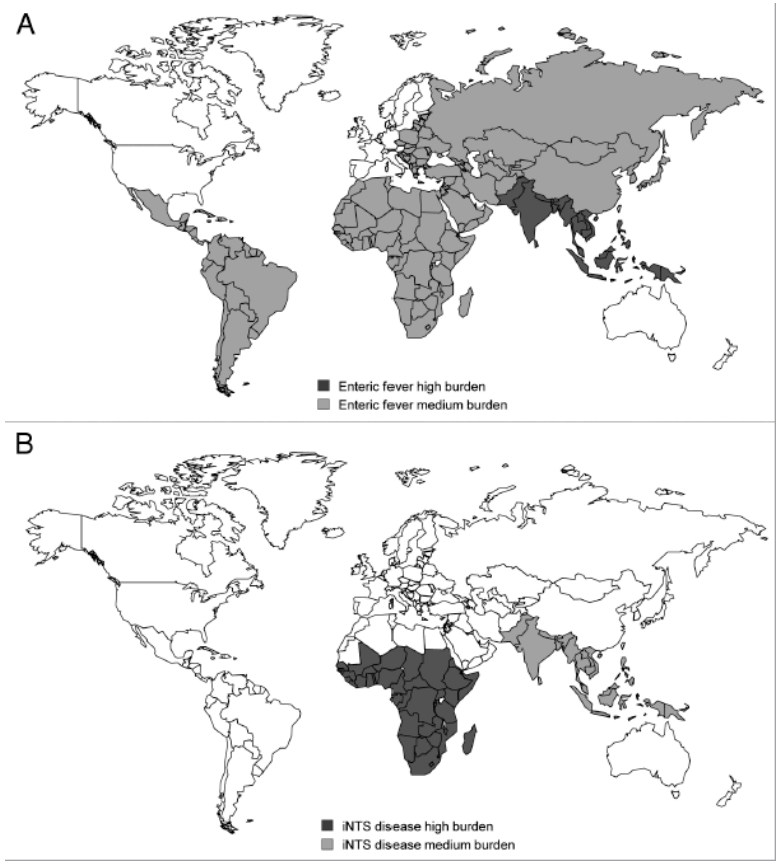
NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

Invasive enteric infections

Immunity

- Immunity depends on IgM, IgG & T-cell response.
- NTS may cause local gut inflammation in healthy individual.
- *Salmonella* Typhi targeted entry via M cells? ↓immune response.
- NTS – major problem in Africa due to malaria and HIV.

Burden of enteric fever vs iNTS

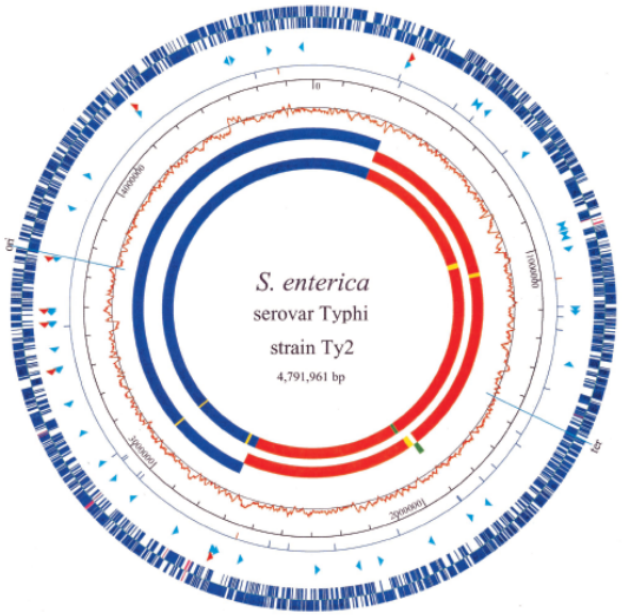


MacClennan et al, 2014

NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

Ty21a

- Attenuated live oral vaccine.
- Three – four doses on alternate days.
- Enteric coated / given in buffer.
- Not available in RSA (Vivotif®).
- Derived from Salmonella Typhi Ty 2.
- Gal E mutant – incomplete LPS; cell lysis with uptake of galactose.



NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

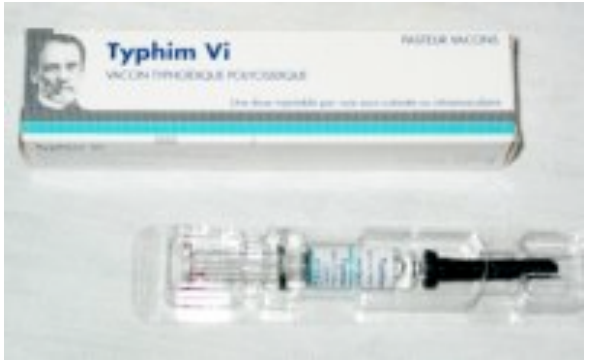
Clinical information

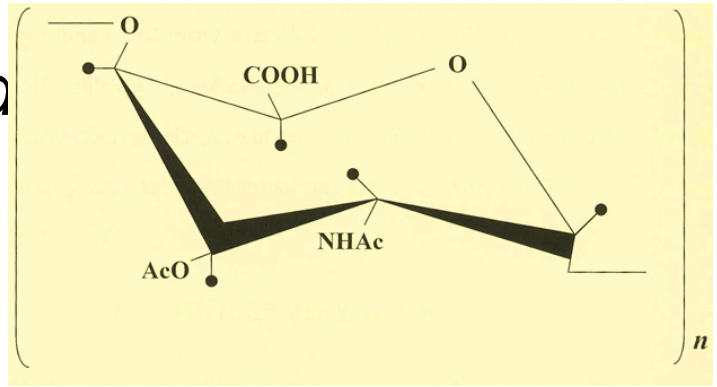
- Cold chain must be maintained.
- Protection occurs 10 – 14 days after 3rd dose.
- Approved for children > 5 years.
- S.E.s: nausea, vomiting, abdominal pain (milder with enteric coated tablets).
- Three year cumulative efficacy: 51% (95%CI 36-62%) (Fraser *et al*, 2007).
- Precautions: antibiotics; immunosuppressive states (incl. pregnancy).
- Booster after 3 years recommended.

NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

Vi vaccine

- Vi polysaccharide capsule
- Single IM dose.
- Available in RSA (Typhim Vi®; Typherix®).
- CPS - antiphagocytic.
- Common to *Citrobacter freundii* and *Salmonella Paratyphi* C.
- α1→4,2deoxy-2-N-acetyl galacturonic acid – variable O acetylation at C3 group.





NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

Clinical information

- No cold chain to be maintained.
- Protection occurs after 7 days; reaches maximum at 28 days.
- Approved for children > 2 years.
- S.E.s: pain/swelling @ injection site.
- Three year cumulative efficacy: 55% (95%CI 30-70%) (Fraser *et al*, 2007).
- Precautions: febrile illness, pregnancy.
- Booster after 3 years recommended.
- May last 7 years.

NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

New vaccines

- Vi-rEPA
  - Vi conjugated to *P. aeruginosa* exoprotein A.
  - Phase III trials Vietnam: efficacy 89% (95%CI 76-97%).
  - Side effects – no erythema/swelling; mild fever.
  - China – four doses given to infants as part of EPI – well-tolerated & immunogenic.
- New protein conjugates investigated
- Vaccines for paratyphoid fever

NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

New ideas

- More immunogenic formulations of attenuated *Salmonella* Typhi:
  Δ*aroC*/Δ*aroD* mutants.
  phoP/*phoQ* mutants.
- Alternative proteins for vaccination:
  OMP (porin protein) of *Salmonella* Typhi
- Use of Ty21a as vaccine vector:
  Shigella sonnei, *Escherichia coli*, *Vibrio cholerae*, *Bordatella pertussis*, *Plasmodium falciparum*, *Bacillus anthracis*, *Listeria moncytogenes*.
- New methods of vaccine delivery
  Intranasal vaccination
- Other conjugates
- Vaccines for paratyphoid fever

NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

Non-invasive enteric vaccines

- Cholera vaccine developed in 1884 – for parenteral administration.
- Short-lived response of SIgA with parenteral boosters in immunised individuals.
- Shift to oral vaccines d.t. recognition of role of mucosal immunity in last 35 years.

NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

Diarrhoeal deaths by pathogen, children 0 – 59 months

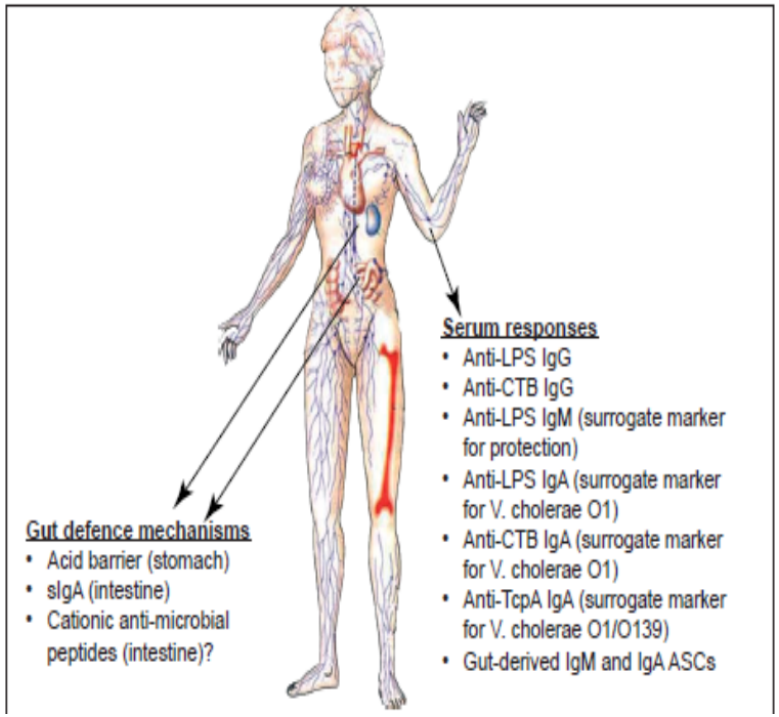
Pathogen	Medians restricted to add 100%		
	Median	No. Deaths (×1000)	95% CI (×1000)
Viruses			
Rotavirus	27·8%	197	110–295
Calicivirus	9·9%	71	39–113
Astrovirus	2·1%	15	9–26
Adenovirus	3·1%	22	12–37
Bacteria			
EPEC	11·1%	79	31–146
ETEC	6·0%	42	20–76
Shigella spp	3·9%	28	12–53
Campylobacter spp	3·2%	22	11–50
Salmonella spp	2·5%	18	10–30
Vibrio cholerae O1	1·3%	9	0–37
Parasites			
Cryptosporidum spp	2·0%	14	3–31
Giardia lamblia	2·3%	16	0–66
Entamoeba histolytica	0·2%	1	0–19
Episodes with unknown etiology	24·5%	176	56–304
Total	100·0%	712	491–1 049

Lanata et al, 2013

NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

Cholera vaccines

- WHO prequalified – vaccination should be given in area under threat.
  - Dukoral - WCrBS (cholera) - V. cholerae O1, El Tor & Classical - expensive
  - SHANCHOL – Killed whole cells: *V. cholerae* O1, El Tor & Classical, O139 – cheaper, but not licensed in most African countries
- Vaccine protection is still short-lived (2 years), 70% effective.
- Some protection for ETEC infect (travellers diarrhoea).



NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

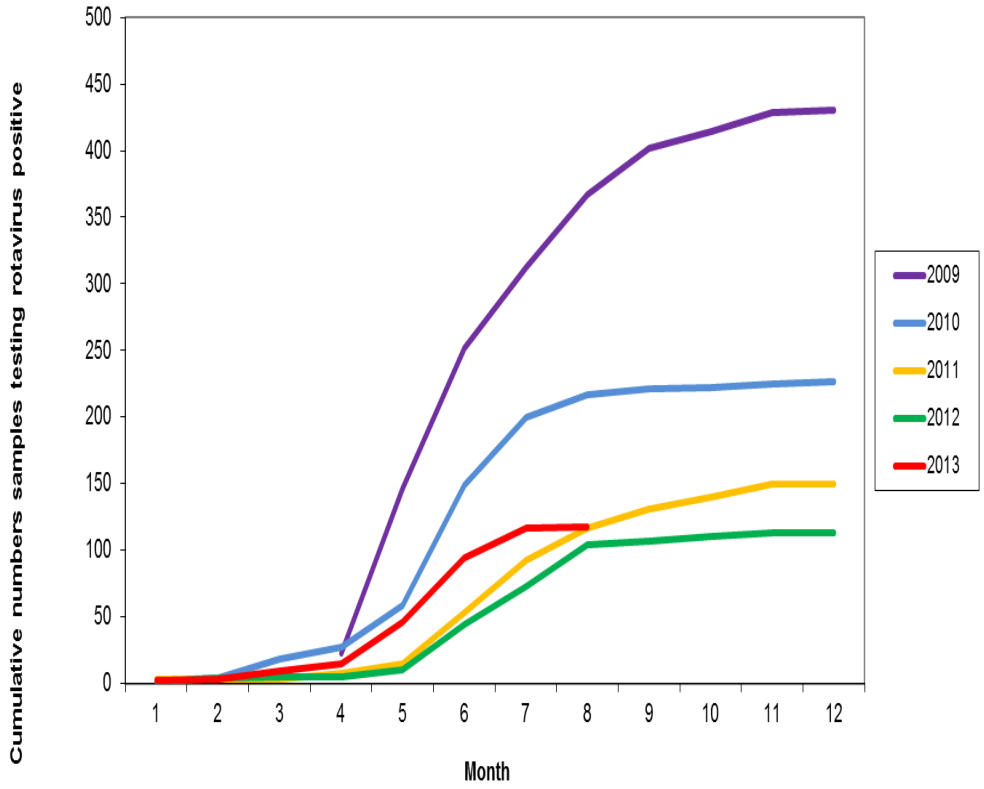
New cholera vaccines

- Development of live attenuated & killed oral vaccines.
- Live vaccines - concern about the use in immunocompromised patients.
- LPS subunits, DNA vaccines and rice seeds containing toxin subunits.
- Alternative drug delivery systems: microparticles, proteoliposomes.

NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

Rotavirus vaccine

- Introduced in RSA in 2009.
- In all children < 5 years old, a reduction of 54-58% in rotavirus diarrhoea between 2009 and 2010/2011
- Vaccine coverage moderate with majority on-time
- The 2013 rotavirus season part of “surge” year phenomenon
- Intussusception surveillance has been implemented in South Africa



Data courtesy of Dr N Page; CED, NICD

NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

New candidate vaccines - DEC

- ETEC
  - Diverse serotypes make O antigen poor candidate
  - Toxin based (LT & ST)
  - Addition of CFA in oral live attenuated & inactivated vaccines show reduction in diarrhoea severity.
- EPEC
  - Candidate vaccines based on virulence proteins: BfpA, intimin, EspB
  - Antigenic potential reacts with human sIgA
  - Live oral *eae* mutant – not protective in human studies.
- EHEC
  - Protein fusions of different virulence factors, including Stx1 & Stx2, zot and intimin.
- EAggEC
  - No studies currently being done, but proteins are immunogenic.
  - Lactoferrin inhibits adhesion.

NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

New candidate vaccines - niNTS

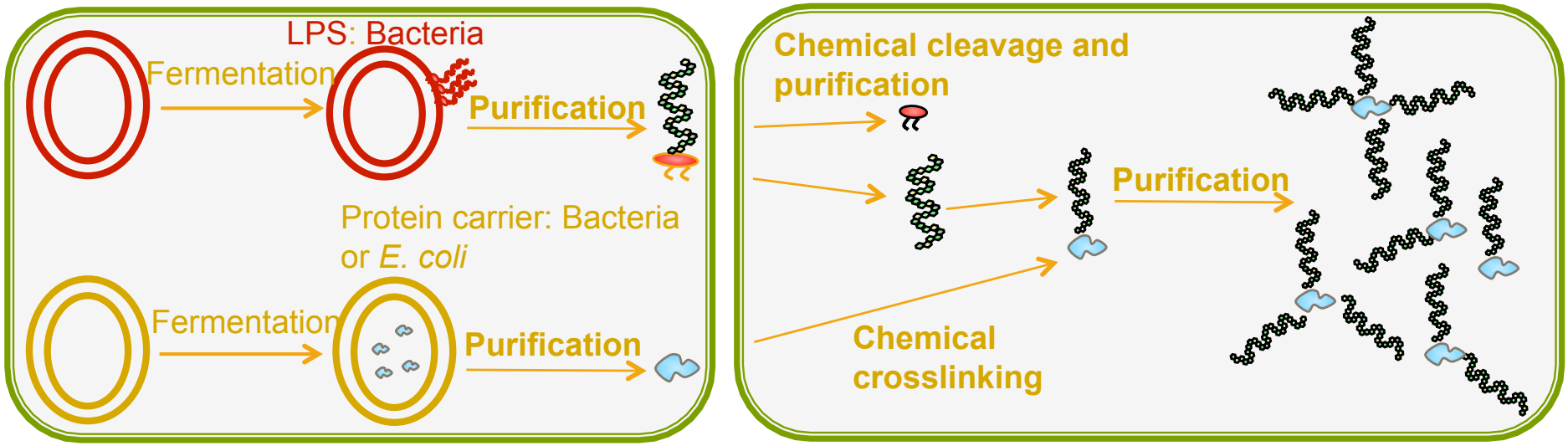
- *Salmonella* Enteritidis and *Salmonella* Typhimurium commonest serotypes internationally.
- Researchers have looked at glycoconjugate, attenuated and OMP candidates.
- Lack of commercial incentive for development.
- Mechanisms of testing (mouse models):
  - Oral immunization & oral challenge (high protection)
  - Oral immunization and parenteral challenge (not done)
  - Parenteral immunization and oral challenge (high protection)
  - Parenteral immunization and parenteral challenge (high protection)

NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

New candidate vaccines - *Shigella*

- Which serotypes to include?
  - GEMS: quadrivalent vaccine; O antigens from *S. sonnei*, *S. flexneri* 2a, *S. flexneri* 3a, and *S. flexneri* 6; presence of common group antigens (3,4; 6 & 7,8) should cover remaining serotypes/ subserotypes.
- Attenuated mutants and hybrid live vaccines with ETEC
- Inactivated glycoconjugates.
- Approach is to cover EIEC as well (similar but less virulent).

