Tackling iNTS disease

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Tackling iNTS diseases

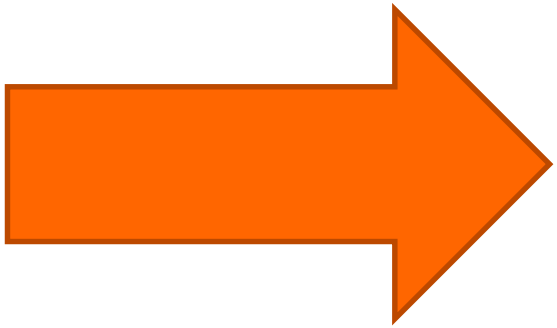
Prevention *AND* treatment

- Treatment
  - Diagnosis remains a challenge
  - Awareness of population at risk and risk factors
  - Changing patterns of drug resistance
- Environmental intervention
  - Mode of transmission?
  - What is the reservoir?
    - Human to human or animal (bird) to human?
  - Environmental persistence?
- Vaccines
  - Burden of disease estimates
  - Identification of target populations
  - Identification of trial sites and endpoints

All three depend on epidemiological research

Why a vaccine for iNTS?

- Difficult to diagnose
- Rapid onset
- Widespread drug resistance
- Other vaccines (Hib, pneumococcal) work well in the African context



- iNTS vaccine attractive
- Likely be feasible to develop and efficacious

iNTS vaccines

Candidate_Name/Identifier	Pre-clinical	Phase 1	Phase 2	POC	Phase 3
Attenuated oral vaccine: CVD 1931(S. Typhimurium Δ*guaBA,* Δ*clipX*) and CVD 1944 (S. Enteritidis ΔguaBA, ΔclipX) [UMB]	X				
Attenuated oral vaccine: WTO5S. (S. Typhimurium Δ*aroC*, Δ*ssaV*) [Microscience Limited]		X			
O:4,5-TT [NIH]	X				
O antigen-flagellin conjugates. O:4,5 : FliCi and O:9 : FliCg,m. [UMB; Bharat Biotech; Wellcome Trust]	X				
Bivalent conjugate (O:4,5-CRM_{197} and O:9-CRM_{197}) [SBVGH]	X				
O:4,5-GMMA and O:9-GMMA [SBVGH]	X				
OmpD [University of Birmingham, SBVGH]	X				

See discussion paper for WHO vaccine priority meeting

http://who.int/entity/immunization/research/meetings_workshops/NonTyphoidalSalmonella_VaccineRD_Sept2014.pdf?ua=1

Timelines for iNTS vaccine 2015 - 2026

- Best case scenario for development
  - Assumes no delays (almost never happens)
  - Minimizes future predictions for burden of disease
- Worst case scenario for resources
  - Potential bottleneck in obtaining epidemiological input
  - Requires major early investment in trials and manufacturing

Timeline and epidemiological implications

2015: Preclinical	2016-2017: Phase 1	2019: Phase 2 & cPoC
Vaccines in development Case for an iNTS vaccine Initial TPP	Production of pilot scale GMP vaccine Trials in healthy adult volunteers	Age de-escalation completed in infants Phase 3 manufacturer engaged
Epidemiology to support early development **Target groups identified** **Epidemiology to support TPP**	**Epidemiology to support case for Phase 3 trials and manufacture** **cPoC criteria identified** **Phase 3 efficacy sites identified**	Epidemiology to support case for deployment Phase 3 trial sites ready Engagement of WHO/UNICEF/GAVI and other public and national health authorities

Timeline and epidemiological implications

2023: Phase 3 Efficacy	2025: Registration	2026+ deployment
Manufacture scaled up Consistency lots Trials in HIV infected adults Phase 3 studies complete Efficacy estimates	National registration	Phase 4 studies WHO prequalification allowing UNICEF/GAVI involvement
Update of burden of disease figures	Preparation for deployment	Vaccine effectiveness studies

Target Product Profile (TPP)

- Target populations (infants, HIV all ages, high incidence areas?)
- Minimum usable efficacy
  - This strongly impacts Phase 3 trial design
- Minimum usable longevity of protection
- A lot of technical stuff re dose, production, formulation etc.,

First 3 require substantial epidemiological input

Case for Phase 3 / manufacturing

The impact of the vaccine over period 2025 -2035?

- Need to know how many are infected now
- Predict changes that will happen in next 20 years and impact on iNTS incidence
- Need to predict impact of vaccine on burden of disease
  - Likely vaccine uptake
  - Likely efficacy
  - Other factors
- Burden of disease and impact need credible range estimates

Timeline and epidemiological implications

2015: Preclinical	2016-2017: Phase 1	2019: Phase 2 & cPoC
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By 2017: cPoC criteria identified

- cPoC is NOT an estimation of efficacy for registration
- Existing animal models and *in vitro* killing activity (SBA, OP assay) but no surrogate for protection in humans
- For Infants
  - *S.* Typhimurium infection – inverse correlation with antibody
    - Loss of passive maternal antibody and low actively induced antibody
    - cPoC may be based on antibody levels
  - *S.* Enteritidis infection – no published data
- For HIV infections – not clear.
- Sero-epidemiology would be useful at least in infants

By 2017: Phase 3 / efficacy sites identified

By 2020 sites ready

- Infants only, HIV adults only, both?
- *S.* Typhimurium, *S.* Enteritidis, or both (and others)?
- Needs stable infection rates
- Needs infrastructure to identify and diagnose cases.
  - *c.f.* RTS,S trials for a disease with much higher incidence.
- Probably needs multiple sites

Efficacy studies – Trial design

- Assumptions
  - Testing a bivalent vaccine in Infants
  - Age distribution similar to that seen in Malawi (MacLennan et al, J Clin Invest. 2008)
  - Vaccination at EPI schedule and followed until 18 months old
  - Vaccine is 80% efficacious
  - Power of the trial is equal to 80%
  - Lower Limit of 95% CI for efficacy rate is ≥10%
  - Vaccine and placebo group ratio is 1:1
- Expect 15 cases in each group in absence of vaccination

10-20,000 subjects needed

assuming similar incidence to that seen in the RTS,S trials

Conclusions

- Vaccines for iNTS are feasible
- Development will require a strong epidemiological basis
  - Burden of disease estimates
  - Identification of target populations
  - Identification of trial sites and endpoints
- Timeline is critical – Delays add to development costs and uncertainties