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UFZ

Workshop

Drug lifecycle control in Subsaharan Africa

From production to responsible safe disposal and elimination in wastewater treatment plants

(Med4Africa)

EBERHARD KARLS
UNIVERSITÄT
TÜBINGEN

Faculty of Science
Pharmaceutical Institute

Substandard and Falsified Medicines in Sub-Saharan Africa

Prevalence and Prevention / Detection / Response

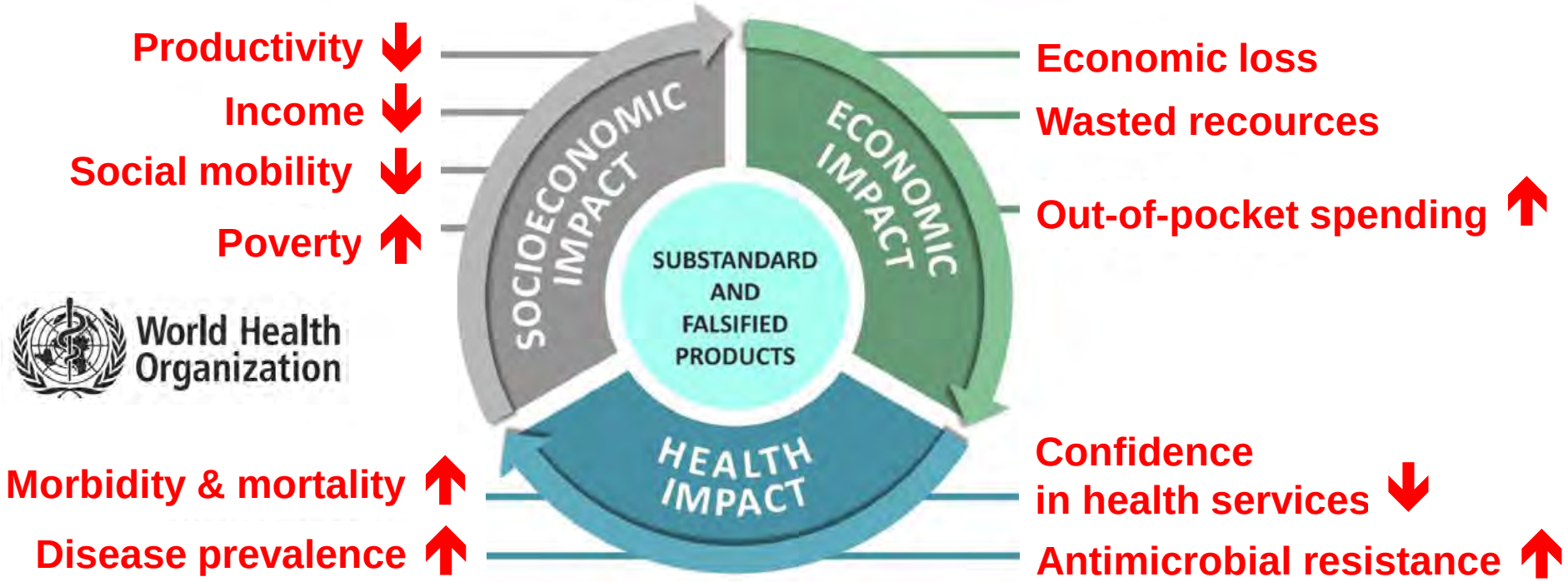
Lutz Heide

Pharmaceutical Institute, Tübingen University, Germany

Workshop "Drug Lifecycle Control in Subsaharan Africa"
Arusha, Tanzania, Aug. 29 – Sept. 3, 2022


SUSTAINABLE DEVELOPMENT GOALS
17 GOALS TO TRANSFORM OUR WORLD
1 NO POVERTY
2 ZERO HUNGER
3 GOOD HEALTH AND WELL-BEING
4 QUALITY EDUCATION
5 GENDER EQUALITY
6 CLEAN WATER AND SANITATION
3 GOOD HEALTH
3.8 Achieve access to
• safe
• effective
• quality
• affordable
essential medicines and vaccines for all.

Impact of substandard and falsified medical products



World Health Organization

Expenditure for substandard and falsified medicines in low- and middle income countries: **30.5 billion US $ per year** (WHO, 2017)

Estimated deaths from substandard and falsified medicines :

in childhood pneumonia: **74,000 – 169,000 deaths per year** (WHO, 2017)

in malaria: **31,000 – 116,000 deaths per year** (WHO, 2017)

Comparison: Ebola epidemic in Africa 2014/15: total 12,000 deaths

Falsified hydrochlorothiazide in Cameroon

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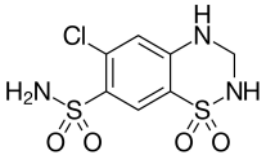
Found in:

- **Government health facilities**
- **Church health facilities**

Analysis of falsified hydrochlorothiazide at Tübingen University

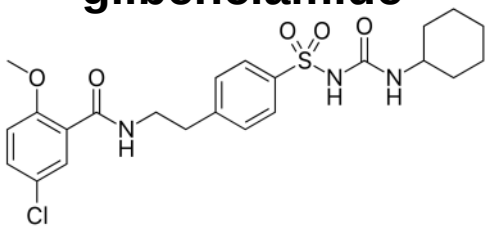
EBERHARD KARLS UNIVERSITÄT TÜBINGEN

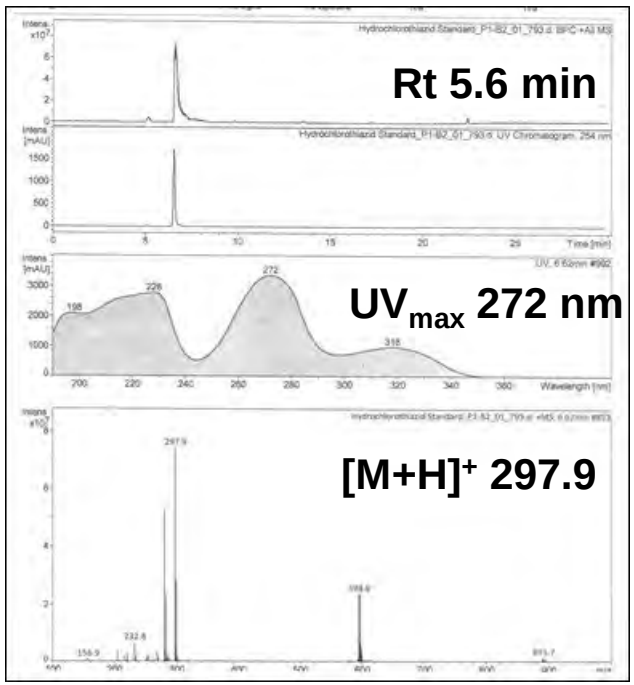
Reference substance hydrochlorothiazide

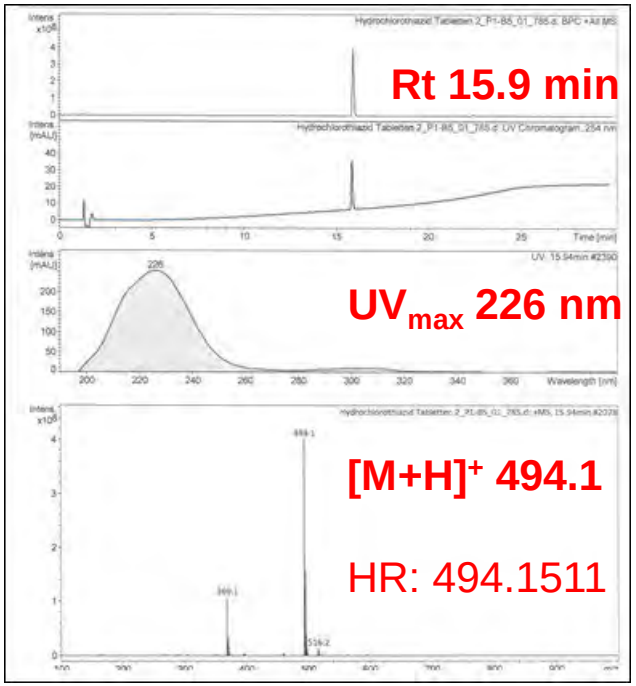


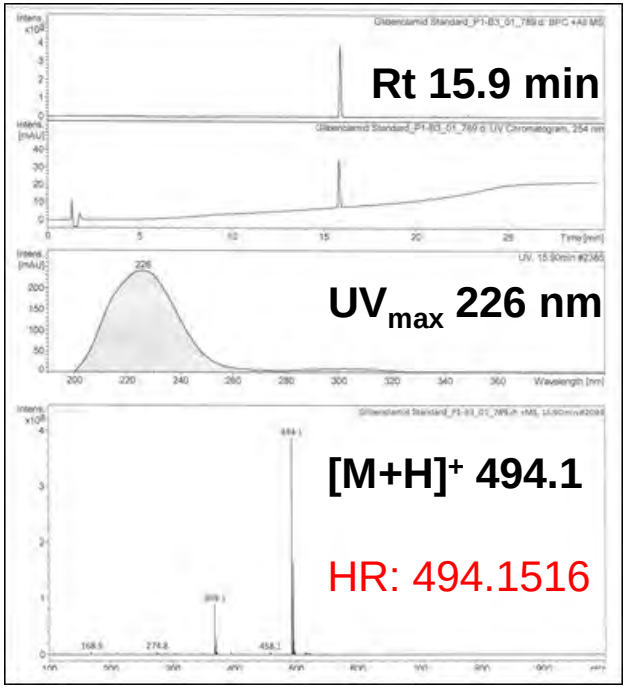
"Hydrochlorothiazide tablets Sterop"

