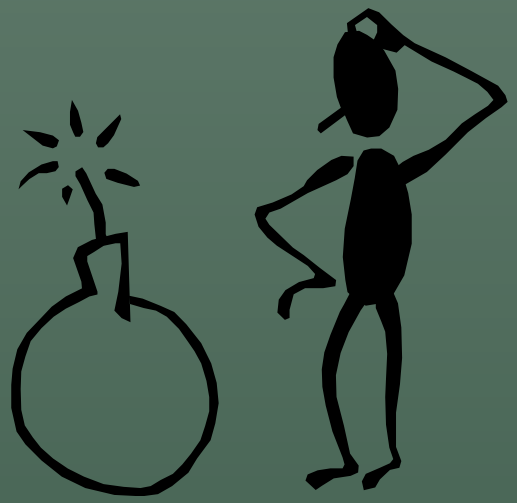
# Substandard and fake medicines:
## undermining health security in the GMS

Douglas Ball

RECAP regulatory specialist (consultant)

Sustainable Development and Climate Change Department
Asian Development Bank

# Overview



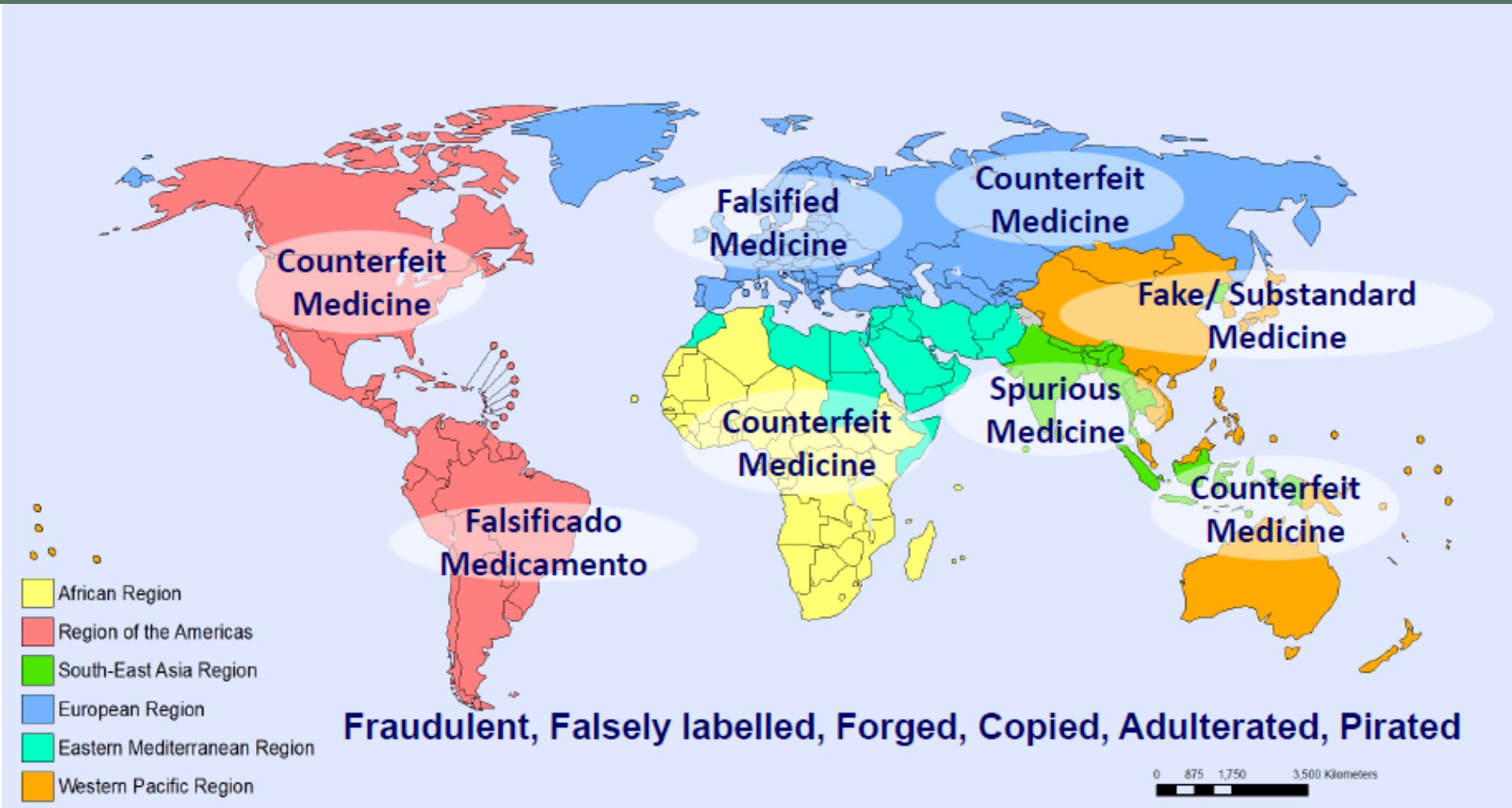
- Definitions, definitions, definitions!!!
- What is the problem?
- How widespread is it?
- What can be done about it?

