Drug safety and use of databases in drug utilization research

MURIA Workshop July 28th at University of Botswana, Gabarone, Botswana

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Disposition

- Presentation and background
- Drug safety studies
- Use of databases for epidemiological research
- Conclusions

A northern European country

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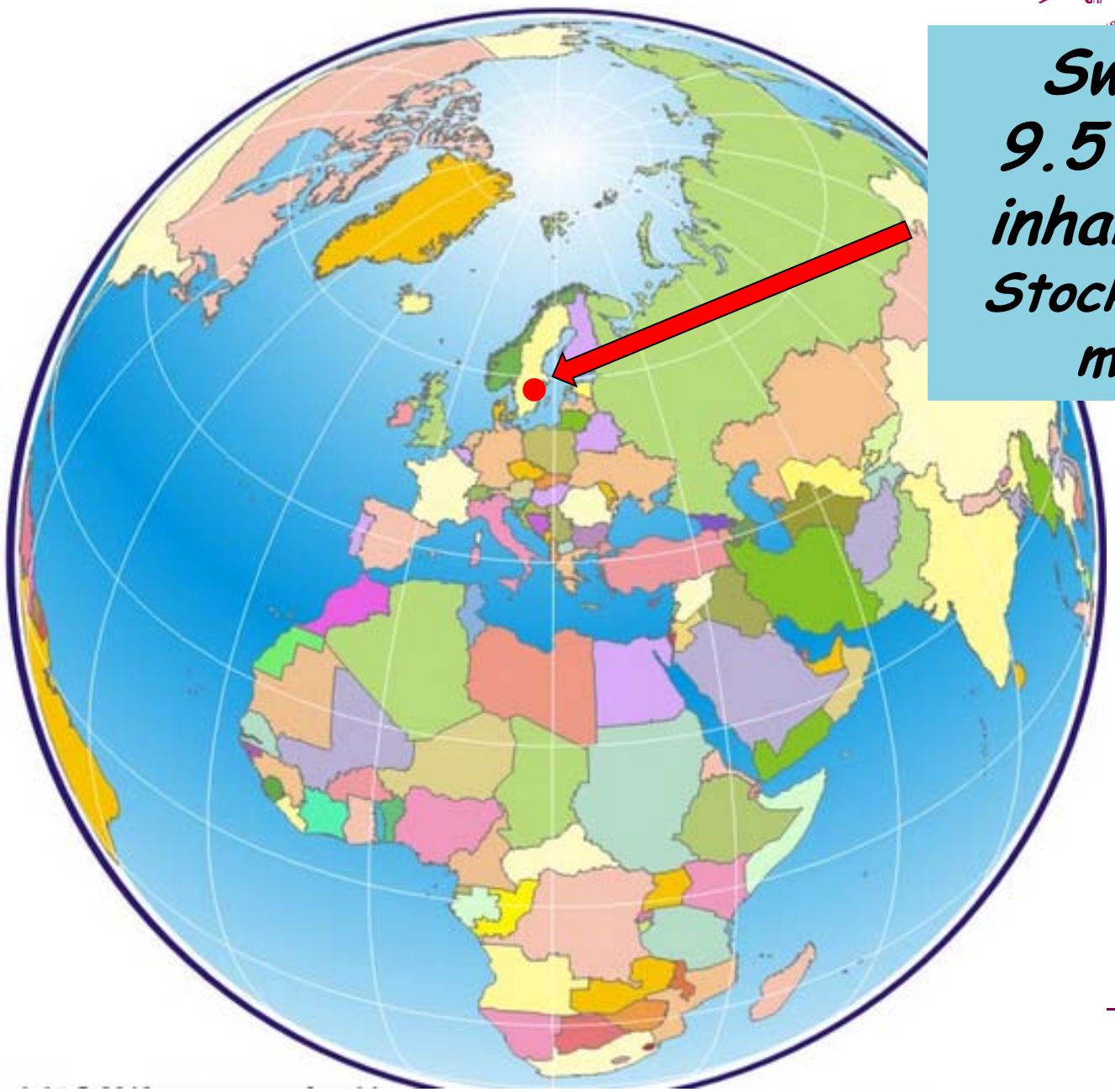

Sweden
9.5 million inhabitants
Stockholm: 2 million

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Stockholm and Sweden

Sweden

- One of the safest countries in the world
- 90% of population speak English
- Temperate climate with four distinct seasons

