Assuring the quality and safety of essential medicines

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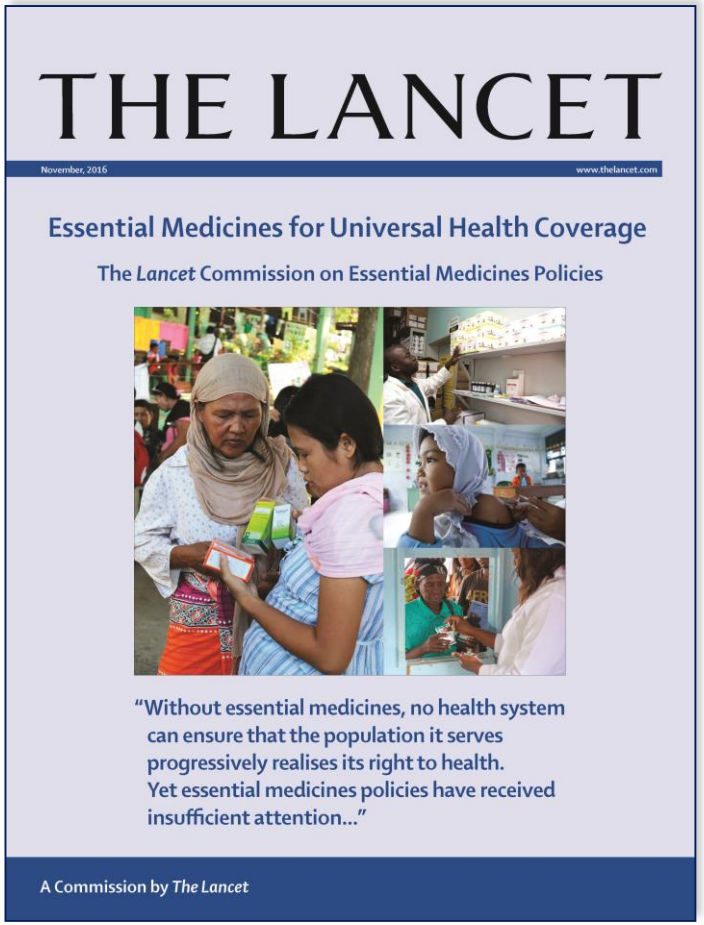
THE LANCET

Essential Medicines for Universal Health Coverage

Lancet Commission on Essential Medicines Policies



Introduction: Three eras of the EM concept

First era (1970s-1990s)

- **1st WHO Model List of Essential Medicines (1977)**
- **Alma Ata Conference (1978)**
- **Uptake of national EMLs and NMPs**

Second era (1990s-2010s)

- **Growing complexity**
- **New global financing mechanisms**
- **Medicines as part of health systems**
- **New focus on essential medicines for children; expensive medicines**

Third era - 2010 to present –
UHC demands essential medicines, national health insurance

Goal 3.8 “[…] access to safe, effective, quality and affordable essential medicines and vaccines for all”

Goal 3.b “Support research and development of vaccines and medicines for communicable and non-communicable diseases primarily affecting developing countries….”

Why are essential medicines important?

Doctors like to think about patients, not about pills

Richard Horton, 2014

Post 2015 Development Agenda (Sustainable Development Goals):

Essential medicines remain essential for the future

- **Most of 7.6m child deaths/yr can be averted by simple drugs; but:**
  - **Only 34% of acute diarrhoea receive oral rehydration**
  - **Only 29% of children with pneumonia receive antibiotics**
- **30% of pregnant women are anaemic, need Fe, B12, FolAcid, VitA**
- **225m women lack access to modern contraception**
- **10m HIV/AIDS patients need to start on HIV treatment**
- **Non-communicable diseases kill 8m people below 60y per year; but:**
  - **5/6 patients with hypertension do not receive medication**
  - **80% of global cancer patients receive only 5% of cancer care**
  - **20% of global population consumes 90% of opioid analgesics**

Missing essential medicines

New essential medicines are also needed

- **Lancet Commission on Global Health identified following needs:**
  - **Single-encounter antimalarials (now 3 days)**
  - **Shorter treatment for latent and active tuberculosis (now 6-24 m)**
  - **Medicines for neglected tropical diseases (no investment)**
  - **New antibiotics with newer mechanisms of action (no investment)**
- **WHO: Better formulations are also needed:**
  - **Fixed-dose combinations for HIV in children**
  - **Dispersable tablets of amoxycillin**
  - **Heat-stable oxytocin, insulin**
  - **Very small dosages for neonates (e.g. gentamycin)**