- Substandard and falsified antimalarials in the GMS
- What it means for the GMS and beyond
  - Artemisinin-resistance and malaria elimination
- What ADB and partners are doing

# What's in a name?

- The title of today's talk refers to **substandard** and **fake** medicines
- We are used to referring to '**counterfeit**' medicines
  - There is much debate on the terminology
- National legal definitions vary
  - 'Counterfeit' commonly refers to trade mark violations
- The problem is much wider especially with reference to public health

# What's in a name?




Important to be clear what we are talking about….

# What's in a name?

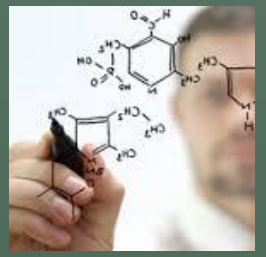
- Terminology differences have led to trade 'disputes'
- Generic medicines seized in EU when sent from India to:
  - **Brazil**: Antihypertensive medication (losartan) (Dec 2008)
    - Paid for by Brazil under national tender
  - **Nigeria**: Anti-AIDS medicine (abacavir) (Feb 2009)
    - Paid for by UNITAID as part of US/Clinton Foundation aid programmes
- Also cases of Alzheimer medicine, antibiotics, antipsychotics
- Multinational pharmaceutical companies used EU legislation on 'counterfeits' to have the products seized/delayed
  - Products were legal in countries of origin and destination
  - Contravened patents/trade marks in EU which was just a transit point

# SSFFC – substandard and falsified

- As a result, WHO member states have been working on the issue by referring to **SSFFC medical products**:
  - Substandard / Spurious / Falsely-labelled / Falsified / Counterfeit
- Public health concerned more with poor quality medicines than trade mark infringements
- November 2016 – finally agreed on definition of "substandard" and "falsified" medicines

# The medicines registration process

- Company develops a medicine
  - Completely novel or a 'copy' of existing medicine



- National regulatory authority (NRA)
  - Assesses quality, safety, efficacy
    - Documentation, processes, inspections


- NRA issues market authorization / registration
  - Medicine can be sold / marketed
    - Manufacturer has proven quality, safety, efficacy

# Substandard medical product

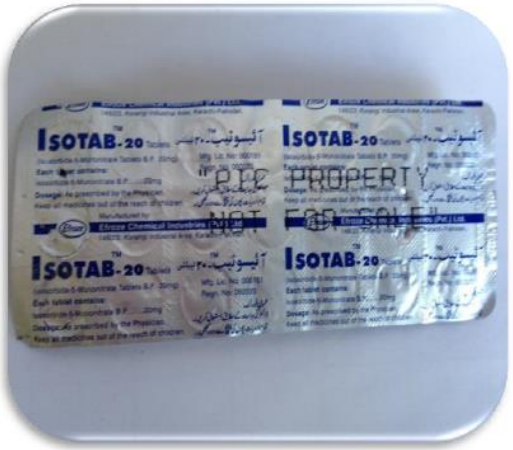
- **Genuine** medical product
  - Normally manufactured in compliance with specifications
  - Has been assessed and registered by NRA

- **But**, due to manufacturing errors, poor storage, degradation in the supply chain, theft, expired
  - **May be out of specification**
    - Less/more active ingredient, too hard/soft, contaminated

→ **SUBSTANDARD**

# Substandard medical product

**Isosorbide-5-Mononitrate**




**Paracetamol**

**Also called out of specification (OOS) products, are genuine medicines produced by manufacturers authorized by the National Medicines Regulatory Authority (NMRA) which do not meet quality specifications set for them by National standards.**