Stockholm

- Business and innovation
- History and culture
- Extensive public transport
- Green space and water
- The 'Capital of Scandinavia' - largest university city in the Nordic countries
- Home of 80 000 students of which 5 000 are international students

CV

MD PhD

Specialist in clinical pharmacology and anesthesiology/intensive care

Professor, senior consultant at Karolinska Institutet and Karolinska University Hospital, Stockholm

Research, education and clinical services on Rational Use of Medicines, tropical clinical pharmacology and decision support since years

Collaborations across Africa since years

Start in Somalia 1985

Chairing IUPHAR Subcommittee for Clinical Pharmacology in Developing Countries

Available at www.cioms.ch /index.php/publications/available-publications/540/view_bl/66/drug-development-and-use/13/clinical-pharmacology-in-health-care-teaching-and-research?tab=getmybooksTab&is_show_data=1

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Scanty data and poor clinical knowledge about drug safety in Africa

- Need for improved training in Rational Use of Medicines across institutions
- Adverse drug reaction reporting in its infancy
- Drug registration and spontaneous reporting to be strengthened
- Need for more clinical trials in Africa
- Clinical drug research has to be strengthened

We need to know the direction!

Unique potential for drug safety research in Africa

- Knowledge on risk for malformations, appropriate dosage and pharmacological effects in neo- and postnatal periods of drugs against malaria, tb, HIV and other parasitic diseases (**pregnancy**)

- Knowledge on appropriate dosage and safety profiles of drugs to treat and cure infants and small children: incorrect dosage common children (**children**)

Definition of Adverse Drug Reaction (ADR)

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Any unwanted effect in humans of a drug used for prevention, diagnosis and therapy in suggested and/or approved dosages for a recommended period of use

Types of Adverse Drug Reactions (ADR)