Reference substance glibenclamide









Severe hypoglycemia observed in patients who took this medicine

Analysis of falsified hydrochlorothiazide at Tübingen University

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World Health Organization

WHO Medical Product Alert

20, AVENUE APPIA – CH-1211 GENEVA 27 – SWITZERLAND – TEL CENTRAL +41 22 791 2111 – FAX CENTRAL +41 22 791 3111 – WWW.WHO.INT

Ref. EMP/SAV/Alert N°6.2019 16 April 2019

Medical Product Alert N° 6/2019

Falsified hydrochlorothiazide (containing glibenclamide) in Cameroon

This Medical Product Alert relates to confirmed falsified hydrochlorothiazide that has been found to contain glibenclamide instead of hydrochlorothiazide, circulating in the WHO region of Africa. Adverse effects attributed to these products have been reported. Genuine hydrochlorothiazide is used as an antihypertensive and diuretic medicine, whereas glibenclamide is an antidiabetic medicine.

In March 2019, WHO was informed by a nongovernmental organization in Cameroon that a medicine presenting as hydrochlorothiazide 50mg had caused hypoglycaemia in patients. Preliminary testing indicated that the product did not contain any of the stated active ingredient, hydrochlorothiazide, and glibenclamide had instead been identified. Verification with the stated manufacturer confirmed this product to be falsified. The local health authorities were informed of this incident.

Severe hypoglycemia observed in patients who took this medicine

Substandard misoprostol tablets in Malawi

- Oxytocin injections and misoprostol tablets: against post-partum hemorrhage
- Chemically not stable: easily degraded

Nhomsai Hagen,
Tübingen University

- Collected in drug outlets and health facilities in Malawi
- Investigate storage conditions using temperature data loggers
- Chemical analysis by HPLC at Tübingen University

Dr. Felix Khuluza,
University of Malawi

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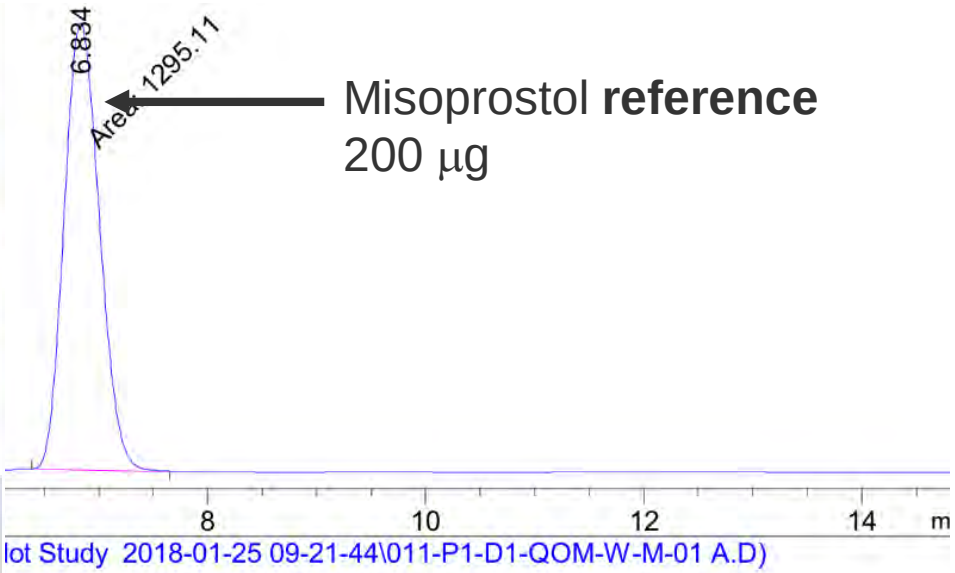
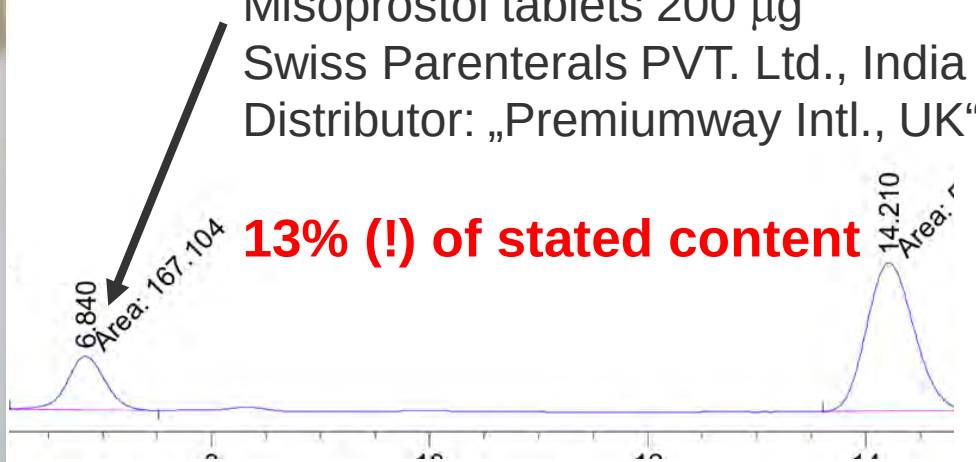
Substandard misoprostol tablets in Malawi