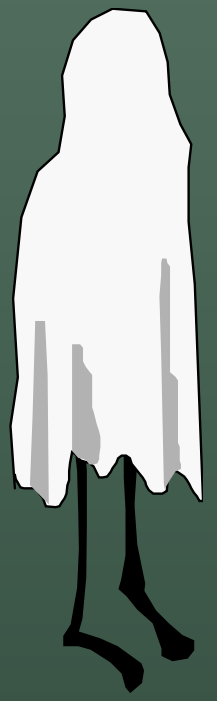
Slide from WHO Global Surveillance System

# Falsified medical product

- Has been **deliberately** made to look like a registered product
  - Identity (name, packaging)
  - Composition (ingredients, expiry date)
  - Source (manufacturer)

- Has not been assessed by the NRA
  - Unknown quality, safety, efficacy
  - Usually poor

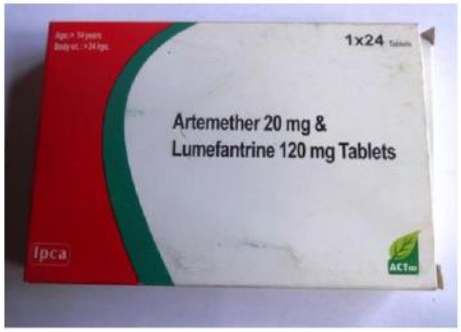
→ **FALSIFIED**



# Falsified medical product

**Heart Disease**


**Anti-malarial**




**Cancer**


**Medical Products which deliberately misrepresent either their identity, and /or composition, and/or source**

Slide from WHO Global Surveillance System

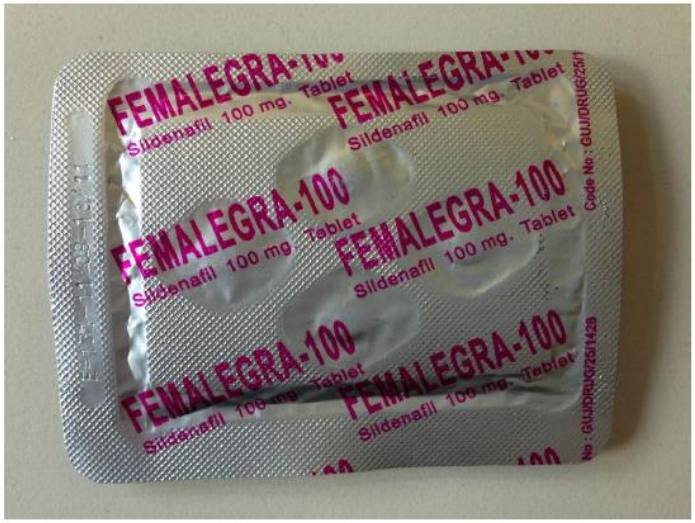
# Falsified medical product


# Unregistered medical product

- Has been legally manufactured in one country/market
- Has been brought into/sold in another country/market where it is not registered

- Has not been assessed for quality, safety, efficacy in the country of marketing
  - Cannot be sure of the supply chain and storage conditions it has passed through
  - Cannot be sure of its identity