Current manufacturing process of conjugate vaccines



- Chemical conjugation to protein carrier is unspefic and difficult to control
- Conjugate vaccine is heterogenous
- Production, characterization, anlysis and release is complex

Slide courtesy of Michael Wacker

Bioconjugation: site specific conjugation

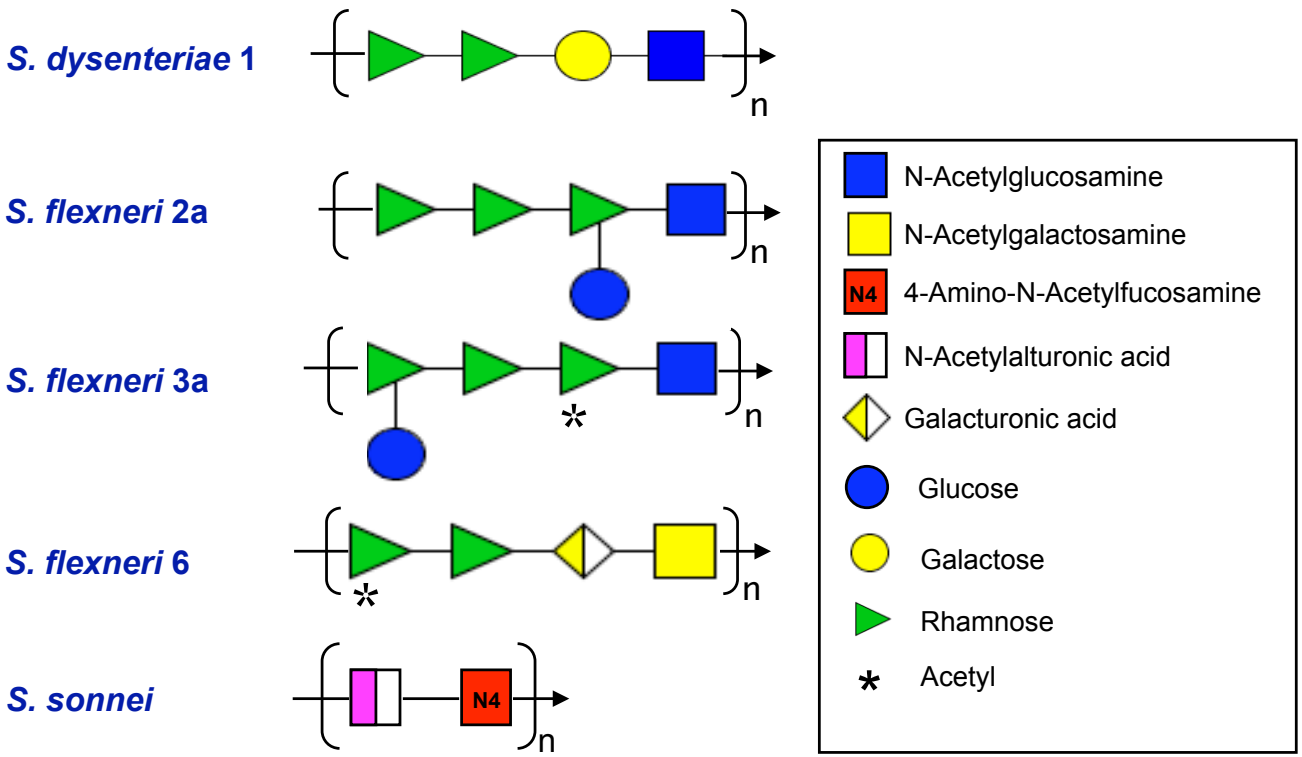
- Solution to overcome unspecific conjugation:
  - Chemistry-free, in-vivo technology in an *E. coli* system
- Benefits:
  - Higher immune response due to natural epitopes
  - Well-characterized and consistent product, leading to high reproducibility
  - Site selected conjugation allows to use homologous protein antigens as carrier, therefore broadening the efficacy of the vaccine:
    - Protection against encapsulated and non-encapsulated strains

Slide courtesy of Michael Wacker

GlycoVaxyn

Components of *Shigella* Vaccine

- Multi target vaccine: Surface polysaccharides of *Shigella* strains (O-antigens) elicit specific immune reaction



Slide courtesy of Michael Wacker

NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

New candidate vaccines - *Campylobacter*

- Disease is complicated by autoimmune and other conditions – GBS, IBS, IBD, reactive arthritis.
- Disease is common in many countries and probably under-diagnosed (3 -15 cases/1000 in various studies in developed countries; 29 cases/ 1000 GEMS).
- Polysaccharide-protein conjugate vaccines in development.
- Live model - no lipooligosaccharide ganglioside mimicry developed.

NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

New candidate vaccines – Enteric viruses

- Candidate vaccines for Norovirus and Adenovirus
- Driven by BoD – although common, mortality & long term morbidity is low
- Live oral vaccines and novel delivery systems:
  - Intranasal
  - Transgenic foods
- Adenovirus also used as a vaccine vector

NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

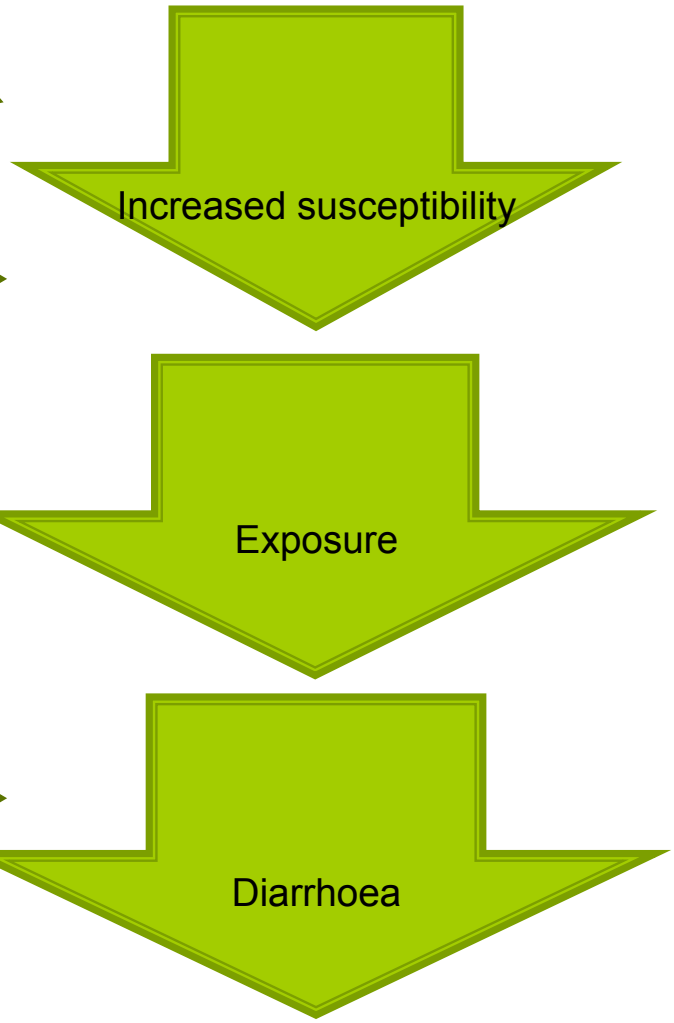
A rational approach to managing enteric infections

Environmental
Water, sanitation, hygiene, hand washing, overcrowding

Nutrition
Breastfeeding, complementary feeding, Vitamin A/zinc

Vaccines
Rotavirus, cholera, typhoid fever,
new enteric vaccines?

Treatment
ORS, HAART, continued feeding, zinc, antibiotics (dysentery), probiotics



Delivery platforms

Promote community-based health and behaviour change

Financial incentives to promote health care seeking

Integrated community case management

Facility-based integrated management of illnesses.

Survival ⟷ **Death**

NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

Conclusions

- Some disease potentially eradicable e.g. typhoid fever.
- Low incidence rates and outbreak driven – may not warrant inclusion in EPI.
- Consider vaccinating those at high risk, during outbreaks if community under threat.
- Think outside the box: Vaccines for NTS/DEC/ *Campylobacter* – vaccinate food animals.
- Control predisposing diseases – HIV & malaria.

NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

Thank you!