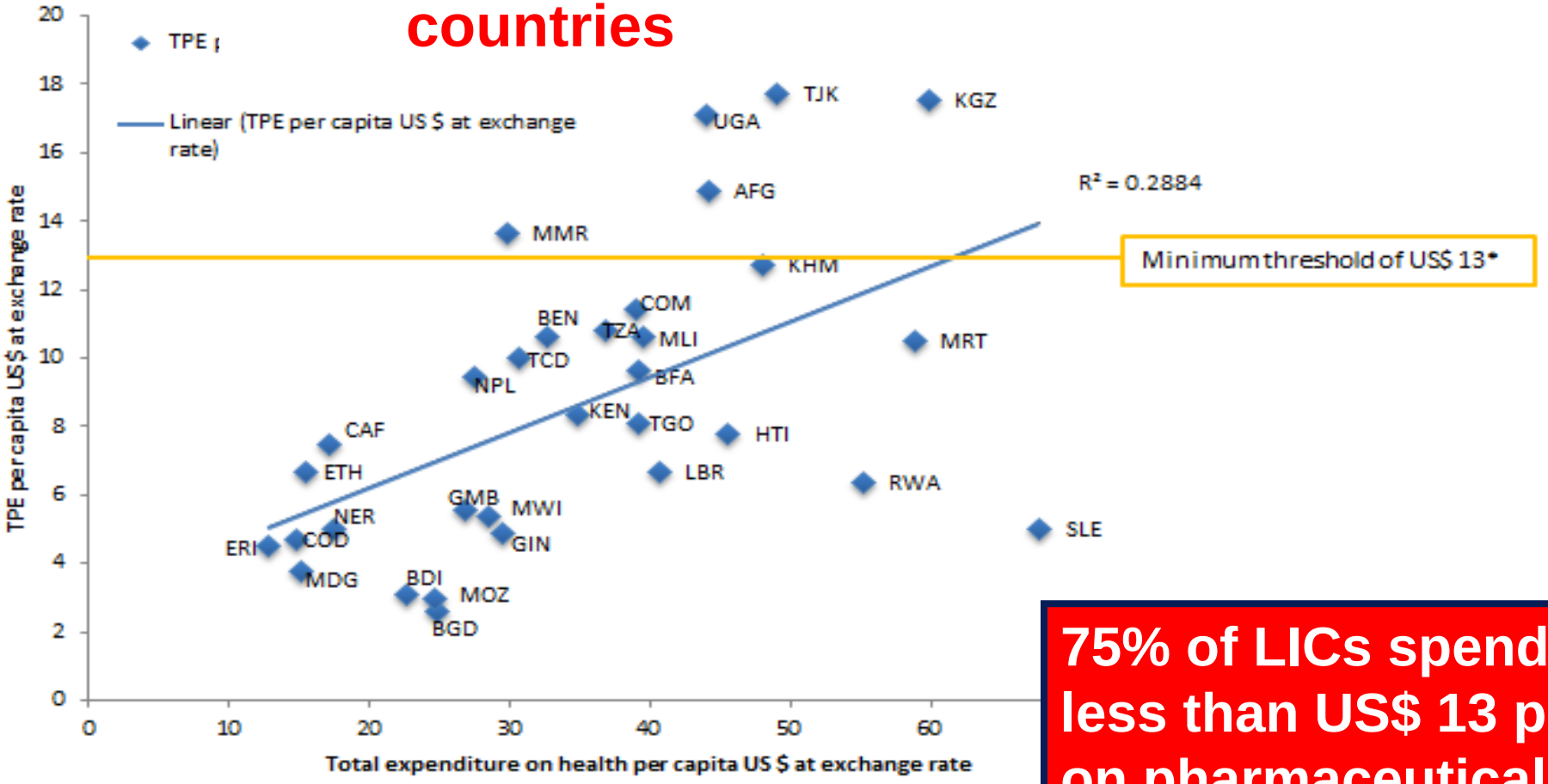
Five key challenges the report addresses

1. Paying for a basket of essential medicines
2. Making essential medicines affordable
3. Assuring quality and safety of essential medicines
4. Promoting quality use of medicines
5. Developing missing essential medicines

Cross-cutting -> 6. measuring progress

Current pharmaceutical expenditure

Low income countries



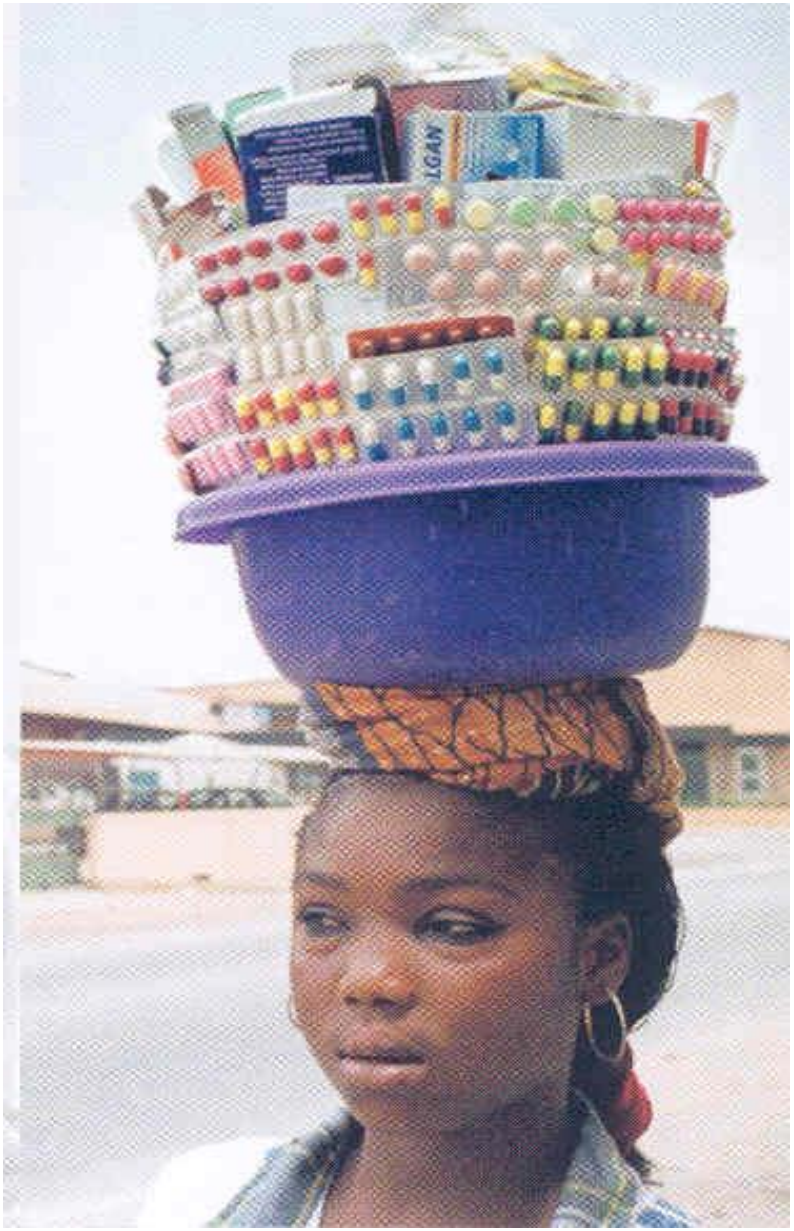
75% of LICs spends less than US$ 13 pp/year on pharmaceuticals

Ghana: Outpatient department, pharmacy (2013)

Ghana: hospital pharmacy (2013)

Uganda,
rural clinic pharmacy

The alternative route



Why is quality assurance needed?