Misoprostol **reference**
200 µg



Misoprostol tablets 200 µg
Swiss Parenterals PVT. Ltd., India
Distributor: „Premiumway Intl., UK“

13% (!) of stated content

Falsified and substandard medicines: Terminology

Previous WHO terms

- „~~Counterfeit medicines~~“: discontinued
- „Substandard/spurious/falsely-labelled/ falsified/counterfeit (SSFFC) medicinal products”

Current WHO terms (2017)

- **Falsified medicines**
  - by intentionally fraudulent manufacturing
    - correct ingredients & acceptable quality
    -  insufficient ingredients or quality
    -  no active ingredients
    -  wrong active ingredients

- **Substandard medicines**
  - by unintentional errors in manufacturing
  - or by degradation (e.g. due to storage conditions)

- insufficient quality:
  - too little of active pharmaceutical ingredient
  - insufficient dissolution
  - other deficiencies

- **Unregistered/unlicensed medicines**
  - Not approved by regulatory authorities

Please name

two or more appropriate actions

to reduce circulation of:

1) **Substandard medicines**
2) **Falsified medicines**

Please estimate the prevalence of:

1) **Substandard medicines: ……%**
2) **Falsified medicines: …… %**

= Overall average prevalence in:

- **different countries of sub-Saharan Africa**
- **different health facilities/drug outlets (government and church facilities, pharmacies, illegal street vendors)**

Conflicting data on prevalence of SF medicines

Review

Poor-quality antimalarial drugs in southeast Asia and sub-Saharan Africa

Lancet Infect Dis 2012; 12: 488

Gaurvika M L Nayyar, Joel G Breman, Paul N Newton, James Herrington

Total number of drug samples	2,297
% **failing** chemical analysis	**35%**
% classified as **falsified**	**20%**

Fake anti-malarials: start with the facts

Harparkash Kaur[1*], Siân Clarke[1], Mirza Lalani[1], Souly Phanouvong[2], Philippe Guérin[3,4], Andrew McLoughlin[5], Benjamin K. Wilson[6], Michael Deats[7], Aline Plançon[8], Heidi Hopkins[1], Debora Miranda[1] and David Schellenberg[1]

Malar J 2016; 15: 86

Total number of drug samples	10,079
% classified as **substandard**	**8%**
% classified as **falsified**	**1%**

Conflicting data on prevalence of SF medicines

Am. J. Trop. Med. Hyg., 96(5), 2017, pp. 1124–1135

Low Prevalence of Substandard and Falsified Antimalarial and Antibiotic Medicines in Public and Faith-Based Health Facilities of Southern Malawi

Felix Khuluza,[1] Stephen Kigera,[2] and Lutz Heide[1,3]*

Total number of drug samples	**155**
% **substandard**	**11%**
% **falsified**	**1%**

Chikowe *et al. Malaria Journal* (2015) 14:127

MALARIA JOURNAL

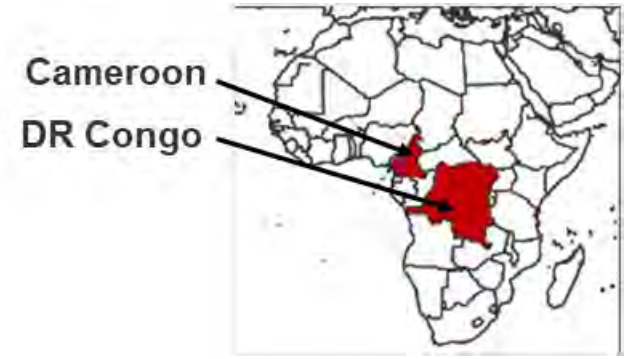
Post-marketing surveillance of anti-malarial medicines used in Malawi

Ibrahim Chikowe[1,2], Dorcas Osei-Safo[1*], Jerry JEK Harrison[1], Daniel Y Konadu[1] and Ivan Addae-Mensah[1]

Total number of drug samples	**112**
% **substandard**	**88%**
% **falsified**	**0%**

Research on prevalence of SF medicines: Medicine quality study in Cameroon and DR Congo

