Ethics in Public Health Intervention Trials

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Outline

- Background
- Clinical development
- Major Public Health Interventions
- Challenges with Consenting Process
- Using placebo vs known working
- Examples from Tanzania; mainly malaria

Background

- **Great strides made in the area of ethics following past bad experiences**
- **Product developers (vaccines and drugs) are very meticulous about provision of information and actual consenting**
- **Major concern seems to be protection of the sponsor as evidenced by lengthy consenting**
- **Role of ethical research in R&D**

Clinical Development

- **Phase I: uses volunteers – seeks to establish safety, tolerance and PK**
- **Phase IIA: in patients – seeks to confirm safety and tolerance and establish efficacy (and PK)**
- **Phase IIB: in patients - determines dose regimen, efficacy, safety & immunogenicity**
- **Phase III: in patients – establishes efficacy and safety of the chosen dosing regimen in larger numbers or patients**

Major Tools

- **Vaccines &Drugs: Safety, efficacy, PK, availability/cost, compliance**
- **ITNs:Despite known benefit, affordability, compliance, safety issues with LLNs and final disposal come up**
- **Insecticides and Biological control: Safety and acceptability**
- **Challenges: Communication with community before, during and after research**
- **Conflicting priorities; crops destroyed by rats**

Phase I Clinical Trials: Difficult to explain but easy to conduct

- First in humans testing
- Small number of healthy volunteers
- Evaluate safety and side effects
- Early evidence of immune response

Example

- **MSP3 phase Ib malaria vaccine trial in children in Korogwe (AMANET). Vaccine safe and immunogenic.** *Lusingu JP et al. Malar J. 2009 Jul 17;8:163.*
- ***Major challenge was explaining why during community sensitization said were goig to give a vaccine that was still trial ("Chanjo ya majaribio")***
- ***Had to go back with district authorities to explain what vaccine candidate means***

Phase II Clinical Trials

- Efficacy of vaccine/drug
- Study of dose range
- Establish clinical performance
- Expand the safety database
- Immunogenicity

Example

- **Phase IIb RTS,S malaria vaccine trial (Mal-49) in children at Korogwe and Kilifi (PATH-MVI). Safe, immunogenic and 53% efficacy. *Bejon P et al. N Engl J Med. 2008 Dec 11;359(24):2521-32.***
- **Challenge was to explain why control arm was given rabies vaccine. Placebo no longer acceptable.**
- **At end of trial, vaccine arm received rabies vaccine**

Phase III Clinical Trials

- Large groups of people (thousands)
- Gather extended safety and tolerability data in subject
- Collect efficacy data along with health economics information
- Demonstrate consistency of manufacturing process

Example

- **RTS,S phase 3 malaria vaccine trial in children: Currently running in Korogwe which is one among 11 sites in Africa. Data from first 6000 children published in 2011 showed 56% protection against malaria disease and 47% against severe malaria (***Agnandji ST and RTS,S Clinical Trials Partnership. N Engl J Med. 2011 Nov 17;365(20):1863-75***.**
- **Challenge: Huge information package and informed consent for study participants**
- **ITNs were accepted by sponsor as standard of care as per national guidelines**
- **Question during dissemination of results: When, where, who, safety, cost?**

Registration

Phase III Clinical Trials may lead to

Regulatory Approval

This is our hope when we conduct clinical trials

Phase IV and indication discovery

- **Additional studies in adults** to deal with specific country regulatory requirements
- **Paediatric studies** – useful in all infectious diseases since the disease immune status of and the PK of drugs in small children, and especially in infants, are not the same as in adults; such populations – may need a different formulation (***AQUAMAT study observed lower artesunate and DHA exposure in smaller children- Hendriksen I et al., submitted***)
- **Studies in pregnant women** – the most neglected patient population because of concerns about teratogenicity and litigation
- **Prophylactic studies** – important in diseases such as malaria where no vaccine available
- **Phase IV PV :** Post-marketing surveillance; Korogwe will participate in such study in prep for RTS,S licensure