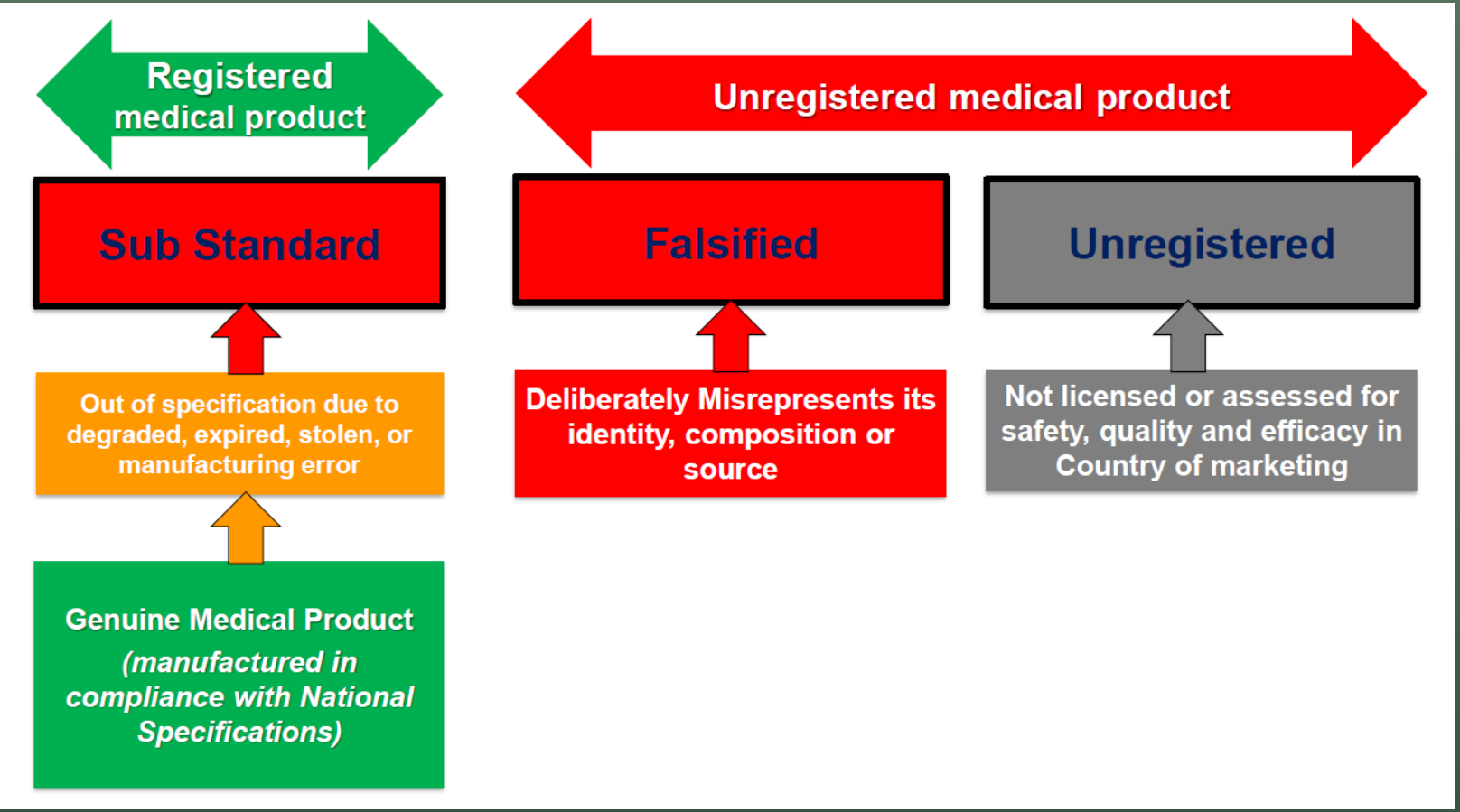
# Unregistered medical product




**Medical products which are not authorized by the competent medicines regulatory authority for marketing and distribution, and have not undergone evaluation of their safety, efficacy and quality for the market in which they are distributed**

Slide from WHO Global Surveillance System

# Working definitions




Slide from WHO Global Surveillance System

# Public health consequences

- Direct patient and consumer health impact
- Reduced confidence in medicines, health providers, health systems
- Antimicrobial resistance
- Undermines vaccination programmes
- Economic damage to health systems, loss of productivity, prolonged treatment regimes, adverse effects
- Increased out-of-pocket expenditure by consumers

Slide from WHO Global Surveillance System

# Democratic Republic of Congo 2015

- Sudden increase in hospitalizations – up to 40 per week
- Acute spasms of face, neck, arms particularly in children
- Traced to expired haloperidol tablets (for schizophrenia) being relabelled as diazepam tablets (for anxiety, convulsions)
- Was being used to treat convulsions of malaria
- Typical toxicity from overdose


Slide from WHO Global Surveillance System

# How widespread is the problem?

- No-one really knows
  - Many surveys using different methodologies, different products, different sources, …
- Problem for high- and low-income countries
  - Globalization of medicines supply means it is a global issue
  - Sophisticated criminal gangs involved as well as small players
  - Internet sale of medicines increases the problem
- Low-income countries with weak health systems have more capacity challenges in preventing, detecting and addressing substandard and falsified medicines
  - Substandards are as much/more of a public health issue as falsified medicines in low- and middle-income countries