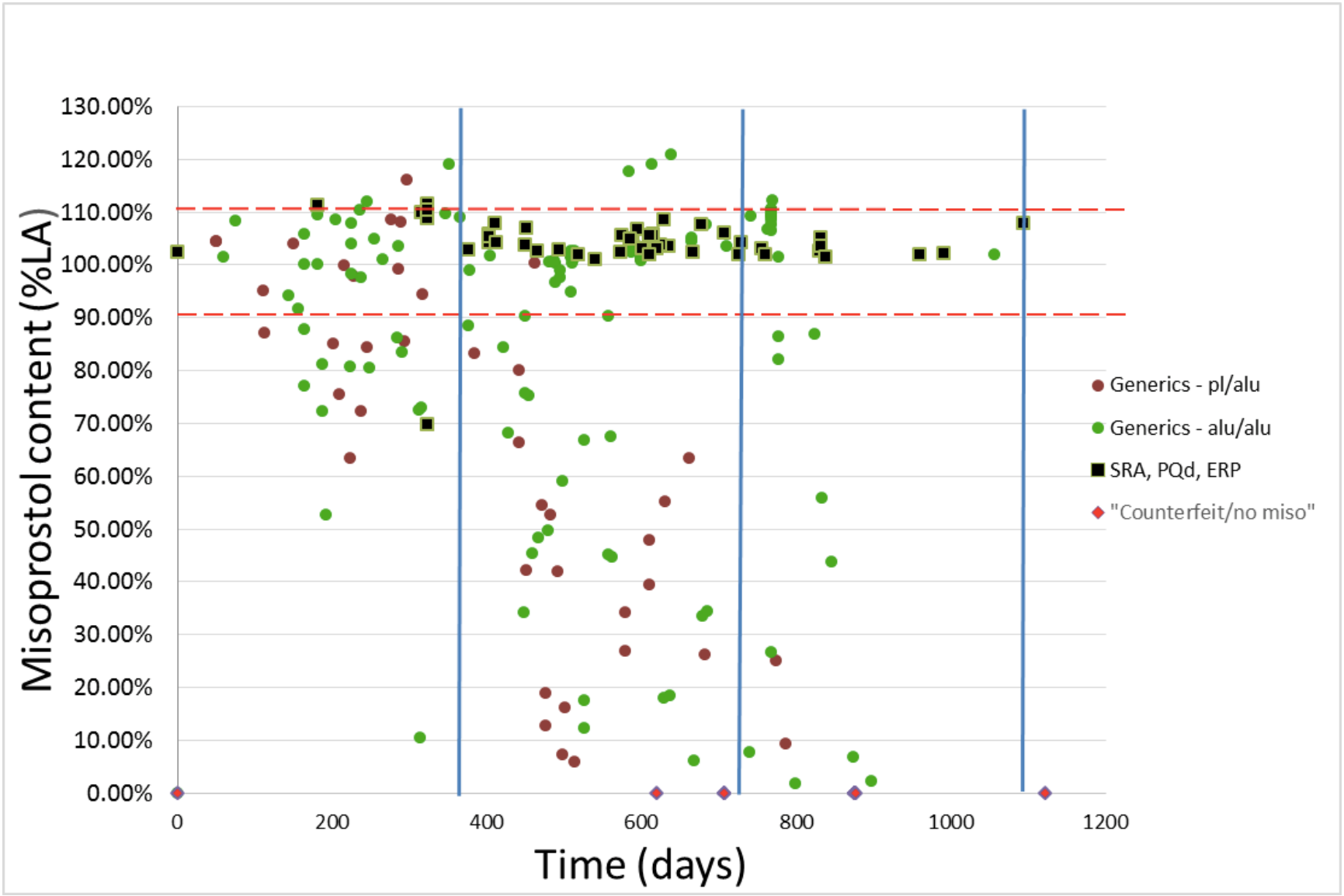
- **Patients cannot verify the quality, safety and efficacy of a product themselves; that is an essential public function**
- **Risk for the patient: Poor-quality medicines can cause serious, even fatal, harm to patients. Money spent on poor-quality medicines is wasted; additional costs are incurred to counteract harm**
- **Risk for society: Poor-quality medicines reduce health outcomes, endanger public health (e.g. antimicrobial resistance) and reduce public trust in the health system**

