

## Fake medicines & antimalarials in South East Asia



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## Fake / Counterfeit drugs : a global business, a global problem



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## WHO definitions

- **Counterfeit drug** "a pharmaceutical product that is deliberately and fraudulently mislabeled with respect to identity, content, and / or source"  
"fake drug" is a **synonym** commonly used (not by WHO)
- **Substandard drug** "a pharmaceutical product with genuine packaging with incorrect quantity of ingredient (not deliberate)"



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## The lay press was first to publish substantial information, which remains globally scarce

**Le Monde** Faux médicaments : enquête sur un trafic criminel  
26 Oct. 1996

Dans les pays africains, 60 % des médicaments vendus peuvent être des faux, ... entraînant la mort de centaines d'enfants... L'OMS et l'industrie pharmaceutique tirent le signal d'alarme. L'OMS estime qu'au moins 7 % des médicaments vendus chaque année sur la planète sont en réalité des contrefaçons.... Philippe Broussard

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## Counterfeit medicines : a worldwide problem

- Fake drugs (FD) = 10 % of the world drugs market (US FDA), fuelled by the Internet e-commerce
- 30-billion \$ profit / year; up to 75-b. by 2010 (WHO, 2006) ?
- 60% of FD are shipped to **deprived countries** (WHO, 2000)
- Few accurate / reliable data on FDs volume and market
- International agencies, WHO, NGOs non reactive until 1999

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## Milestones of FD and their health impact

1. UK, 1989 : fake "best seller" Zantac proton pump inhibiteur
2. Haiti, 1990 : fake paracetamol syrup containing ethylene glycol (*antifreeze*) caused hundreds acute renal failure and 89 deaths in children
3. Niger, 1995 : fake meningococcal vaccine was administered to 50,000 people during an epidemic ; fake toll estimated 2,500 deaths
4. Worldwide, fake antibiotics result in uncontrolled infections ; fake contraceptive pills in thousand of unwanted pregnancies and abortions : number of related deaths unknown, but probably huge
5. 192,000 deaths have been estimated caused by fake or substandard drugs in China in just one year (2001)

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## Examples of fake drugs from SE Asia

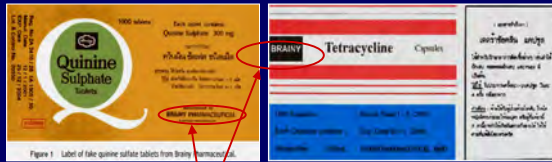


Figure 1 Label of fake quinine sulfate tablets from Brainy pharmaceutical.

Note : « Brainy Pharmaceutical » (India) simply does not exist...

Fake quinine & tetracycline found in Cambodia 7

## Which drugs and what is the impact ?

Drugs	Impact
<p><u>1. Affordable countries</u></p> <ul style="list-style-type: none"> <li>viagra ++ (world's leader)</li> <li>anti-acids</li> <li>corticosteroids – hormones</li> <li>lipid lowering drugs</li> <li>sedatives</li> </ul> <p><u>2. Low income countries</u></p> <ul style="list-style-type: none"> <li>anti-malarials</li> <li>antibiotics</li> <li>anti retrovirals</li> </ul>	<p><u>1. Health</u></p> <ul style="list-style-type: none"> <li>* drug inefficiency</li> <li>* drug resistance antibiot./ antimalar.</li> <li>* 4,000s of avoidable deaths (China)</li> </ul> <p><u>2. Economic</u></p> <ul style="list-style-type: none"> <li>* financial loss for the drug C<sup>e</sup></li> <li>* cost of battle against fraud</li> <li>* family micro-economy</li> </ul> <p><u>3. Ethic</u></p> <ul style="list-style-type: none"> <li>* most exposed are the poor</li> <li>* loss of confidence in drug / doctors</li> </ul>

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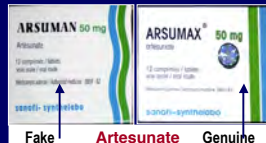
9