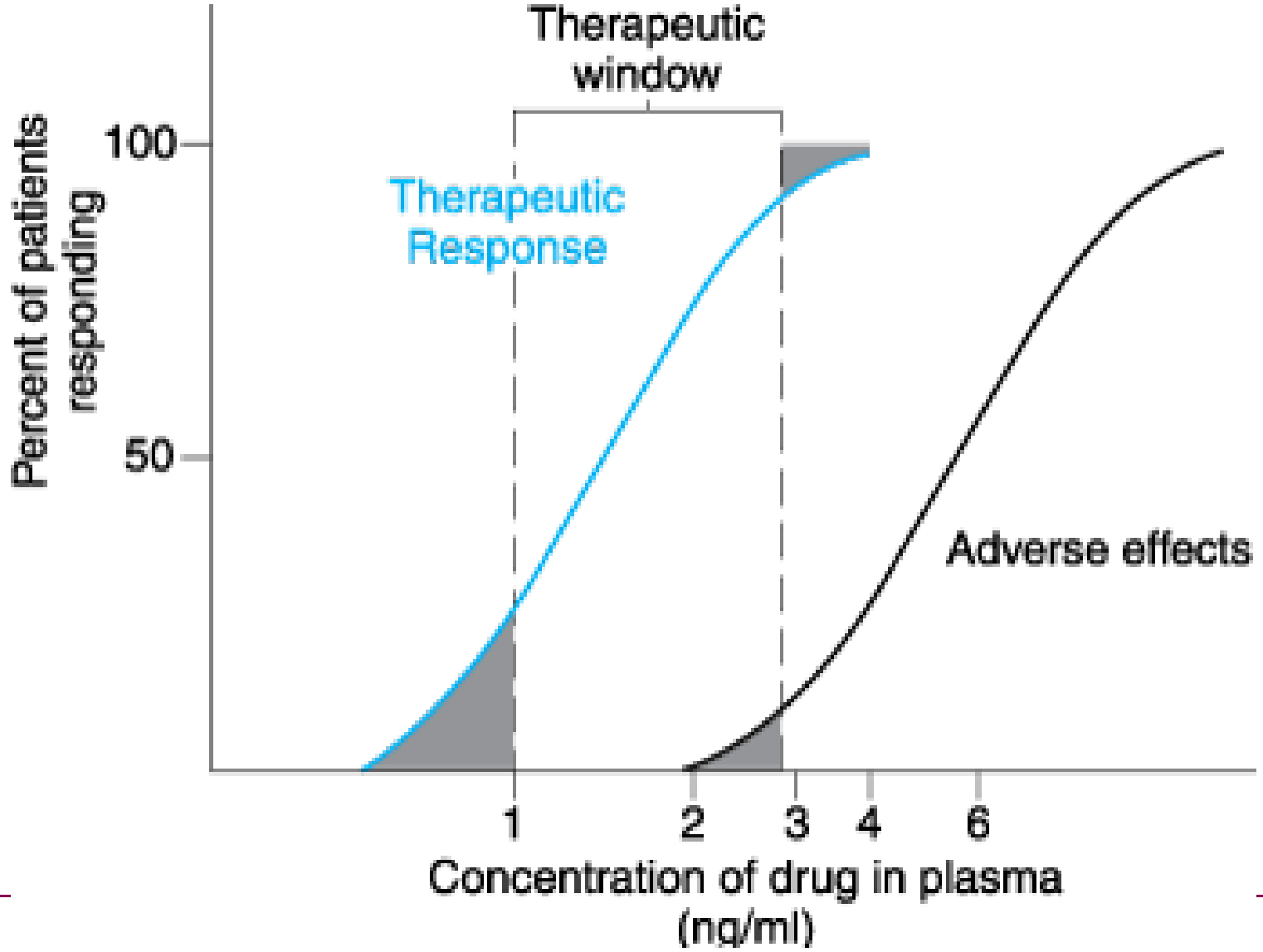
Type A:80%

Predictable from pharmacology of the drug, dose-dependent and preventable

Type B:20%

Bizzare, unpredictable from known pharmacology without dose-dependency

Pharmacological concepts govern efficacy and safety of drugs



Causality Assessment

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Known reaction

Time-relationship

Disappear at Dechallenge

Reappear at Rechallenge

Cannot be explained by other medications

Cannot be explained by the underlying diseases

Explore what is going on …

Explore what is going on …

Pharmacovigilance

The science and activities related to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem

Example I: Drug utilisation approach to monitor drug safety of HIV-drug therapy in practice

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Early Warning Indicators for HIV Drug Resistance in Adults in South Africa at 2 Pilot Sites, 2008–2010

Nomathemba M. Dube,[1,2,3] Khin S. Tint,[3] and Robert S. Summers[1,4]

Clinical Infectious Diseases 2014

Example I: Indicators help to monitor HIV-therapy

EWI 1: On-time pill pickup	EWI 2: Retention in care	EWI 3: Pharmacy stockouts	EWI 4: Dispensing practices	EWI 5: Virological suppression
Target:	*Target:*	*Target:*	*Target:*	*Target:*
Red: <80%	*Red: <75%*	*Red: <100%*	*Red: >0%*	*Red: <70%*
Amber: 80 – 90%	*Amber: 75 – 85%*	*Green: 100%*	*Green: 0%*	*Amber: 70 – 85%*
Green: ≥90%	*Green: ≥85%*			*Green: ≥85%*

EWI=Early Warning Indicator of Drug Resistance

Example I: Results easy to interpret and compare

		EWI 1: On-time pill pickup	EWI 2: Retention in care	EWI 3: Pharmacy stockouts	EWI 4: Dispensing practices	EWI 5: Virological suppression
		Target: *Red: <80%* *Amber: 80 – 90%* *Green: ≥90%*	*Target:* *Red: <75%* *Amber: 75 – 85%* *Green: ≥85%*	*Target:* *Red: <100%* *Green: 100%*	*Target:* *Red: >0%* *Green: 0%*	*Target:* *Red: <70%* *Amber: 70 – 85%* *Green: ≥85%*
A	2009/2010	(181/220) 82.3	(178/207) 86.0	(5/12) 41.7	(0/223) 0	(149/178) 83.7
B	2009/2010	(214/269) 79.6	(187/274) 68.2	N/A	(0/278) 0	(66/97) 68.0

How many ADRs are avoidable?

Definitely	**8.6%**
Possibly	**63.1%**
Not avoidable	**28.1%**

72 % of ADRs were definitely or possibly avoidable

in admitted patients

Pirmohamed et al Br Med J 2004

In Africa: nobody knows!