Examples of lack of quality and safety in LMICs

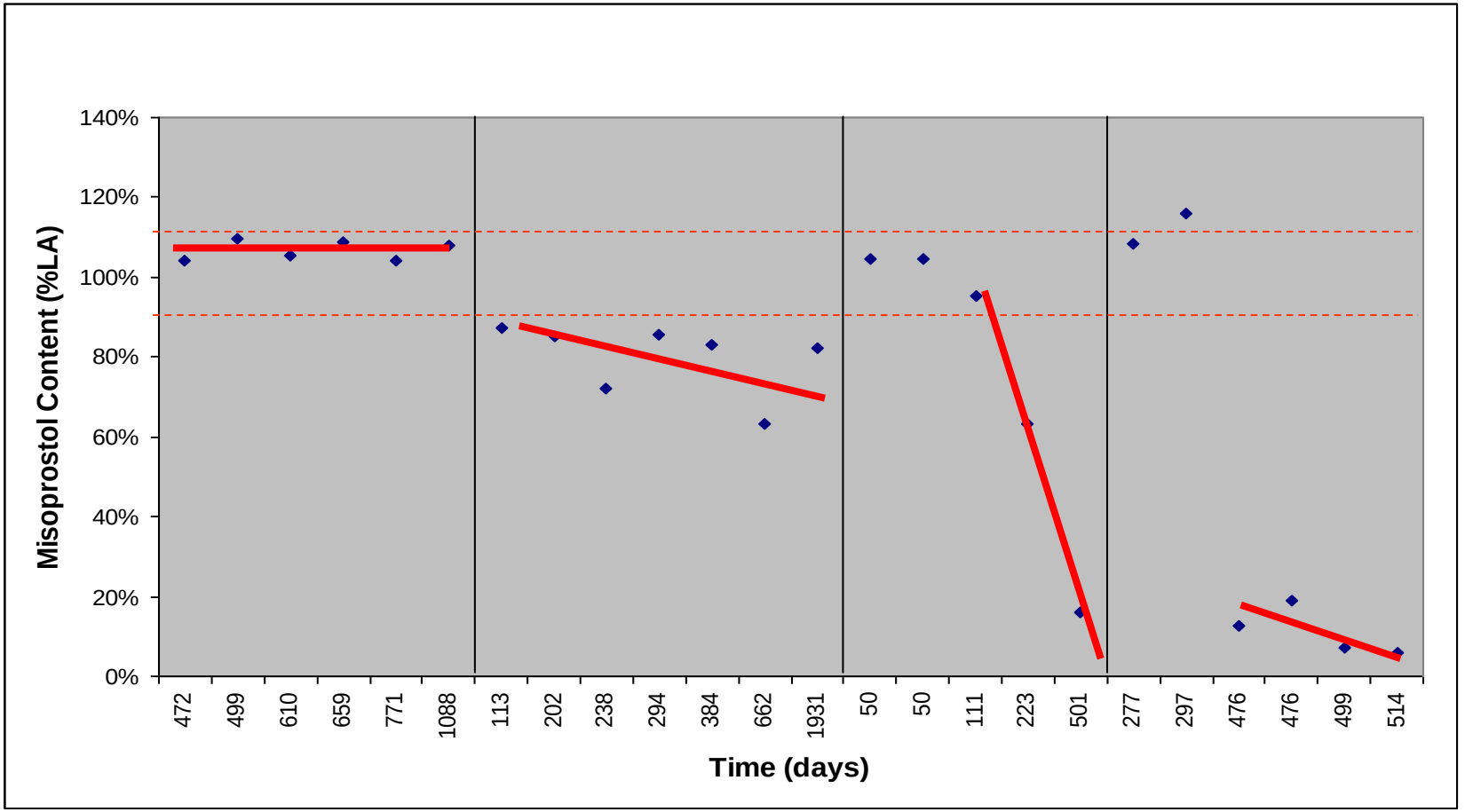
- In 2008 76/267 (28%) antimalarial medicines in Cameroon, Ethiopia, Ghana, Kenya, Nigeria, and Tanzania were substandard.
- In 2009, 33/291 (11%) anti-tuberculosis medicines from Armenia, Azerbaijan, Belarus, Kazakhstan, Ukraine, and Uzbekistan failed; (rifampicin capsules 28%)
- Dramatic incidents:100 children in Panama, 230 adults in Pakistan
- 57/66 (86%) studies on substandard and falsified medicines focus on infectious diseases; little known about medicines for NCDs

Example:

Active ingredient in misoprostol tablets in 15 LMICs

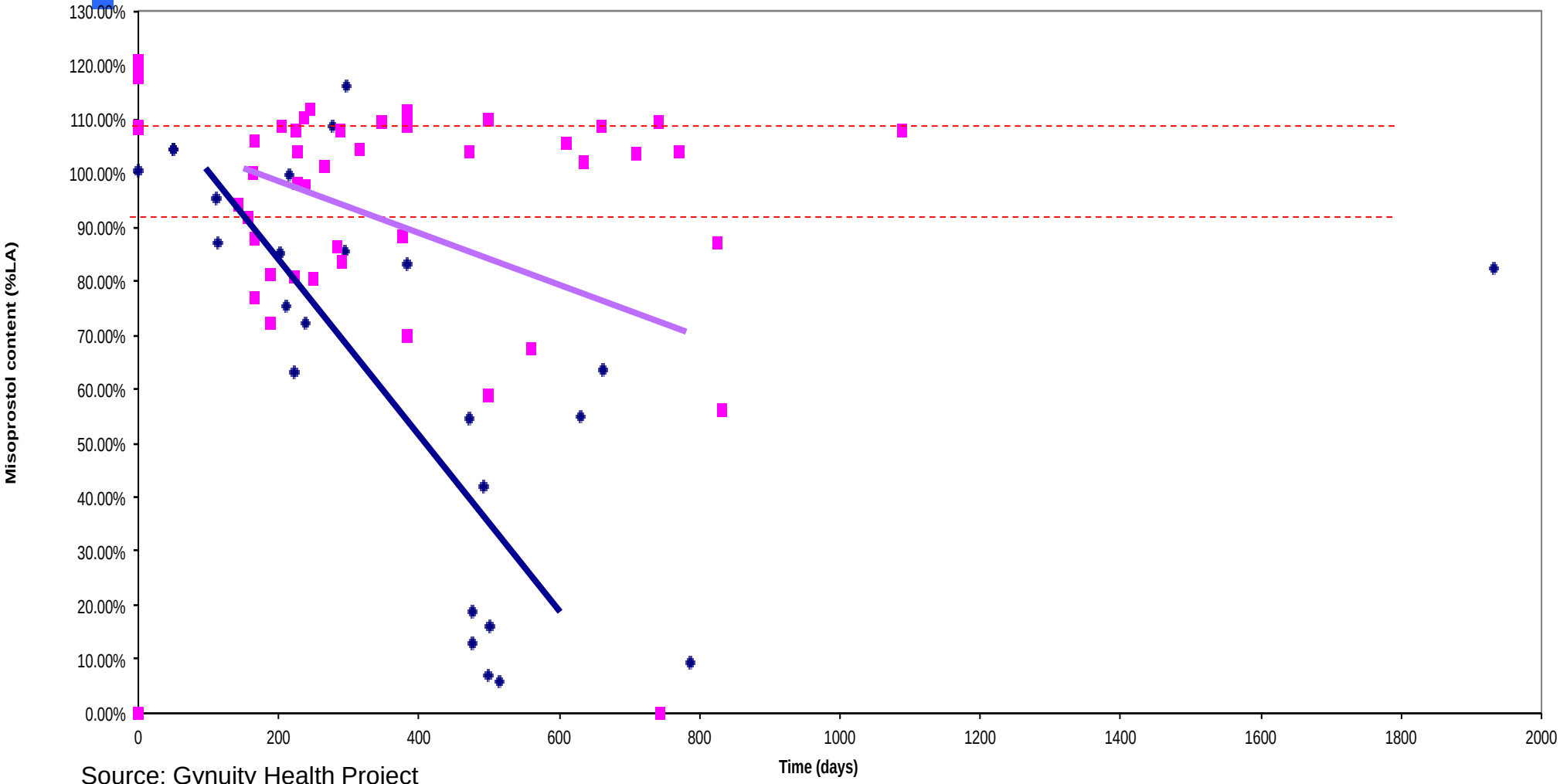


Misoprostol content by age and manufacturer



Source: Gynuity Health Project

Effects of packaging on misoprostol content by age



Source: Gynuity Health Project

Core components of the Commission's strategic direction to improve quality assurance

- **Emphasis on international harmonization and regional collaboration**
- **Redirect activities of NMRAs to those that add value**
  - **Less emphasis on national sovereignty**
  - **No repeat assessments**
  - **Focus on targeted enforcement**
- **Involve other stakeholders and the general public in quality assurance, through new technologies**
- **Promote transparency of information, e.g. outcome of assessments and inspections**
- **Promote accountability, through independent assessment of the performance of NMRAs**

Five areas of opportunity:

1) Regulatory harmonization

- **International standard regulatory dossier that covers both format and content; promote use of electronic dossiers**
- **More international collaboration and joint assessments**
- **Prevent repeat-assessments that do not add value**

Five areas of opportunity:

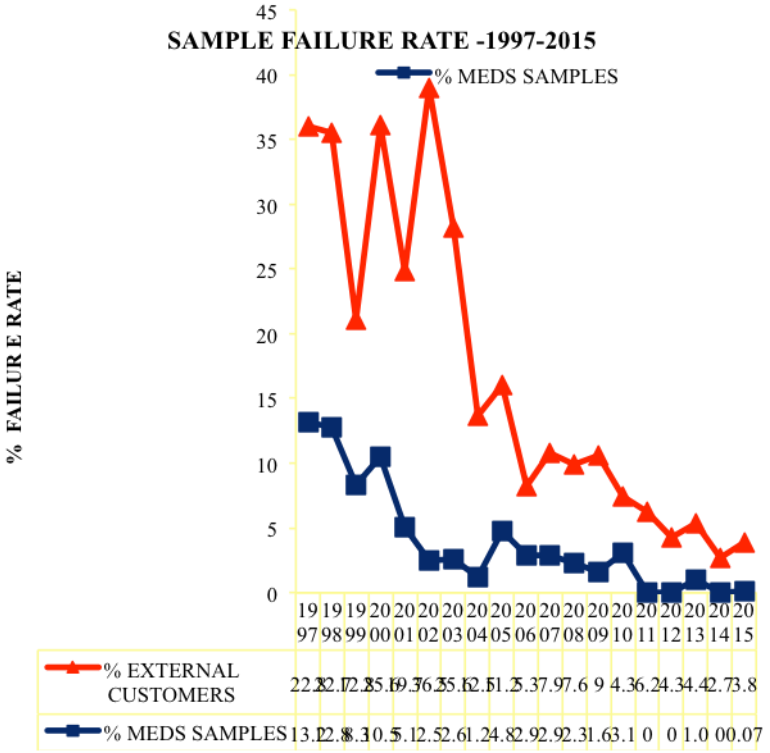
2) Evolve the WHO / UN Prequalification programme

- **WHO should evolve the WHO/UN Prequalification Programme to maintain a moving focus on new essential medicines, and on those with regulatory challenges, such as human insulin, biosimilars**
- **PQ standards, WHO Public Assessment Reports and WHO Public Inspection Reports should form the basis for regulatory convergence and mutual recognition, leading to rapid regulatory approval**
- **A sustainable financial base must be created to maintain its full independence from donors and manufacturers.**

Five areas of opportunity:

3) Better quality assurance in procurement agencies

- **Payers and procurement agencies must adopt good procurement practices that incorporate effective and transparent quality assurance**
- **Quality assurance mechanisms must exist at all points in the supply chain. Appropriate quality assurance systems require investment**
- **Sharing test results and findings of inspections can avoid duplication and increase efficiency**

