Pregnancy Exposure Registries in Resource Limited Settings

Dr. Melba Gomes
Tropical Diseases Research
MDGs 4 and 5 (maternal and infant mortality) Challenges

- High maternal and neonatal mortality ratios
- Annual decline in MMR <1% from 1990 globally
- 68,000 of maternal deaths from unsafe abortion
- 63% of births attended by a skilled health professional globally
- Wide variations between regions & within countries.
- +7 million babies are stillborn or die within the first 4 weeks of life per year
- Low IPTp & PMTCT coverage - the inadequate integration of vertical malaria, HIV & MCH services
Antenatal Care At Least 1 Visit
birth in 3 yrs preceding the DHS survey-
updated Oct. 07

African Country

% Pregnant women

- Tanzania 04
- Malawi 04
- Rwanda 05
- Uganda 06
- Zambia 96
- Botswana 88
- Senegal 05
- Ghana 03
- South Africa 98
- Benin 01
- Kenya 03
- Namibia 00
- Cote d'Ivoire 99
- Mozambique 03
- Comoros 96
- Cameroon 04
- Zimbabwe 99
- Togo 98
- Madagascar 03/04
- Guinea 05
- CAR 94/95
- Burkina Faso 03
- Egypt 05
- Eritrea 02
- Morocco 03/04
- Mauritania 00/01
- Nigeria 03
- Mali 04
- Chad 04
- Niger 98
- Ethiopia 05
Malaria and HIV
Geographic overlap in sub Saharan Africa

- 55% of HIV+ adults are reproductive aged women; 80% of the world’s infected women
- 44% of 43 sub-Saharan African countries with malaria have HIV seroprevalence ≥ 10% among antenatal clinic attendees
- A small effect of malaria on HIV or vice-versa could have substantial population-level implications
Policy Statement Unchanged on Artemisinins in Pregnancy

- **WHO Treatment Guidelines 2006 and 2009**
  - ARTEMISININS should not be withheld if treatment is lifesaving
    - in severe malaria
  - Recommended in 2\textsuperscript{nd} or 3\textsuperscript{rd} trimester for uncomplicated malaria and preferred to QN in severe malaria
  - Only used in 1\textsuperscript{st} trimester if it is the only effective treatment available
- **Need human evidence for policy**
Rationale for a Pregnancy Register

- Lack of background data on birth defects in developing countries
- Large scale deployment of medicines – Malaria, HIV, leishmaniasis
- Limited capacity for assessing congenital anomalies
- Artemisinins – have potential for teratogenicity in >1 animal model (first trimester exp.)
- Malaria endemic areas have high prevalence of other diseases (HIV, TB, parasitic disease, malnutrition etc.) with exposure to other potentially teratogenic treatments
- Concerns about safety in pregnancy could undermine public confidence in life-saving therapies
Pregnancy Register Protocol: A WHO interdepartmental activity, with expert advice

- MPS (Making Pregnancy Safer)
- TDR (Research & Training in Tropical Diseases)
- Global Malaria Programme
- Quality and Safety of Medicines
- Health system Strengthening
- HIV/AIDS Programme
- Tuberculosis Programme
- Neglected Tropical Diseases
- WHO country involvement
Goal

- To promote the health of pregnant women and their children in resource poor settings
- By developing a pregnancy registry
- Provide evidence on safety of public health medicines used in pregnancy
- Malaria and HIV drug exposure as a pathfinder
Quantifiable Objectives

- Quantify baseline risk of major congenital malformations in malaria-endemic countries.
- Quantify risk of major congenital malformations associated with exposure to ACTs in 1st trimester of pregnancy.
- Identify other factors that may contribute to risk of major congenital anomalies and other adverse birth outcomes.
Scoping Visits

- Seeking collaboration between
  - MOH: MCH, Malaria, HIV/AIDS, HMIS
  - Academia/research institutions incl. DSS sites
  - WHO & other relevant NGOs
  - Health facilities (PHC and referral facilities)
- Site visits to ANC clinics and referral hospitals
- Literature search for relevant publications from countries
- Assessment of treatment seeking and health indicators
- 1st Countries: Tanzania, Uganda, Ghana, Mozambique, Kenya
- Country owned data, pooled in a WHO repository
Methods: General Principles

- Sentinel sites selected in areas of high malaria, HIV prevalence and other diseases
- Prospective observational cohort of randomly selected pregnant women. Enrollment as early as possible in pregnancy
- Generic study design enabling assessment of other drugs
- Active group: pregnant women with confirmed first, second or third trimester exposures to ACTs.
- Comparison groups:
  - Healthy pregnant women with no malaria and no exposure to ACTs during pregnancy
  - Pregnant women with malaria not exposed to ACTs
  - Women with no malaria being treated with other medication
- Primary outcome: major congenital anomalies at birth
## Making Pregnancy Safer

### Woman presenting at AnteNatal Care Site

Randomly selected patients plus all reporting history of Drug exposure of interest between 2-10 wks after LMP

**Enrolment and Initial Assessment**

**Initial ANC Assessment**

**Follow-up ANC Assessment/s**

**Labour/Delivery (CRF 2)**

**ANC Visit 2 – ANC Visit X (CRF 1 cont)**

**ANC VISIT 1 (CRF 1)**

**Confirmatory Assessment of Congenital Anomalies detected at birth**

**Neonatal (and Maternal) Assessment at Birth**

**National Registry**

**Report within 1 week**

**Line list of recruits**

**Monthly submission**

**Exclusion of women declining consent**

**Exclusion of non-pregnant women**
Pilot Study: Ghana, Kenya, Uganda, Tanzania, Mozambique

- Objectives
  - Assess feasibility of CRFs and all processes
  - Identify problems that are likely and consider local solutions to address these
  - Assess acceptability of registry by community and health staff

- Methods: qualitative studies, and quantitative analysis of data quality
- Feasibility assessment of data capture methods during pilot study (e.g. paper vs. hand-held device vs. desktop)
- Development of an open access data management system
To do this, first we have to........

- Build capacity to assess, monitor birth outcomes especially for congenital malformations and other adverse pregnancy outcomes.
- Develop culture of drug safety awareness through (antenatal, postnatal) service delivery in selected sentinel sites in participating countries.
- Contribute towards building capacity in participating countries to detect, assess and manage major congenital anomalies.
Management Challenges

- Consultation with national and local authorities, programmes, health staff and ethics committees
- Assess training and infrastructure needs at sites, development of training curricula
- Staff training & remuneration. Tasks shifting?
- Quality of birth examinations
- Appropriate informed consent procedures
- Maintaining constant communication and reporting from sites
- Ensuring appropriate follow-up, feedback and communication to sentinel sites and communities
- Data quality, electronic access to data
- Suitable model for involving pharmaceutical industry
Current and Ongoing Activities

- Development of a Registry Co-ordinating team
- International Birth Defects Panel for the pilot study
- Concurrent pilot testing of data capture & management tools
- Training:
  - Development of SOPs
  - Surface exam training video
  - Registry training programme
Why MPS is interested in this research?

Possible outcomes of the PR:

- Strengthened ANC comprehensive services
  - in providing integrated service delivery
  - in improving quality of care and case management
- Increased country capacity on birth defects detection and management and on drugs safety in pregnancy (not only for ACTs or ARVs)
- Increased demand by the communities for quality services during pregnancy and child birth.
Collaboration

- Pooling of data
  - Similar data quality
  - Reliable surface exams
  - Internal control group

- Official Call for contributions
  http://www.who.int/tdr/svc/grants/calls/call-contributions