## Which drugs and impact ? affordable and poor resource countries differ



Fake Lipitor

Affordable countries  
most counterfeit are  
not essential drugs ;  
fakes do not cause deaths



Fake Artesunate

Poor resource countries  
most counterfeit are  
essential drugs ;  
fakes cause deaths

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## Why do people buy fake drugs ?

the 3 "A" : awareness, affordability, availability

- FD awareness is low
- FD are affordable (*cheaper than genuine*)
- FD circulate in the "informal economy sector" that is daily used by poor people for any of their needs
- FD are available in poor resource countries : at *street pharmacies / pharmacie trottoir* sometimes the only ones available
- FD may also be sold by officially authorized pharmacies

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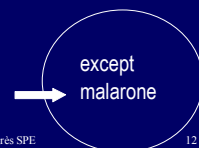
## Fake antimalarials

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## All antimalarials have been counterfeit

- Chloroquine
- Quinine
- Sulphadoxine-pyrimethamine (Fansidar™)
- Mefloquine
- Halofantrine
- Primaquine
- Artesunate
- Intramuscular artemether
- Dihydroartemisinin ?



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## The true story of fake Artesunate

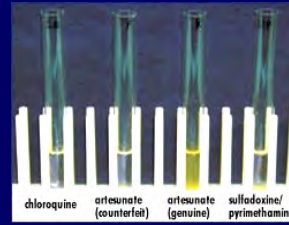
- Genuine Artesunate (AS) was, and is still developed in Guilin, Guangxi province, China
- AS is vital in SE Asia, where wide range resistance has emerged to most available other antimalarials
- AS part of the artemisinin derivatives combination therapy (ACT) policy of WHO to tackle malaria in most areas of the world



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## Fake artesunate began to appear in 1998



Rapid dye test allows rapid identification (Mike Green)

- An epidemic of death and morbidity hidden among the rural poor



Courtesy P Newton

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## News on fake drugs in the lay press

*The New Light of Myanmar. Online Edition*

Nov 2007  
"Injection Artemether" (Kunming Pharmaceutical C<sup>o</sup>) found to be an imitation..... Lab analysis found **no active Artemether**"



\*\*\*\*\*  
*The Phnom Penh Post Monday, 24*

Nov 2008  
« Interpol in Phnom Penh **seized 6.65 million US \$ of counterfeit drugs** from across SE Asia ... »

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## The scientific press reacted later

*nature* 10 March 2005 Vol 434 Issue n°7030

**Killers on the loose**

**Murder by medicine**

Across the developing world, people are dying after being prescribed fake pharmaceuticals. These deaths beguile from treatment. Now, where scientists, doctors and regulators battle against counterfeit drugs



drugs street vendors Phnom Penh

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## Murder by medicine

- The first documented death due to fake antimalarial in 1999.
- A 33-year healthy Cambodian male who died after treatment with mefloquine failed
- After his death, the mefloquine specimen proved to be fake and to contain no mefloquine at all.

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## Counterfeit and substandard antimalarial drugs in Cambodia

C.T. Lon<sup>1,a</sup>, R. Tsuyuoka<sup>2,b</sup>, S. Phanouvong<sup>3</sup>, N. Nivanna<sup>4</sup>, D. Socheat<sup>1</sup>, C. Sokhan<sup>5</sup>, N. Blum<sup>6</sup>, E.M. Christophel<sup>1</sup>, A. Smine<sup>6</sup>

Transactions of the Royal Society of Tropical Medicine and Hygiene (2006) 100, 1019–1024

## Manslaughter by Fake Artesunate in Asia— Will Africa Be Next?

Paul N. Newton<sup>1</sup>, Base McGready, Facundo Fernandez, Michael D. Green, Manuella Sunjic, Carinne Bruneton,

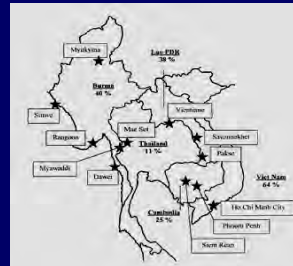
PLoS Medicine | www.plosmedicine.org June 2006 | Volume 3 | Issue 6 | e197