Example II: Limited knowledge about ADRs in Africa

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Adverse drug reactions in patients admitted on Internal Medicine wards in a district and Regional Hospital in Uganda

Tumwikirize WA[1,2], Ogwal-Okeng JW[1], Vernby A[2], Anokbonggo WW[1], Gustafsson LL[3], Lundborg SC[2]

4.5% of hospital admissions caused by ADRs, 3 of 5 explained by quinine therapy

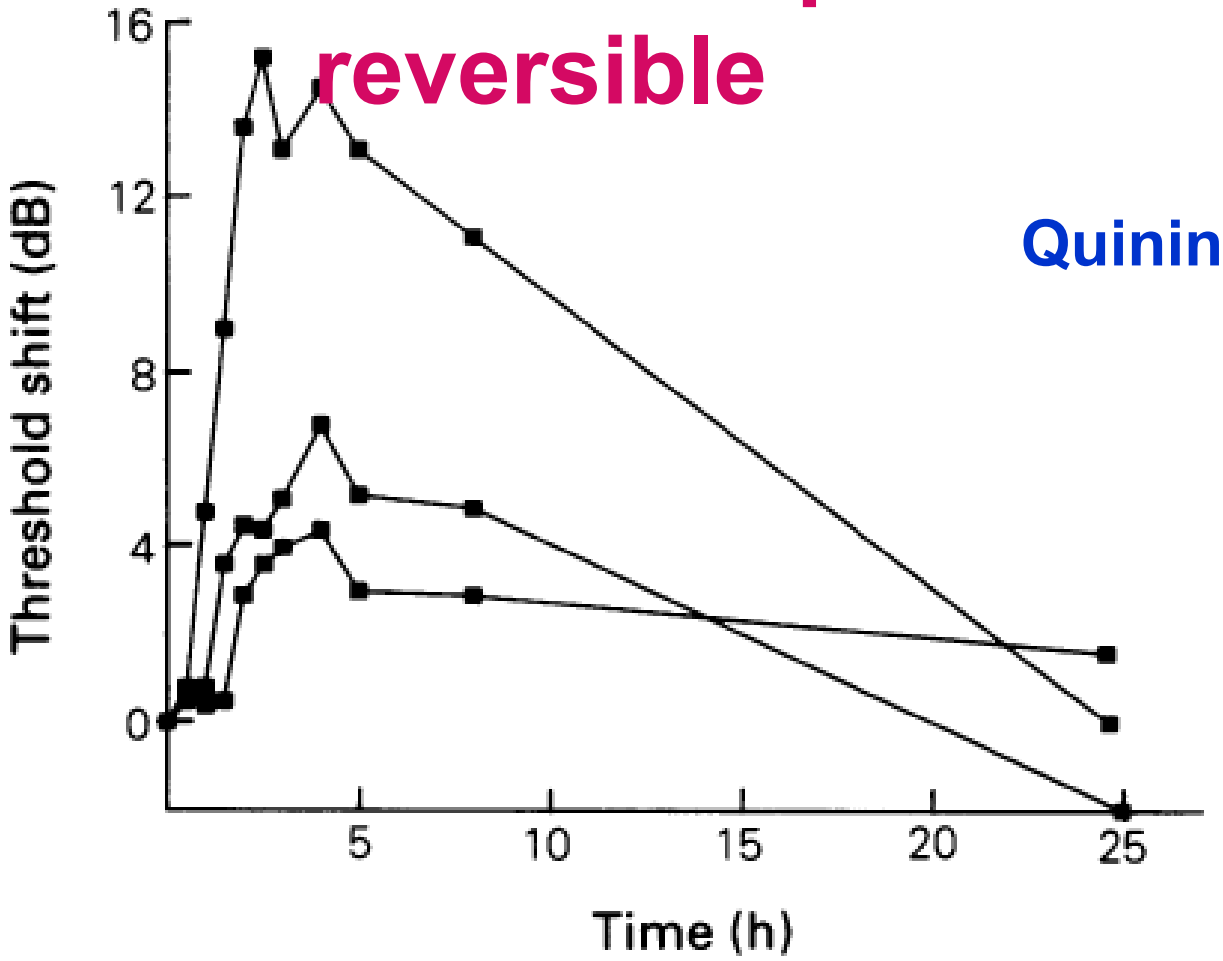
Afr Health Sciences 2011

Example III: Quinine causes concentration-dependent hearing loss

Quinine causes concentration- dependent reversible hearing loss in experimental studies and after malaria drug therapy with 7.5mg/kg 3 times daily

Tumwikinze et al 2011

Example III: Hearing effect is dose-, concentration dependent and reversible



Quinine

Alván G et al 1991

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Databases in epidemiological and drug utilisation research in Africa

- Comprehensive data management in surveillance sites (Kilife Kenya and Nouna Burkina Faso): increasingly using smart phones/electronic tools

- Electronic health records with mobile access: open source systems can manage text, audio and images