Drug Trials1: AQUAMAT

- **A multi-centre open label randomised comparison of injectable Artesunate and quinine in patients with severe falciparum malaria in Africa (AQUAMAT): Sponsor: Univ of Oxford, Wellcome Trust**
  - **Major findings influenced policy on treatment of severe malaria (*Dondorp AM. et al.* *Lancet. 2010 Nov 13;376 (9753):1647-57*).**
  - **WHO recommendation in April 2011 for injectable artesunate to be used in parallel with quinine for severe malaria**
  - **Challenge: Giving ART vs QN (known standard); Mortality and neurological sequale end points**

Drug Trials-2: Kili-IPTi

- **Between 2006 and 2008, a trial of IPTi using SP, chlorproguanil-dapsone (CD) or mefloquine (MQ) was conducted in Same and Korogwe, NE Tanzania.**
- **IPTi using a long acting, efficacious drug such as MQ can reduce episodes of malaria in infants in a moderate transmission setting but tolerability problem (***Gosling RD, Lancet. 2009 Oct 31;374(9700):1521-32***.)**
- **Challenge was stopping recruitment in Same where malaria had declined drastically- Approval was given**
- **WHO issued a policy recommendation on use of SP-IPTi strategy in areas without SP resistance.**

HIV Research

- **In a PMTCT trial in Tanga looking at cART to prevent ARV resistance, stigma was a major issue (***Theilgaard ZP et al. AIDS Res Ther. 2011 Aug 2;8(1):28. PMID: 21810224***).**
- **Referral success in the same PMTCT was low (***Anne Arreskov et al. International Health. Online 29 January 2010***).**
- **In an ancillary study linked to InterACT project at Teule, looking at interactions between ARVs and Alu, several lab tests and frequent contact with project staff was seen as providing a service better than routine hospital care** *(Reynolds J et al. Submitted***).**

HIV Research-cont

- **Another ancillary study within InterACT project noted a difference in ways that Tanzanians report harms data compared to South Africans** (*Allen EN Eliciting harms data from trial participants, Trials. 2011 Dec 13;12 Suppl 1:A10.*
- *Mangesho P et al (Abstract ACTc 2012 AGM),* ***observed*** **perceptions of drug strength compelled people with HIV and malaria to separate drug taking time to avoid anticipated harm to the body and to facilitate daily activities**

Epidemiology: Community Surveys

- Community sensitization
- Consenting
- Challenge with re-consenting, one year later, for those <18 years by parents and not guardians. Requirement by sponsor

Early diagnosis and treatment of malaria in 4 villages (CORPs strategy)

- **Data to document declining malaria & for M&E of interventions and MDGs**
- ***Mmbando BP et al. Malar J. 2010 Jul 23;9(1):216.***
- **RDTs reduced malaria overdiagnosis.**
  Ishengoma DS. et al. *Malar J. 2011 Jun 26;10(1):176.*
- **Use of Community owned resource persons (CORPs)**
  Rutta AS et al. *Malar J. 2012 May 3;11(1):152.*

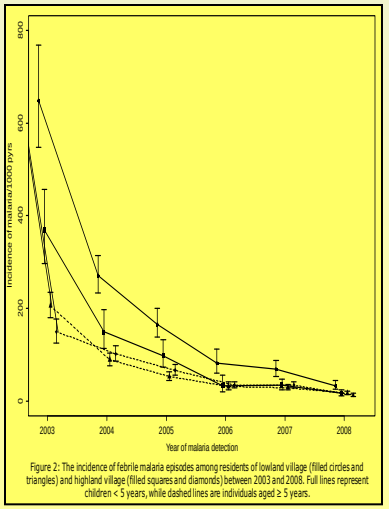
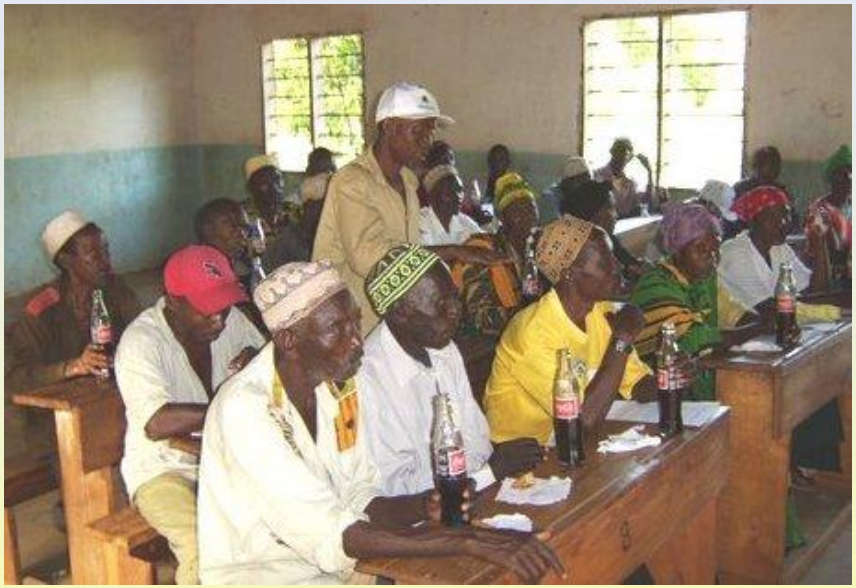