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## Four studies on fake antimalarials in South East Asia (among many more)

## Study 1. Artesunate SE Asia (2000-2001) (Burma, Laos, Thailand, Cambodia, Vietnam)



Shop bought AS :

- 38 % counterfeit,
- containing no active drug

One NGO could buy 100,000 tablets in just one shop

## Study 2. Antimalarials survey (2002-2003) (same area as study 1.)

- Dondorp *et al.*
  - Artesunate 188 samples collected
    - 58 % fake : 'artesunate' blisterpacks contained no artesunate.
    - all were labelled as made by "Guilin Pharma" (China)
  - Mefloquine : 9 % substandard and probably fake
  - Artesunate injection, artemether, dihydroartemisinin : no fakes found

## Study 3. Collaborative epidemiological investigation into the criminal fake artesunate trade in SE Asia P Newton *et al. PLOS Med*, 2008



Artesunate collected at random throughout :

- Myanmar (137)
- Laos (115)
- Thailand (16)
- Cambodia (48)
- Vietnam (75)

A Wellcome Trust  
SE Asian collaboration

## Study 3.

### Method :

- packaging careful investigation ; and, if specimen suspect :
- chromatography (HPLC) and / or mass spectrometry

### Results :

- 49.9% fake AS
- containing no AS, or <12 mg / tablet (50 mg / genuine tablet)
- 16 different fake hologram types identified.

## Genuine Artesunate : package hologram



Genuine « GUILIN PHARMA » label



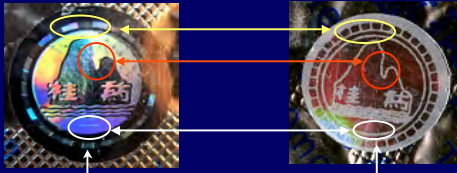
ultra violet light

Courtesy P Newton

## Genuine or fake AS ? check the package hologram

Genuine Hologram

Fake Artesunate 'Type 2'



P Newton et al. have identified so far 12 different types of fake « Guilin » artesunate, with fine or grossly imitated brand holograms

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Courtesy P Newfón

## Genuine Hologram Fake Artesunate 'Type 12'



12 (and probably more) types of counterfeit chinese artesunate

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Courtesy P Newfón

## Study 4. KAP in Lao MD (IFMT, unpublished)

### Perception of fake drugs by Lao medical practitioners : a KAP study, Vientiane, 2008

V Thammabamevong, T Kanthi, V Kelouangkhot,  
P Phimmason, H Barennes, Y Buisson,  
M Strobel (IFMT, Vientiane)

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## KAP study : Method

- Feb to Jun 2008
- 5 provincial & 6 district hospitals
- Standardized questionnaire
- 399 prescribing MD interviewed



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## KAP study. Results : GPs knowledge on fake / substandard drugs (FSSD)

1. 99% GP are aware of the FSSDs
2. 93-97% MD deem FSSD problem as potentially harmful ; however, only 36 % consider it a serious, large scale public health issue
3. knowledge scores of FD and SSDs definition: 15 and 18/30 respectively
4. 53% and 37.5% of MDs cited antibiotics & artesunate as most fakes
5. Health impact was not well perceived : only 33.5% and 11% mentioned drug inefficiency and drug resistance respectively
6. Main sources of MDs information were : peers (65%), private pharmacists (38%), Thai TV (13%), Ministry of health (11%)

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## Fake artesunate in Asia : a brief summary

### Cambodia 1999

- 71% AS market samples are fake
- > 30 known deaths

### Several studies in SE Asian countries (2000-2008)

- 38% - 97% circulating AS fake (depending site & method)
- 2008 multiple country study : 50% artesunate is fake
- burden unknown : n. deaths / year ?
- of major concern : emerging resistance to artemisinines

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## Fake 'artesunate' may contain

- Chloroquine
- Sulphadoxine-pyrimethamine
- Chloramphenicol
- Metronidazole
- Erythromycin
- Paracetamol
- Metamizole sodium
- **Artemisinin**

## Counterfeit artesunate : a neglected Asian public health disaster ?

- Counterfeit artesunate represent a major risk of :
  - large number of avoidable deaths by malaria
  - **failure of malaria control : the disaster !**
- Collectively very little action has been taken

## Implications for the wider world

### Travelers

it is sad to say :

will a few fatal cases due to fake artesunate occurring in rich travelers have more impact than the silent death of thousand rural poor ?