- National and international registries

- Confidential and management issues critical: science gateways for building ”electronic virtual communities” of interest

Example of mobile health data collection

Journal of Clinical Epidemiology 68 (2015) 80–86

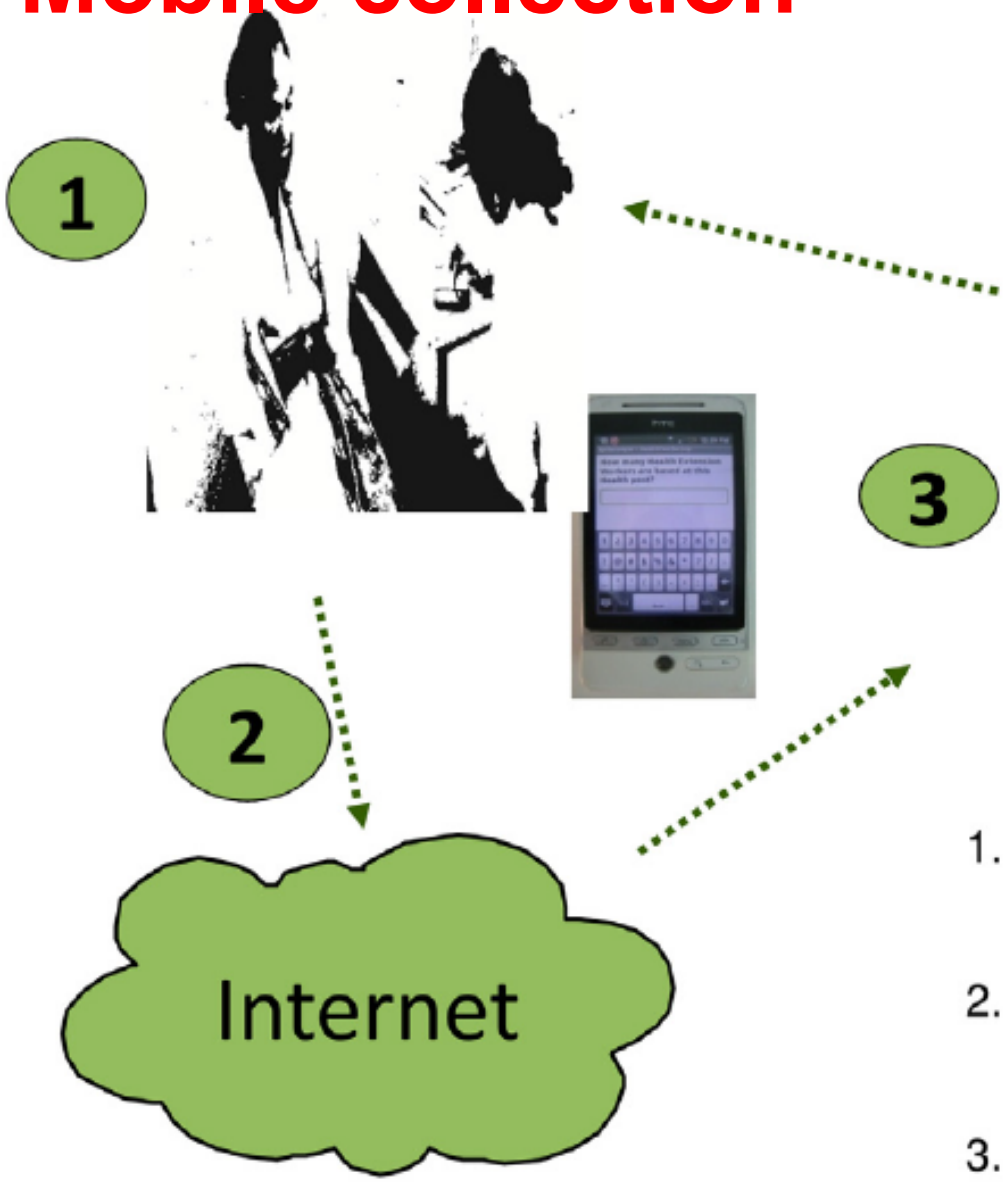
Journal of Clinical Epidemiology

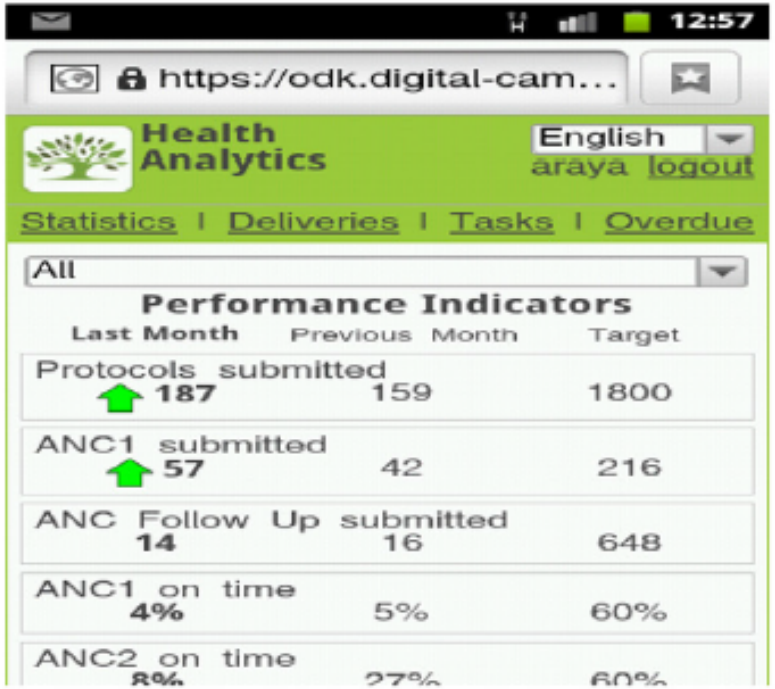
Mobile health data collection at primary health care in Ethiopia: a feasible challenge

Araya Abrha Medhanyie[a,b,c,*], Albine Moser[b], Mark Spigt[a,b,c,d], Henock Yebyo[a], Alex Little[c,e], GeertJan Dinant[b], Roman Blanco[c,e]

2015

Mobile collection





Medhanyie et al 2015

Workflow

1. Maternal health care forms filled by health workers using smartphones
2. Forms automatically uploaded to server whenever GPRS connection available
3. Data instantly available via the scorecard dashboard (web and mobile)

Fig. 2. Workflow followed in the study.

Example IV: innovative and electronic capture of pregnancy and neonatal data

Mehta *et al. BMC Pregnancy and Childbirth* 2012, **12**:89
http://www.biomedcentral.com/1471-2393/12/89

BMC
Pregnancy & Childbirth

STUDY PROTOCOL Open Access

Protocol for a drugs exposure pregnancy registry for implementation in resource-limited settings

Ushma Mehta[1], Christine Clerk[2], Elizabeth Allen[3], Mackensie Yore[4], Esperança Sevene[5], Jan Singlovic[6], Max Petzold[7], Viviana Mangiaterra[8], Elizabeth Elefant[9], Frank M Sullivan[10], Lewis B Holmes[11] and Melba Gomes[8*]