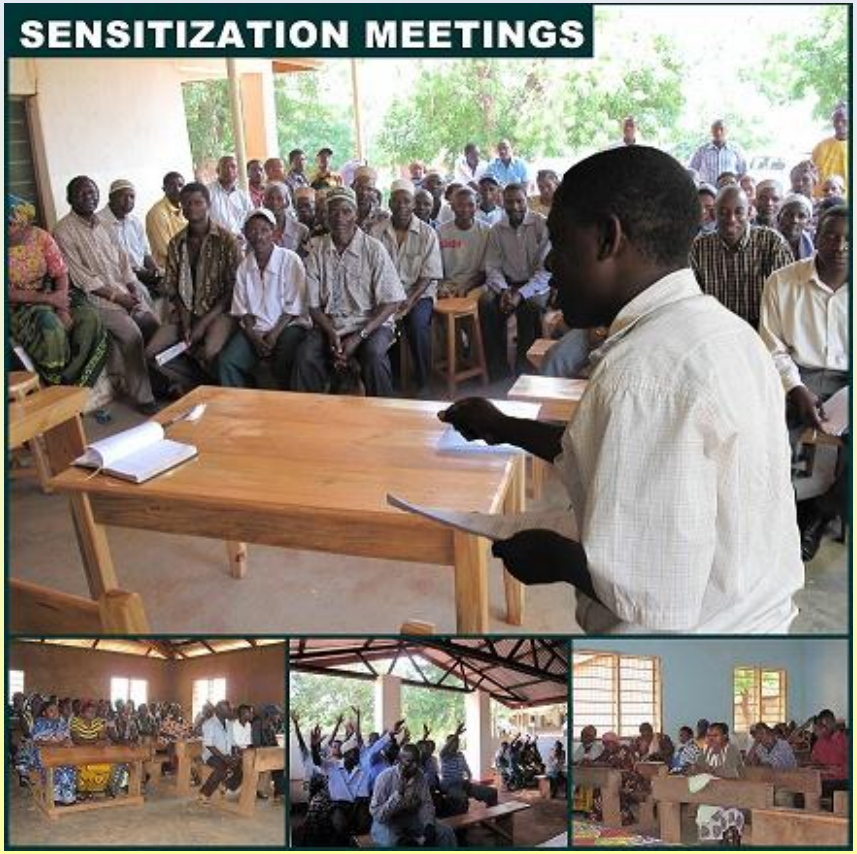
Figure 2: The incidence of febrile malaria episodes among residents of lowland village (filled circles and triangles) and highland village (filled squares and diamonds) between 2003 and 2008. Full lines represent children < 5 years, while dashed lines are individuals aged ≥ 5 years.

Community Sensitization



- **Community sensitization meeting for a malaria vaccine trial**

Malaria Vaccine Trial in Korogwe



NIMR Tanzania
www.nimr.or.tz

NIMR Tanga Centre
www.nimrtanga.org

Vaccination Centre

- **Mothers taking children to be vaccinated in a phase IIb malaria vaccine trial in Korogwe**

Monitoring efficacy of antimalarials at sentinel sites

- NIMR Tanga participates in sentinel site monitoring of efficacy of antimalarials
- Has worked closely with other institutions to provide data to the NCMP for reviewing antimalarial drug policy
- Challenge now is to delivery more comprehensive informed consent at HF level where support teams are used to routine case management; and malaria burden is declining

Lab facilities to support clinical and biomedical research at Korogwe and Tanga

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End Thank You

- **For more info about NIMR Tanga visit:**
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