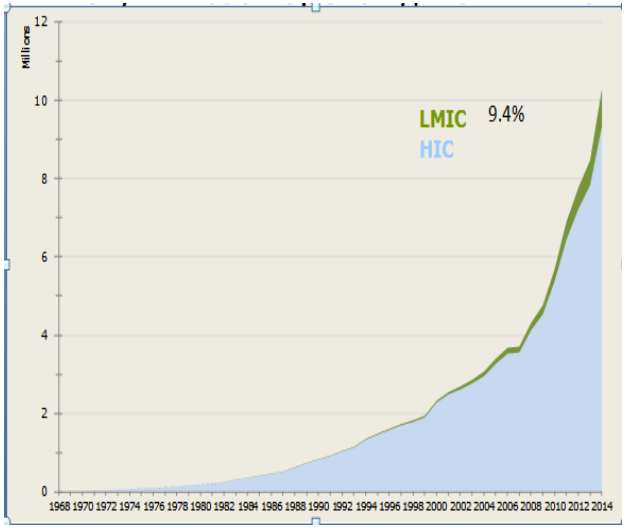


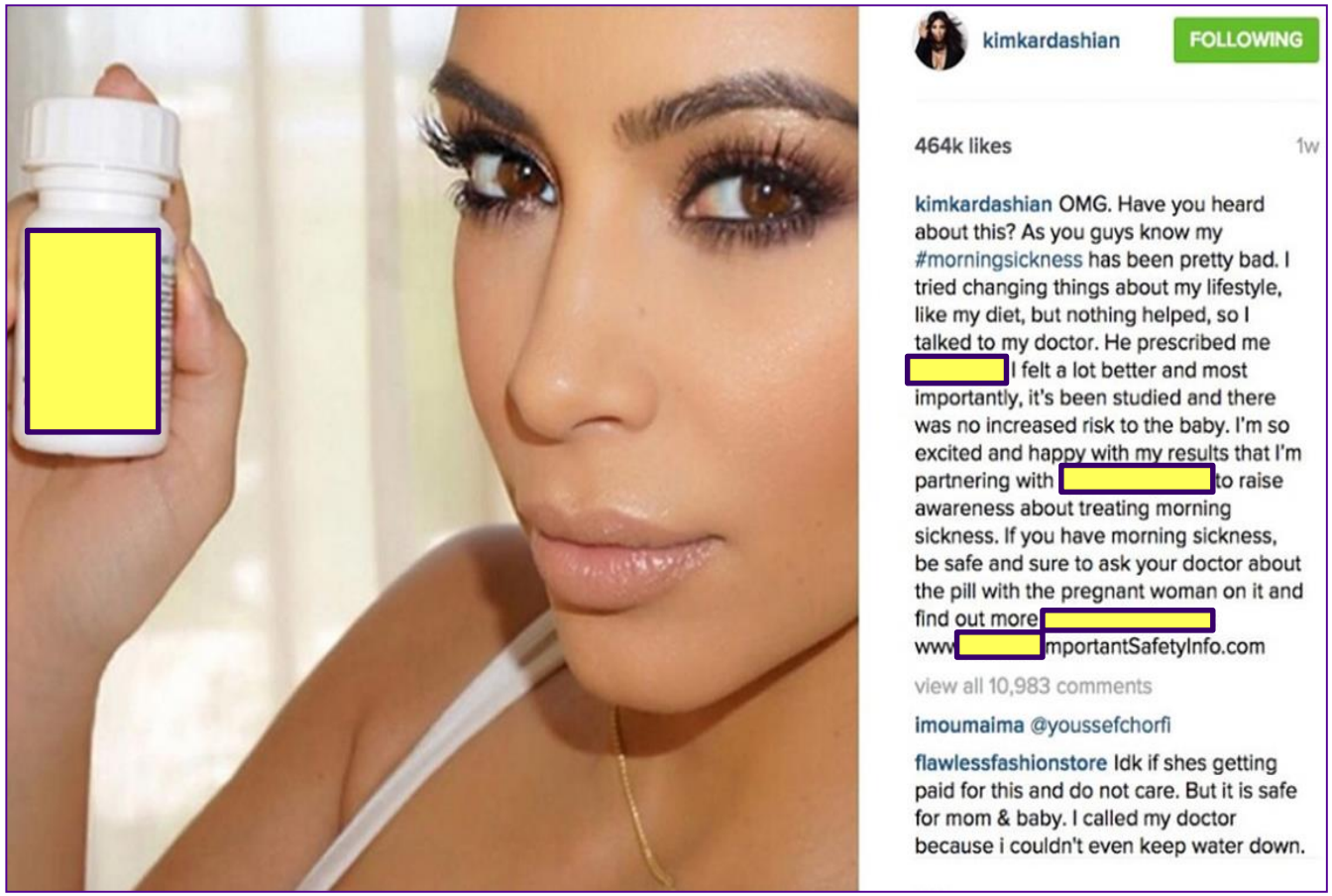
Five areas of opportunity:

4) Redirect activities of NMRA to those that add value:

Examples of essential functions which are often lacking:

- **International harmonization to prevent duplicative efforts**
- **Single or central NMRA within a country**
- **Inspections and enforcement of regulations**
- **Assessments of new essential medicines for neglected diseases in their jurisdiction**
- **Targeted pharmacovigilance**
- **Regulation of medicine promotion**
- **Transparent reporting on the prevalence of substandard medicines**





In 2015 an Instagram posting featuring Kim Kardashian promoted a morning sickness medicine to her 42 million social media followers. The US FDA ordered the manufacturer to remove the posting, on the grounds that it was “false or misleading”.
By the time the decision was reached the post had received nearly half a million “likes” and 11,000 comments

Five areas of opportunity:

5) Engage the public and other stakeholders

- **Involvement of patient and stakeholder representatives before regulatory decisions are taken**
- **Use of product quality verification at point of sale, through:**
  - **Unique barcodes, scratch labels**
  - **Portable low-cost quality-control equipment**
  - **Other technical devices linked via smartphones and the internet**
- **Encourage the public to report suspect products or advertisements; and act on them**

Proposed performance indicators for NMRAs

- Public regulatory website with legislation, approved products
- Product applications and assessment dossiers published
- Regulatory committees with patient representation
- Inspections performed and inspection reports published
- Domestic manufacturers supported in achieving GMP
- Risk-based surveys, and samples tested / failed
- Pharmacovigilance reports collected and submitted to UMC
- Regulation of products intended for export
- Absence of legal obligation of TRIPS-PLUS, e.g. patent linkage and extended periods of data exclusivity

The importation of essential medicines into Uganda

- **The public medicine procurement agency issues a tender for essential anti-retroviral medicines; a company wins the tender (cheapest medicine) but the product is not registered in the country. What should the regulatory agency do?**