# What can be done about it?

- Strengthening NRAs
- Securing supply chains
- Increased post-marketing surveillance & reporting
  - Field screening devices
  - Authentication & verification
  - Trace & trace
- Policies, regulations, penalties
- Public and professional education

# Malaria in the GMS

- Tremendous strides to reduce malaria in recent decades
- Countries in the Greater Mekong Subregion aiming for malaria elimination by 2030
  - Falciparum and vivax malaria
- Artemisinin-containing combination therapies (ACTs) are the mainstay of therapy
  - Vivax needs an additional medicine

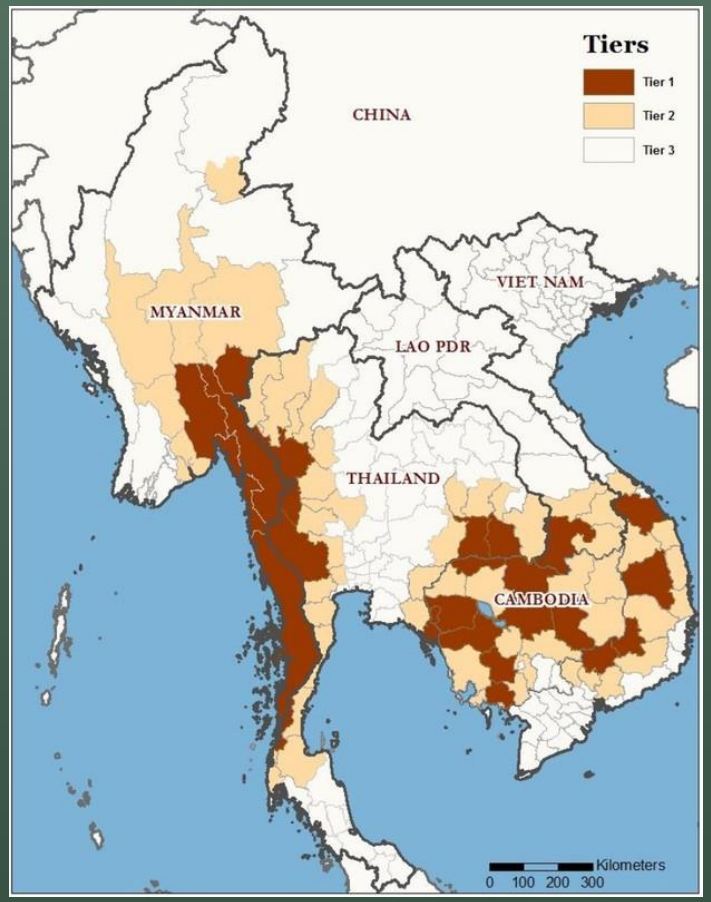



Image from WHO. Status report on artemisinin-resistance. Sept 2014. http://www.who.int/malaria/publications/atoz/status-rep-artemisinin-resistance-sep2014.pdf

# Malaria and regional health security

- Drain on health resources
- 2 billion at risk; 50,000 annual deaths in AP
- Disproportionate impact on poor in remote areas
- Affects development: agriculture, tourism, industry

- Elimination is a sound investment
  - 10% reduction in burden → 0.3% increase in growth
  - $5-8/averted case
  - Potential $300 billion cost saving/social benefits

# Artemisinin-resistance in the GMS

- Increasing reports of artemisinin-resistance in GMS
  - Remote border areas, migrant populations
- Access antimalarials through informal market
- Resistance to artemisinin threatening to undermine progress
  - If resistance spreads to Africa….!!!
  - Elimination is best way to address the threat