## Implications for Africa ?

what if fake artemisinin derivatives reach Africa where the malaria burden is worse than SE Asia and where regulations are weaker... ?

## Fake artesunate has already reached Africa



2 artesunate samples bought in Cameroon; note differences in names and hologram "Guilin Pharmaceutical" which manufactures the drug in China ; this is a « gross » imitation

Photograph by Manúela Sunjio

## Fake artesunate in Africa (2)



2 samples bought in Kumasi, Ghana in 2008 with very similar packages ; fake labelled in english / german ; genuine in spanish / french this is a « fine » imitation



## Resistance is the main concern : an avoidable disaster ?

*will small quantities of artesunate present in fakes drive  
P. falciparum resistance to artemisinin derivatives ?*

## What can we do ?

1. Inform / educate : both public and health care workers
2. Enforce regulations & law at borders, factories, pharmacies
  - tackle the organized crime which controls the FD market
  - enhance drug surveillance and inspection
  - develop easily interpretable tests to detect fakes (*by the police*)
  - provide / support good quality controlled drugs
3. Undercut the counterfeit business
  - lower the price of genuine antimalarials to make them affordable
  - **or give them free – as in Laos -**

## Yes we can !

i) tackle crime



ii) innovate : \* develop simple rapid tests to identify fakes  
\* provide quality drug at cheap price or free

*The Guardian, 11 Sept 2008*  
« The drugs don't work »  
scientists are developing a quick  
inexpensive method of testing for  
counter-feit medicines

In Laos,  
Co-artem can not be purchased in  
pharmacies, but is delivered free  
at any health centre or hospital

## Pharmaceutical companies : a tradition of secrecy

- companies have developed a culture of secrecy : no legal duty to report fakes to the FDA equivalent
- much less prosecutions against fake medicine producers than against generic producers
- needs to be much more sharing of information

## The Global Threat of Counterfeit Drugs: Why Industry and Governments Must Communicate the Dangers

Robert Cockburn\*, Paul N. Newton\*, E. Kyremateng Aggariko, Dora Akunyili, Nicholas J. White

## Fake medicines, not a new issue : fake quinine report dating back... the 17th century

[ 164 ]  
From the year 1640, that the Peruvian  
Bark was first imported into Spain, its  
reputation increased till the old unpeeled  
trees becoming scarce, the inhabitants of  
Loxa, mixed other Barks with it, which  
being detected, it fell into such discredit,  
that, in the year 1690, several chests of it

An account of fake  
chinchona bark crisis.  
From: Sanders W (1782).

*The Wellcome trust  
Library London UK*

In : *Lancet Infect Dis*  
2006;6:602-13  
P Newton et al.

## A couple of selected electronic references

- [paul@tropmedres.ac](mailto:paul@tropmedres.ac)
- [http://www.jr2.ox.ac.uk/ndm/Tropical\\_Medicine/News.htm](http://www.jr2.ox.ac.uk/ndm/Tropical_Medicine/News.htm)
- [www.who.int/medicines/organization/qsm/activities/qualityassurance/cft/Fake\\_Artisanate\\_Warning\\_25\\_08\\_2005.pdf](http://www.who.int/medicines/organization/qsm/activities/qualityassurance/cft/Fake_Artisanate_Warning_25_08_2005.pdf)
- [http://www.cdc.gov/malaria/travel/counterfeit\\_drugs.htm](http://www.cdc.gov/malaria/travel/counterfeit_drugs.htm)



and please keep in mind that...