Fake medicines & antimalarials in South East Asia


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

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)"

Fake / 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

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

Démenti 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

Milestones of FD and their health impact

1. UK, 1989: fake “best seller” Zantac proton pump inhibitor
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 administrated to 50,000 people during an epidemic; fake toll estimated 2,500 deaths
4. Worldwide, fake antibiotics result in uncontrollable 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)
Examples of fake drugs from SE Asia

Fake quinine & tetracycline found in Cambodia

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

Which drugs and what is the impact?

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Affordable countries</td>
<td>* drug inefficiency</td>
</tr>
<tr>
<td>viagras + (world's leader)</td>
<td>* drug resistance antbiot/ antimalar.</td>
</tr>
<tr>
<td>anti-acids</td>
<td>* 1,000s of avoidable deaths (China)</td>
</tr>
<tr>
<td>corticosteroids – hormones</td>
<td>2. Low income countries</td>
</tr>
<tr>
<td>lipid lowering drugs</td>
<td>* anti-malarials</td>
</tr>
<tr>
<td>sedatives</td>
<td>3. Ethic</td>
</tr>
<tr>
<td></td>
<td>* antiretrovirals</td>
</tr>
</tbody>
</table>

Which drugs and impact? affordable and poor resource countries differ

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

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

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

Fake antimalarials

All antimalarials have been counterfeit
- Chloroquine
- Quinine
- Sulphadoxine-pyrimethamine (Fansidar™)
- Mefloquine
- Halofantrine
- Primaquine
- Artesunate
- Intramuscular artemether
- Dihydroartemisinin?
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 artemisinine derivatives combination therapy (ACT) policy of WHO to tackle malaria in most areas of the world.

Fake artesunate began to appear in 1998

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

News on fake drugs in the lay press

The New Light of Myanmar. Online Edition

"Injection Artemether" (Kunming Pharmaceutical C°) found to be an imitation... Lab analysis found no active Artemether.

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.
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.

(same area as study 1.)

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

Study 3. Collaborative epidemiological investigation into the criminal fake artemesunate trade in SE Asia

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
ultraviolet light

Courtesy P Newton
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 Phimmasone, H Barennes, Y Buisson, M Strobel (IFMT, Vientiane)

KAP study: Method

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

KAP study. Results:

GP’s 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 MD and FSSD's definition: 15 and 15/30 respectively
4. MD cited antibiotics & artesunate as most fake
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 (66%), private pharmacists (38%), Thail TV (13%), Ministry of health (11%)

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
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

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 antimarials 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

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

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


P Newton et al.
A couple of selected electronic references

- paul@tropmedres.ac
- http://www.j2.ox.ac.uk/ndm/Tropical_Medicine/News.htm

and please keep in mind that...