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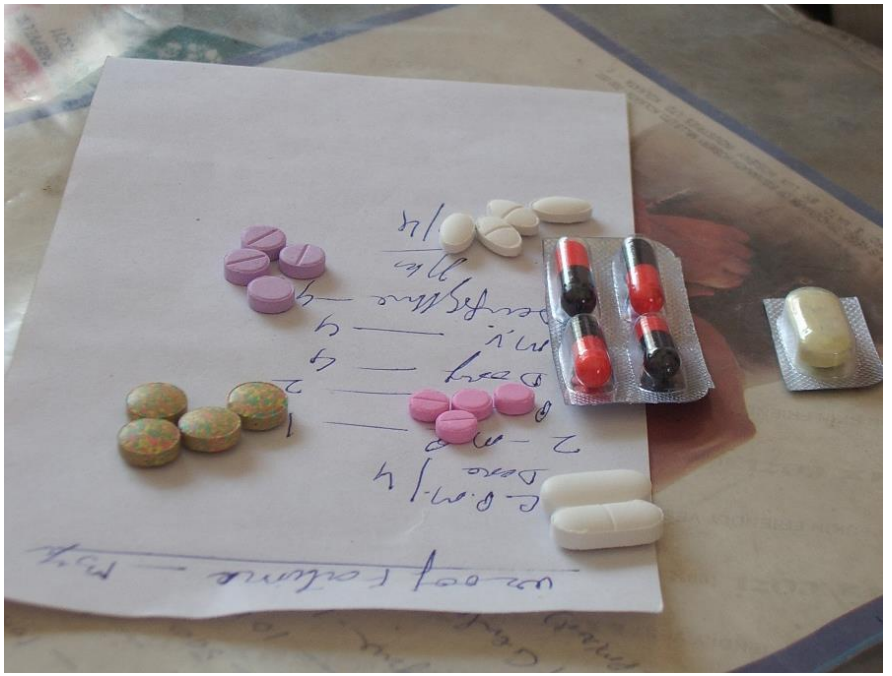
- **A hospital receives a donation of ARV combination therapy from Belgium, but it is not registered in the country. What should the regulatory agency do?**

In a rural health clinic, somewhere in India, a women with a sick child …..

..and these are the medicines which were given to the child

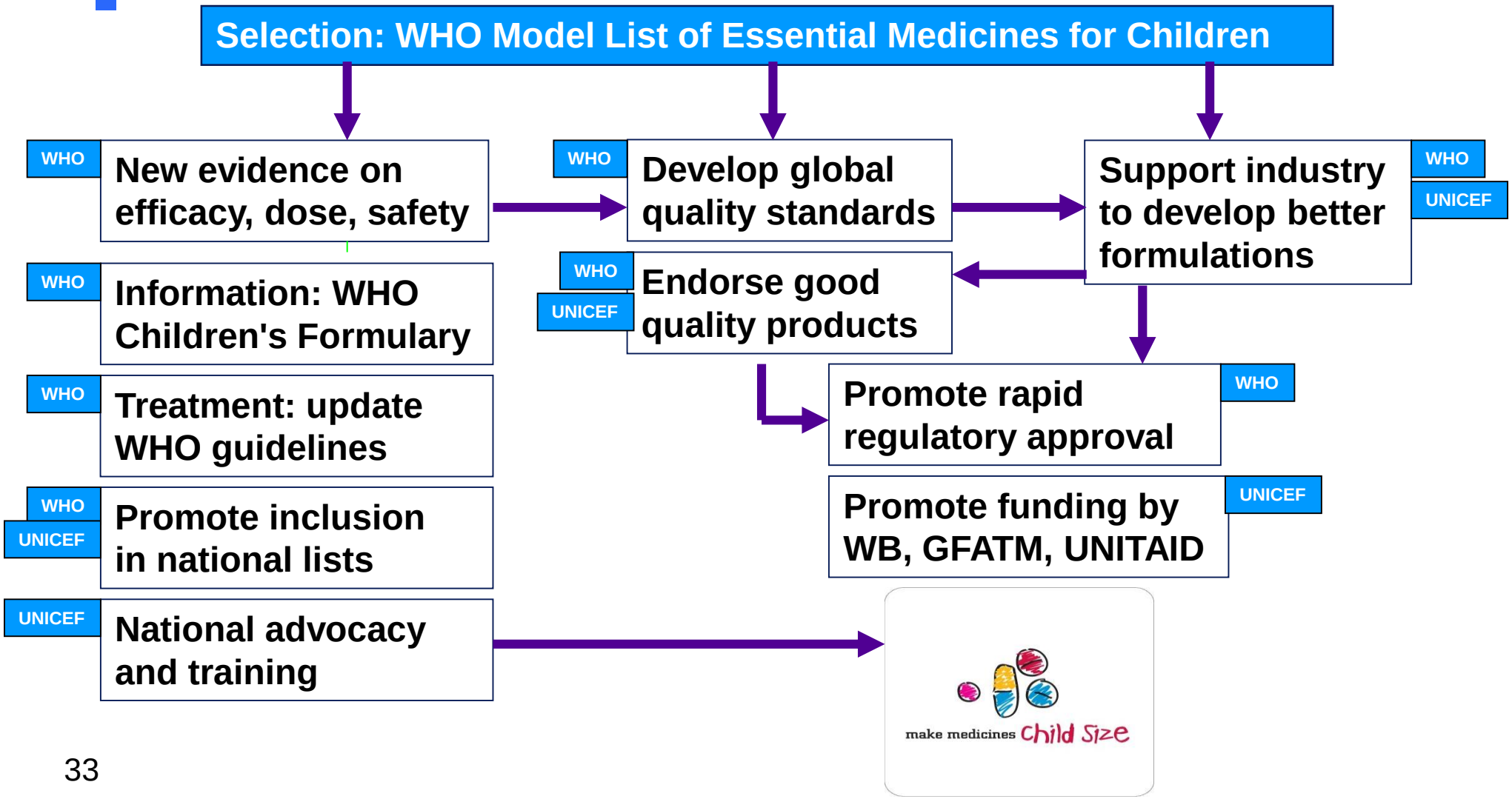


Photograph: Noël Cranswick, 2006

Survey of 29 countries: Problems with Children's Medicines for Malaria, TB and HIV