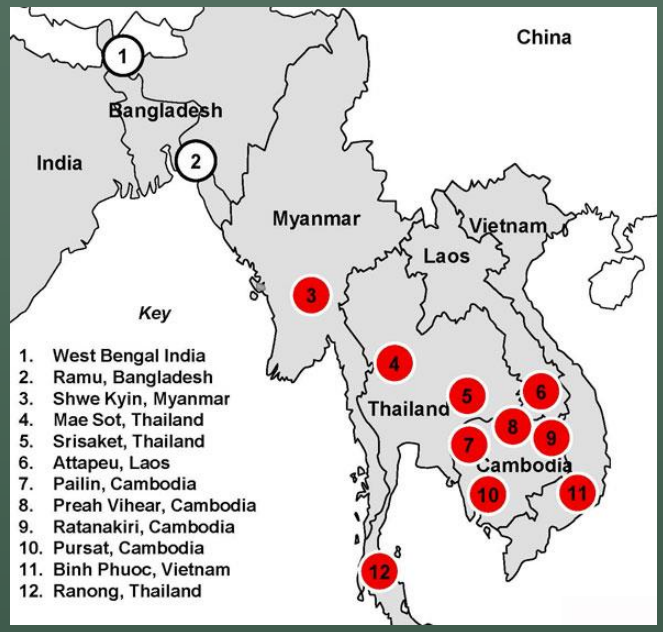



Image from http://www.malaria.com/featured/antimalaria-resistance-mekong

# Substandard and falsified antimalarials in the GMS

- Poor quality antimalarials contribute to development of artemisinin resistance and treatment failure
- Inappropriate treatments found (oral artesunate monotherapy)
- Substandard products identified
- Falsified ACT products identified
  - First described 2000
  - Contained other antimalarials, antimicrobials, chemicals
- Significant threat to malaria elimination efforts


Map image from: journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.0050032

# Examples of falsified antimalarials

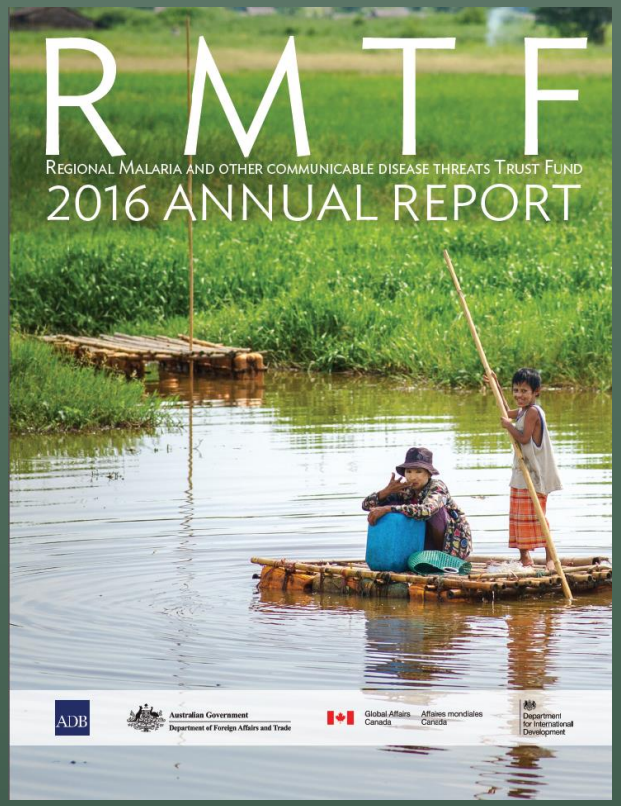

Image borrowed from Oxford University, Centre for Tropical Disease 2004.




# What is being done?

- WHO and other partners
  - Emergency response to artemisinin-resistance (ERAR)
  - Global plan for artemisinin resistance containment (GPARC)
  - Other activities and initiatives e.g. ACTWatch, WWARN
  - Asia Pacific Leaders Malaria Alliance (APLMA)

- Regional Malaria and other Communicable Disease Threats Trust Fund (RMTF)
  - ADB administered



# Regional Malaria Trust Fund (RMTF)

- Established 2013
- DFID (UK), DFAT (Australia), DFTAD (Canada)

- Support DMCs to develop regional, multicountry, cross-border, and multisector responses
  - Range of financing products – grants, TA
  - Leverages cofinancing from other partners
  - Links to Regional Health Security Project in the GMS

- No longer business as usual

- Using malaria as a foothold for greater systems strengthening and improving regional health security