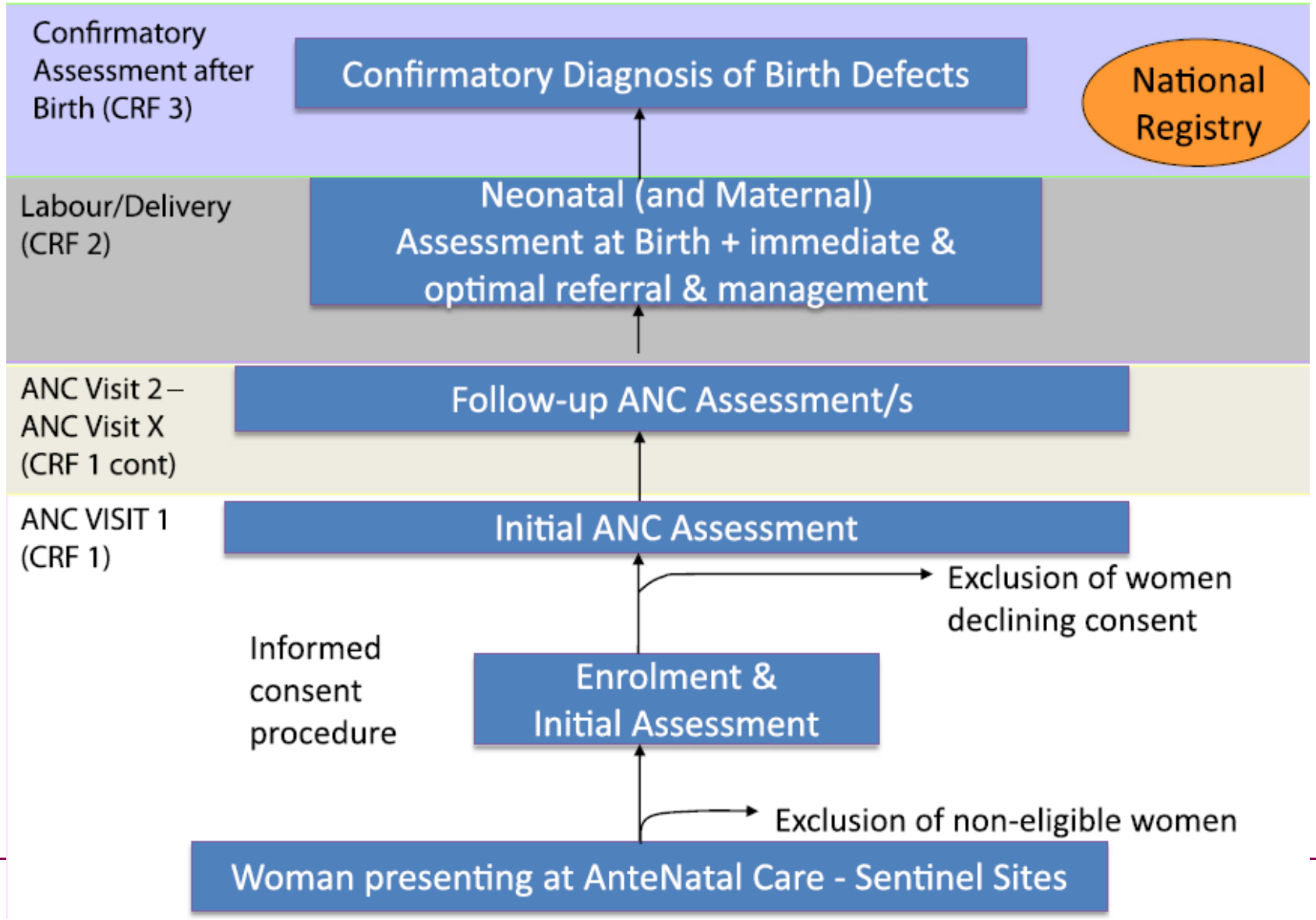
2012

Example IV: Study of birth defects in Africa

The primary endpoint is major external/visible congential anomalies and the secondary endpoint is other adverse birth outcomes including stillbirth, prematurity and neonatal death within 24 hours of birth.

Simple straight-forward endpoints

Example IV: Integrated data-collection



Use open-source softwares

Data management

The WHO Pregnancy Registry database has been developed using the free access software OpenClinica. The database has been designed to accommodate electronic and paper-based CRFs depending on the preferences of the contributing sites.

www.community.openclinica.com

or

www.redcap.vanderbilt.edu

REDCAP=REsearch Data CAPture

Example V: Open-source softwares for data collection

Ngari *et al. BMC Research Notes* 2014, **7**:845
http://www.biomedcentral.com/1756-0500/7/845

OpenClinica

BMC Research Notes

TECHNICAL NOTE Open Access

Experience of using an open source clinical trials data management software system in Kenya

Moses M Ngari[1*†], Naomi Waithira[1†], Roma Chilenqi[2], Patricia Njuguna[1], Trudie Lang[3] and Greg Fegan[1,3]

11 trials and 6000 study patients

Experience of Redcap and possibilities to use Science Gateway: discuss with Jaran Eriksen and myself