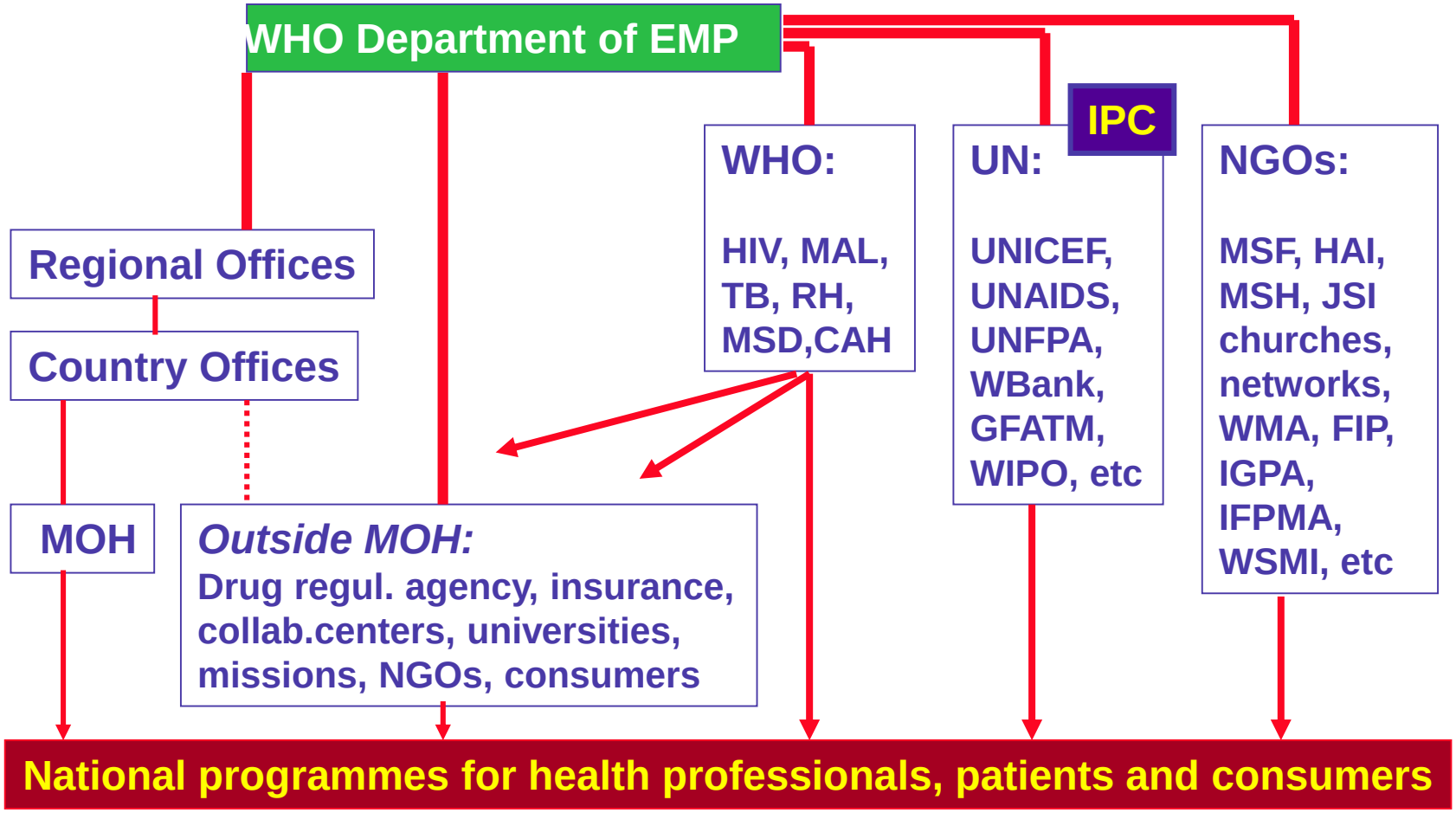
- **Lack of appropriate paediatric formulations**
  - **Artemisinin derivatives in tablet form only**
  - **No paediatric dose forms available for isoniazid, pyrazinamide, ethambutol, rifampicin**
  - **Many countries no paediatric HIV medicines**
- **Cost of medicines**
  - **ARV syrup formulations, artemisinin combinations**
- **Need standard methods for adapting adult medicines to children**
- **Costs of special storage conditions for unstable products**

WHO / UNICEF joint action plan



WHO has many implementation channels

Example: Essential Medicines Programme (EMP) produces WHO Model List of Essential Medicines and WHO quality standards



Important aspects for donors, related to quality assurance

Medicine donations:

- **Respect the WHO / Interagency guidelines for medicine donations**
  - **Core components: donate what is needed (not what you want to donate); respect national regulatory system; respect national EML; no double standards in quality; relate donationa value to international non-profit generic prices**
- **Focus on medicines with WHO/Prequalification and/or registration by stringent regulatory agency**
- **Make long-term (at least five year) commitments**

Important aspects for donors, related to quality assurance

Technical assistance

- **Provide technical assistance to the national regulatory agency, in line with WHO guidelines**
- **Do not donate written-off laboratory equipment (respect the WHO and EPN guidelines for donations of equipment)**
- **Support training opportunities for national regulators, e.g. at stringent authorities, or at WHO**
- **Give financial support to WHO's regulatory support programme**
  - **Training and attachment possibilities (e,g, WHO/PQ programmes**
  - **Participation in WHO inter-country joint assessments of new/complicated essential medicines**

Saving lives
with the right (to) medicines

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