1 Strengthened leadership

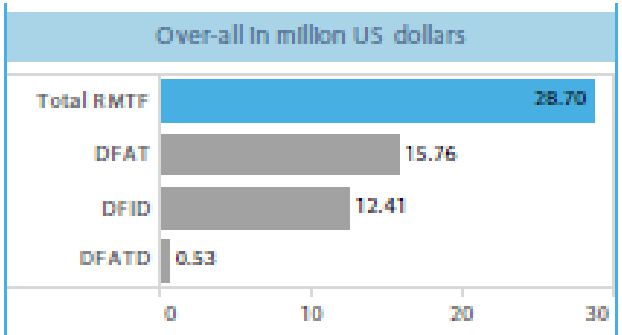
2 Increased financing

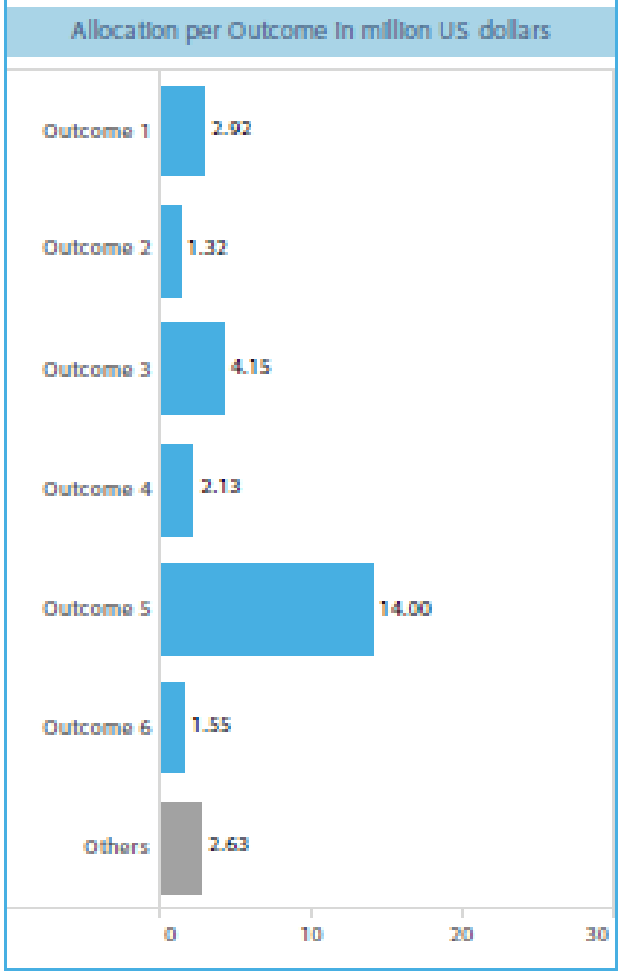
3 Quality medicines

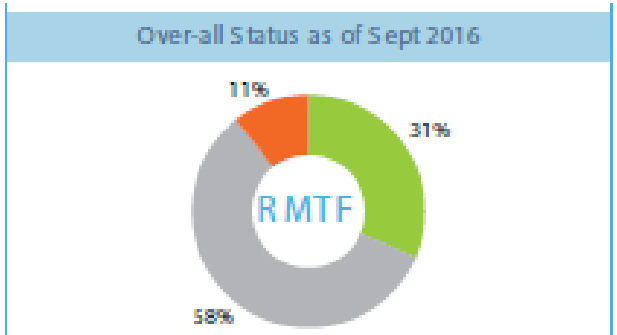
4 Improved information systems

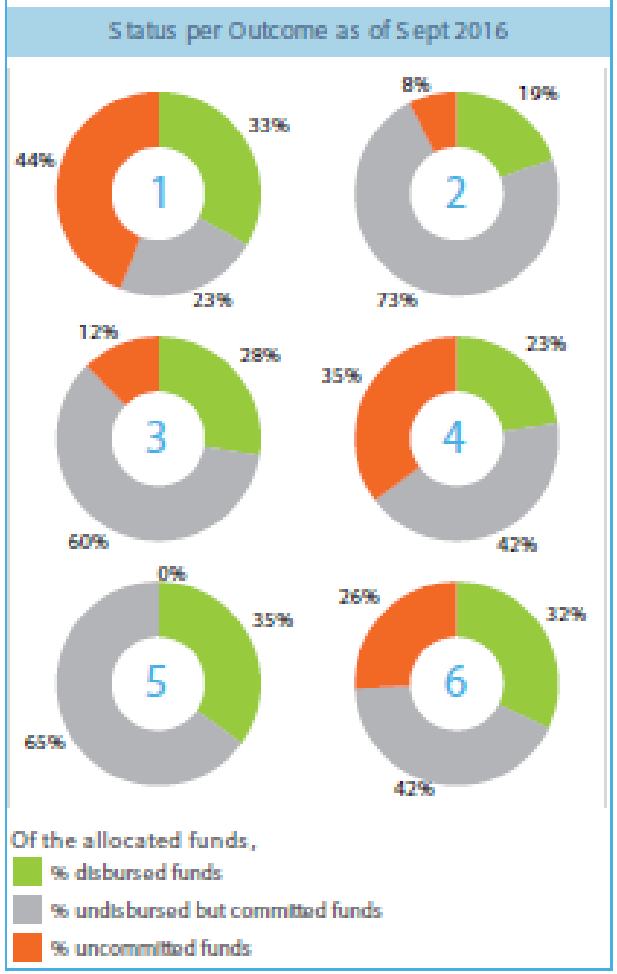
5 Strengthened laboratory diagnostics and surveillance