Example VI: Huge longitudinal outcome study of HIV-therapy

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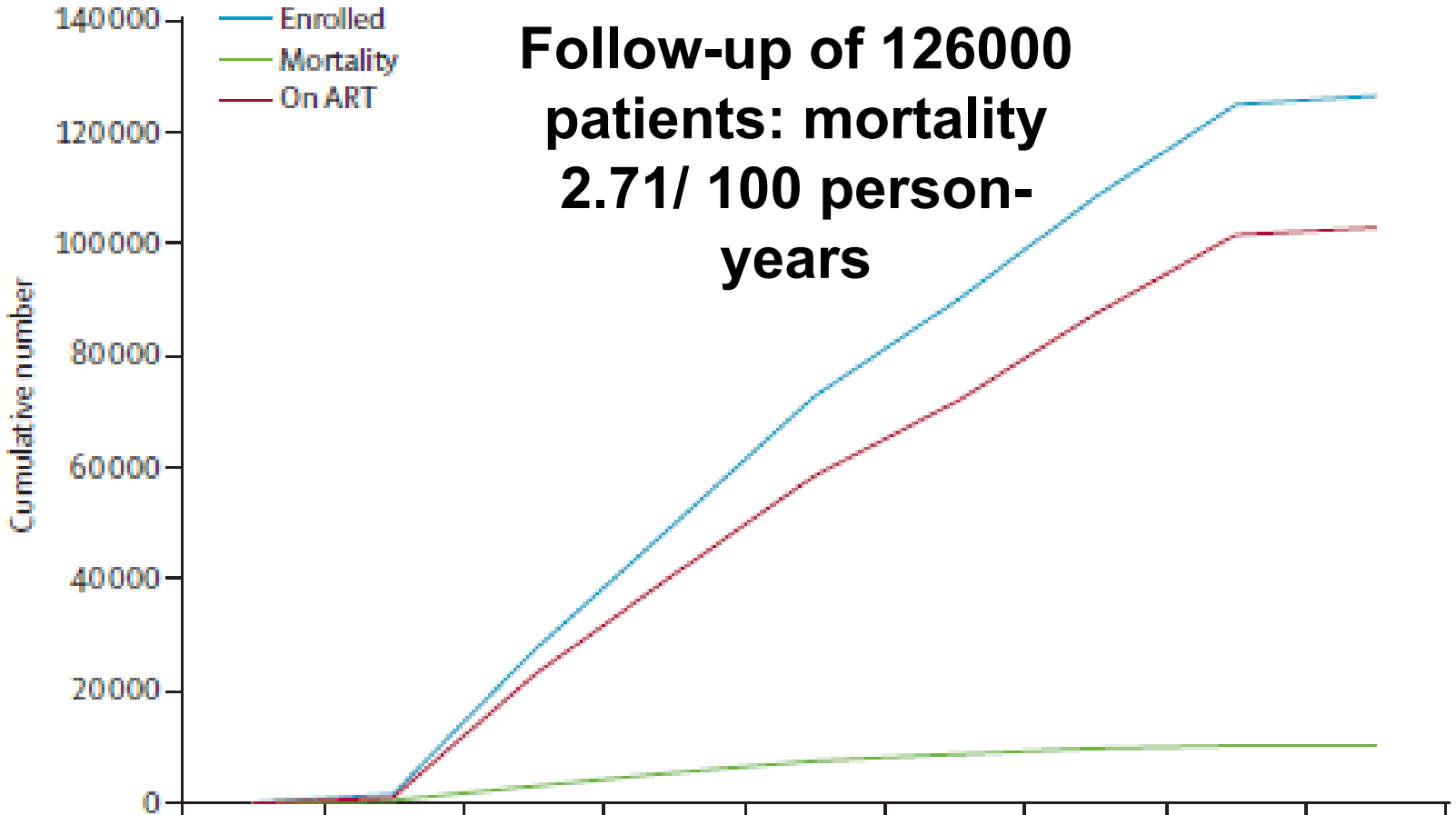
Outcomes of the Botswana national HIV/AIDS treatment programme from 2002 to 2010: a longitudinal analysis

Mansour Farahani, Anusha Vable, Refeletswe Lebelonyane, Khumo Seipone, Marina Anderson , Ava Avalos, Tim Chadborn, Hailu Tilahun, Danae Roumis, Themba Moeti, Godfrey Musuka, Lesego Busang, Tendani Gaolathe, Kolaatamo C S Malefho, Richard Marlink

Lancet Global Health 2014

Electronic health record data

Example VI: Follow-up of HIV-therapy



Follow-up of 126000 patients: mortality 2.71/ 100 person-years

Patients								
Enrolled	140	1547	27129	49711	72598	89529	108165	124651	126263
Mortality	88	496	3038	5441	7485	8750	9733	10217	10230
On ART	29	958	22763	40797	58464	71499	87385	101474	102713

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Unique research potentials

- Risk for malformations, appropriate dosage and pharmacological effects in neo- and postnatal periods (HIV, malaria, tb and parasitic diseases)

- Appropriate dosage and safety profiles of drugs to treat and cure of infants and small children: incorrect dosage common children

- Effectiveness and safety of major implementation of new therapies and antibiotics

- Intoxication with drugs and herbal medicines

We need knowledge make easy to follow guidelines

Guidelines

Make things simple