6 Prevention of communicable disease threats in infrastructure projects



# NRA capacity development

- Centre of Regulatory Excellence (CoRE) in Singapore
  - Established 2014 at Duke-NUS
- Engaged as a partner to guide capacity development of NRAs in GMS
  - Cambodia, Lao, Mynamar, Thailand, Viet Nam

- **Phase 1** – baseline assessment of NRA capacity gaps
- **Phase 2** – develop capacity development plans and deliver targeted training programs

➢ Increase access to quality antimalarial medical products of public health importance

➢ Improved post-marketing surveillance to remove substandard and falsified products from the market

# WHO Global surveillance reporting training

- WHO Global Surveillance System
  - Rapid Alert System for substandard/falsified medical products
  - Report suspected substandard/falsified medical products
    - React to urgent cases
    - Develop an evidence base

- Training of national NRA focal points
  - Singapore May 2016 (hosted by CoRE)
    - 13 countries
  - Jakarta October 2016
    - 10 countries


➢Increase awareness of and reporting of substandard and falsified medical products

➢Partnered with United States Pharmacopeia (USP) for training on laboratory procedures and analysis

ADB World Health Organization USP U.S. Pharmacopeial Convention CoRE Centre of Regulatory Excellence @ Duke - NUS Medical School

# Field detection devices

- Lao-Oxford-Mahosot Hospital Wellcome Trust Research Unit (LOMWRU) in Vientiane
  - Proven track record in studying quality of antimalarials in GMS
- Engaged as partner to test mobile field detection devices for screening suspected substandard and falsified medical products

➢Utility, cost-effectiveness of existing and novel technologies for use by NRAs in post-marketing surveillance

➢Policy dialogue with NRAs to determine the appropriate technologies and requirements

# Outcomes from the work so far

- **Myanmar** requested WHO for country-specific training on substandard and falsified medical products
- **Follow-up meeting** and workshop for GMS
  - High-level meeting to garner support
  - Practical training on regulatory actions on substandard/falsified products
- **Reports** to WHO Global Surveillance system up – 15 (2 countries) since Singapore; 14 (4 countries) since Jakarta
  - Increased use of the WHO database portal by Member States
  - India expressed willingness to engage in substandard/falsified reporting
  - Development of smartphone app to support reporting
- NRAs in Cambodia, Lao, Thailand, Viet Nam working with CoRE on **capacity assessments**
- **APLMA** engaging NRAs on possible collaboration in regulation of novel antimalarial medical products

aplma
ASIA PACIFIC LEADERS MALARIA ALLIANCE

# Limitations to regulatory strengthening

- Takes time for system change
  - Artemisinin-resistance a problem now
- NRAs see regulation as national responsibility
  - Regional collaboration is starting
  - Regional health security not a priority to NRAs
- Dependent upon high-level support
  - Lack of strategic leadership
  - Need to examine structural issues, funding for sustainability

# Conclusions

- Substandard and falsified antimalarials in the GMS represent a real and present danger
  - Contribute to artemisinin-resistance
  - Threat to regional health security
- Regulatory strengthening under RMTF provides avenue to address root causes and bolster measures to reduce threat from substandard and falsified medicines in the long term
- Regional collaboration and cooperation, with regulatory convergence will help to support regional health security
  - Malaria as a 'foot in the door' to wider effects

# Thank you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