506 samples of 13 different medicines



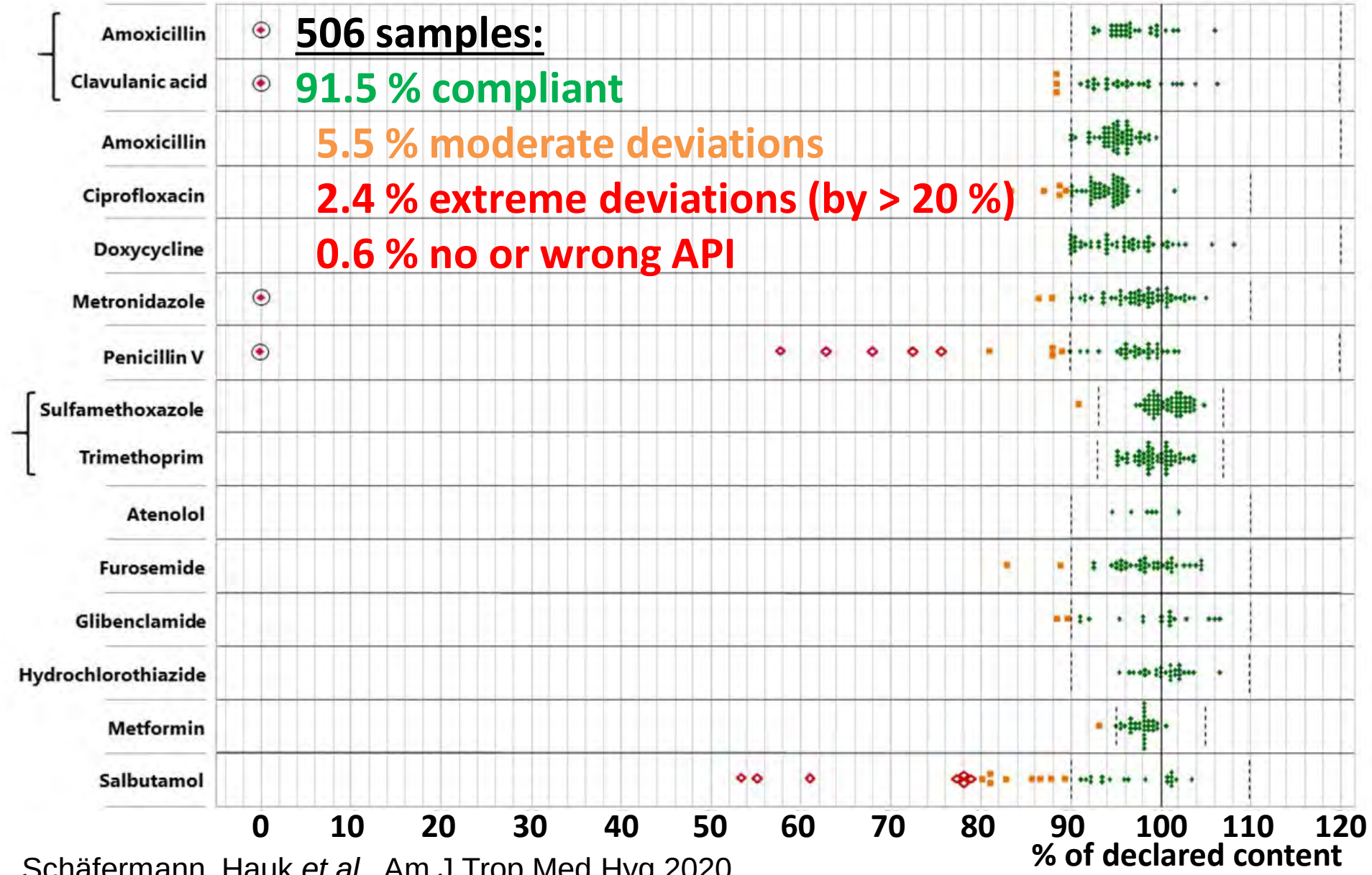
Antibiotics
• **Amoxicillin** (capsules and tablets) • **Amoxicillin + clavulanic acid** (tablets) • **Ciprofloxacin** (tablets) • **Doxycycline** (capsules and tablets) • **Penicillin V** (tablets) • **Metronidazole** (tablets) • **Sulfamethoxazole + trimethoprim** (tablets)
Medicines for non-communicable diseases (NCDs)
• **Atenolol** (tablets) • **Furosemide** (tablets) • **Glibenclamide** (tablets) • **Hydrochlorothiazide** (tablets) • **Metformin** (tablets) • **Salbutamol** (tablets)

Sources
1. Licensed pharmacies 2. Informal vendors 3. Government health facilities 4. Church health facilities

Schäfermann *et al.*, Am J Trop Med Hyg 2020

Medicine quality study in Cameroon and DR Congo:

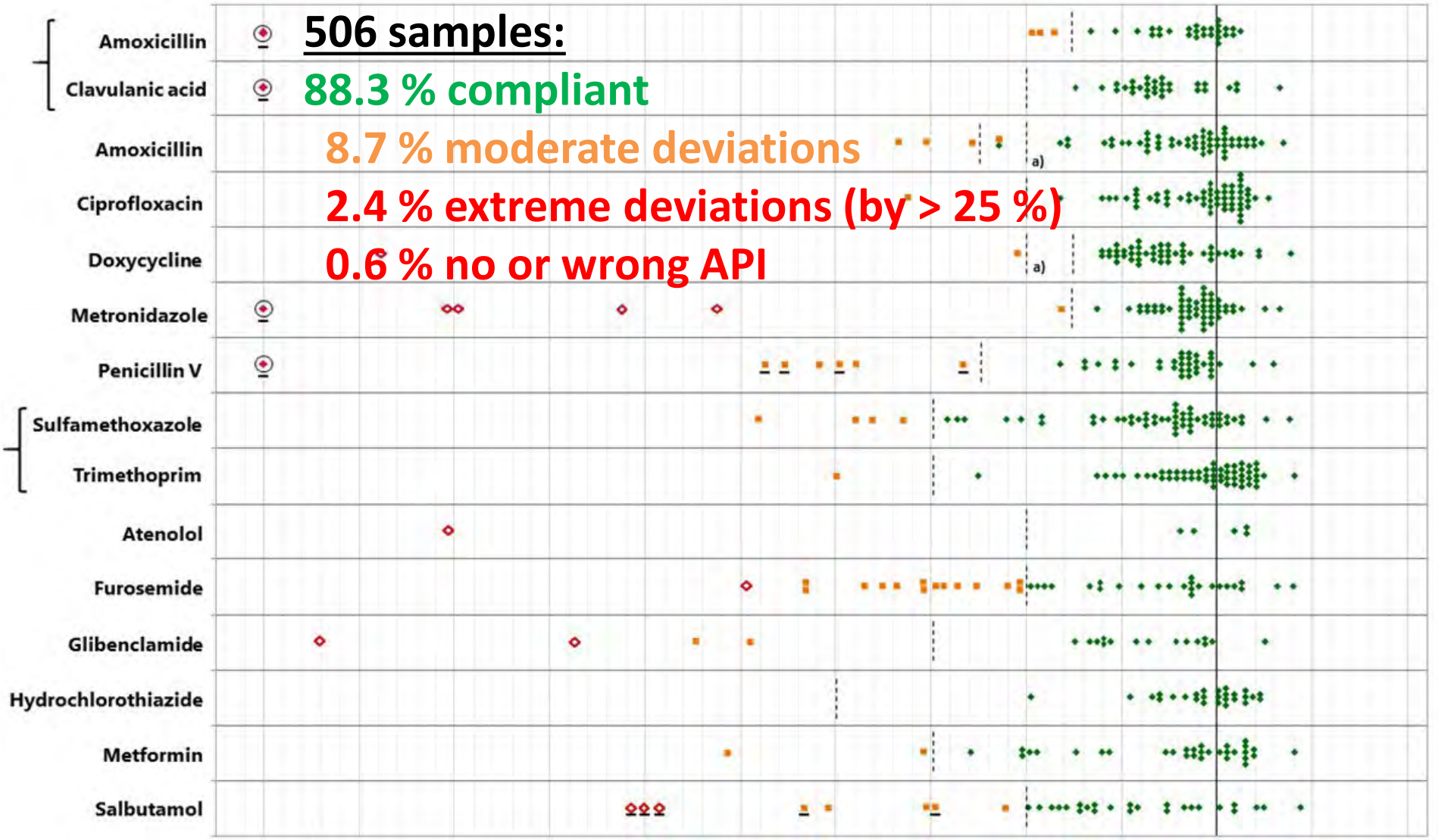
API content (=assay) according to USP



Schäfermann, Hauk *et al.*, Am J Trop Med Hyg 2020

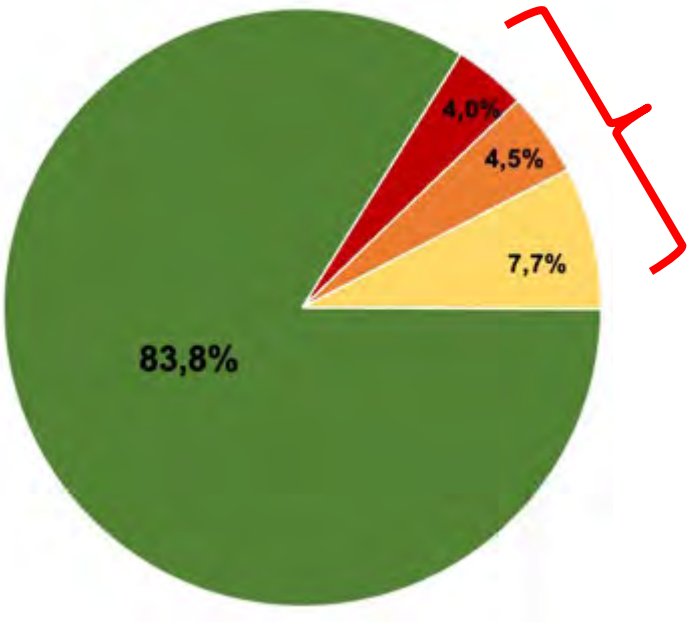
Medicine quality study in Cameroon and DR Congo:

API dissolution according to USP



Schäfermann, Hauk *et al.*, Am J Trop Med Hyg 2020

Medicine quality study in Cameroon and DR Congo:
Overall result



- failed <u>both</u> assay and dissolution
- failed assay
- failed dissolution
- in USP specification

16.2 % of samples out of USP specification for assay and dissolution

0.6 % of samples no or wrong API

Antibiotics	12 %
Medicines against non-communicable diseases	25 %

→ High prevalence of SF among medicines against non-communicable diseases

Legal suppliers	12 %
Informal vendors	28 %

→ High prevalence of SF medicines among informal vendors

Schäfermann, Hauk *et al.*, Am J Trop Med Hyg 2020

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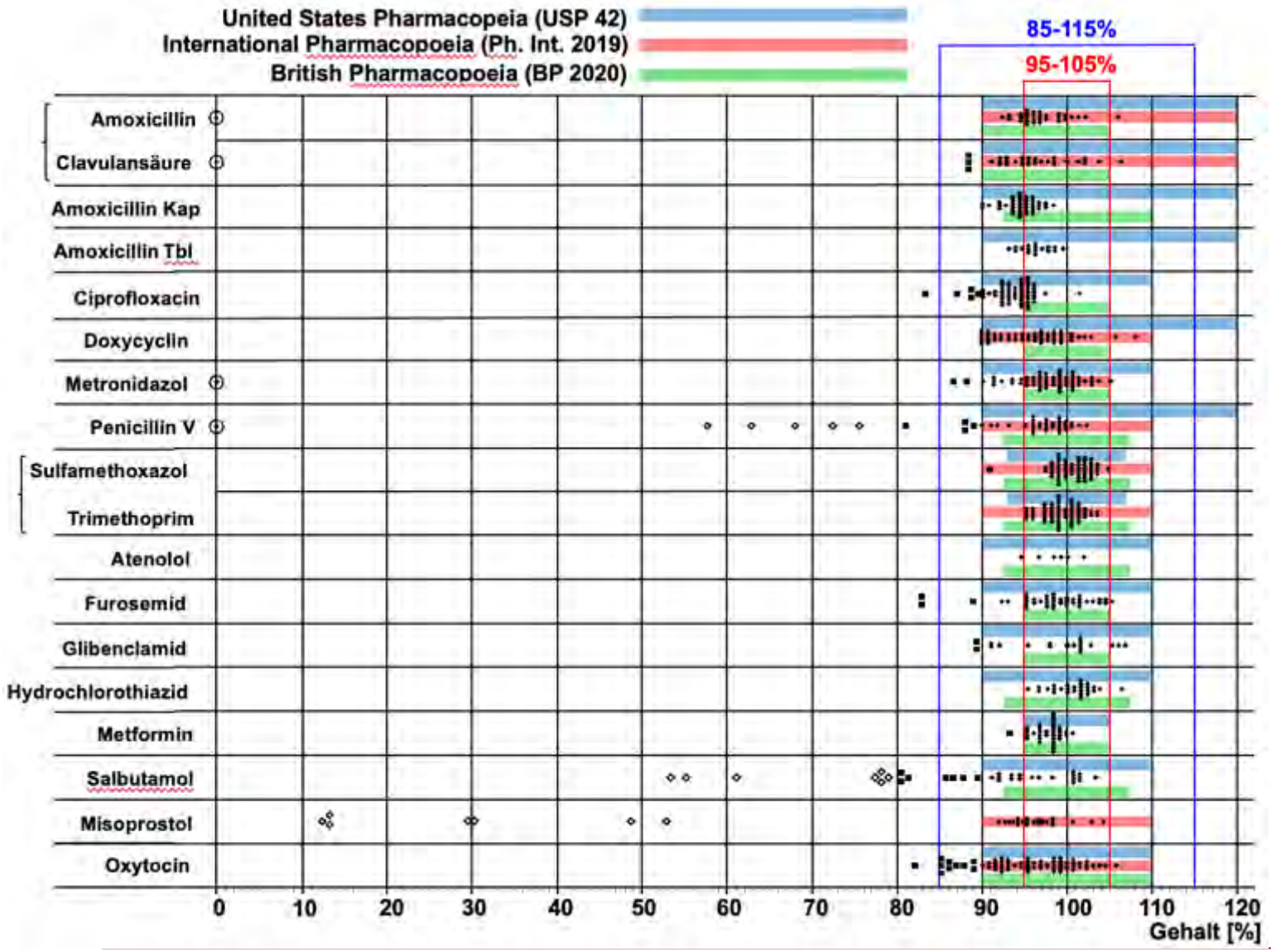
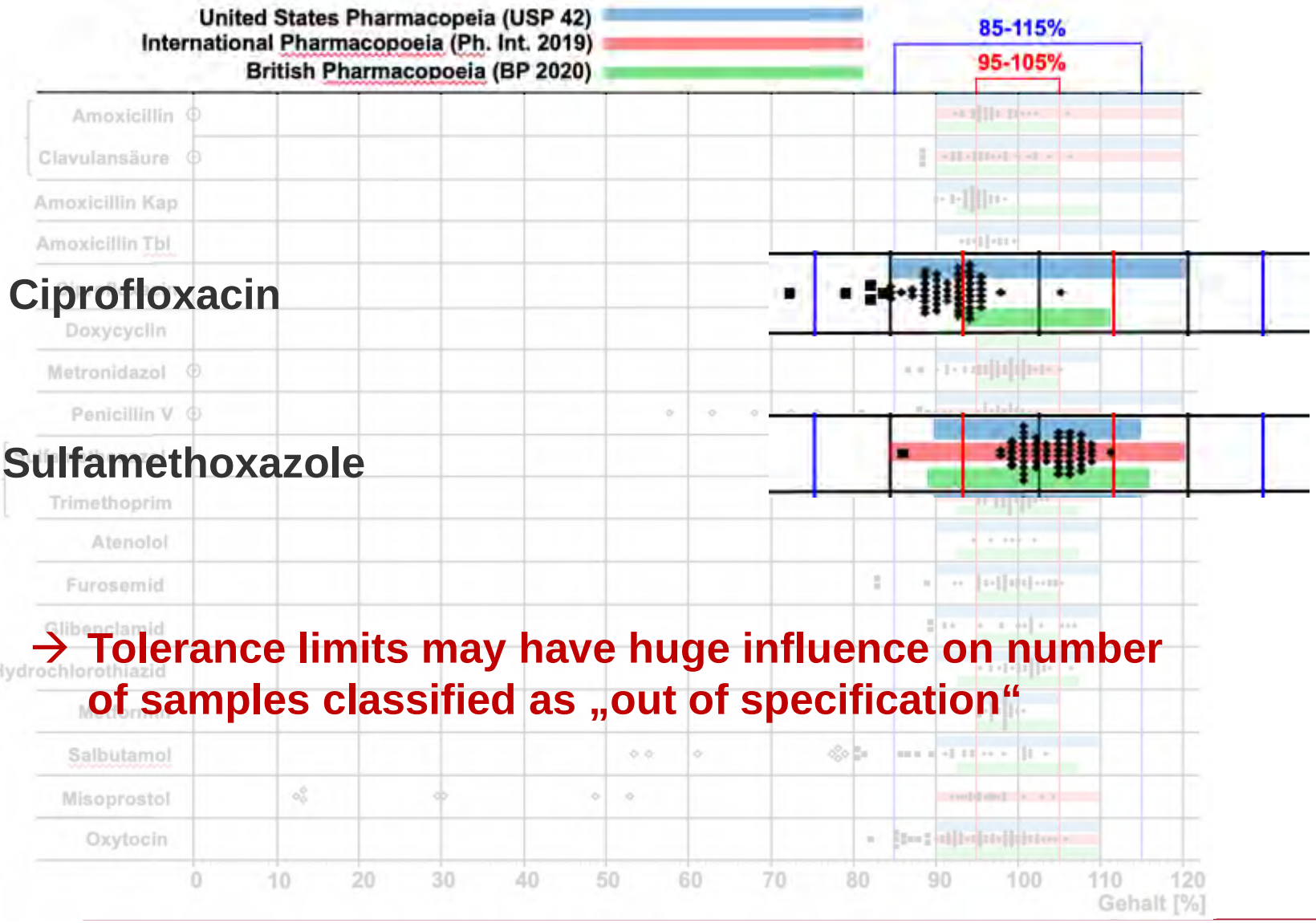
Assay results and tolerance limits



Hauk *et al.*, Am J Trop Med Hyg 2021

Assay results and tolerance limits



Ciprofloxacin

Sulfamethoxazole

→ **Tolerance limits may have huge influence on number of samples classified as „out of specification“**

Hauk *et al.*, Am J Trop Med Hyg 2021

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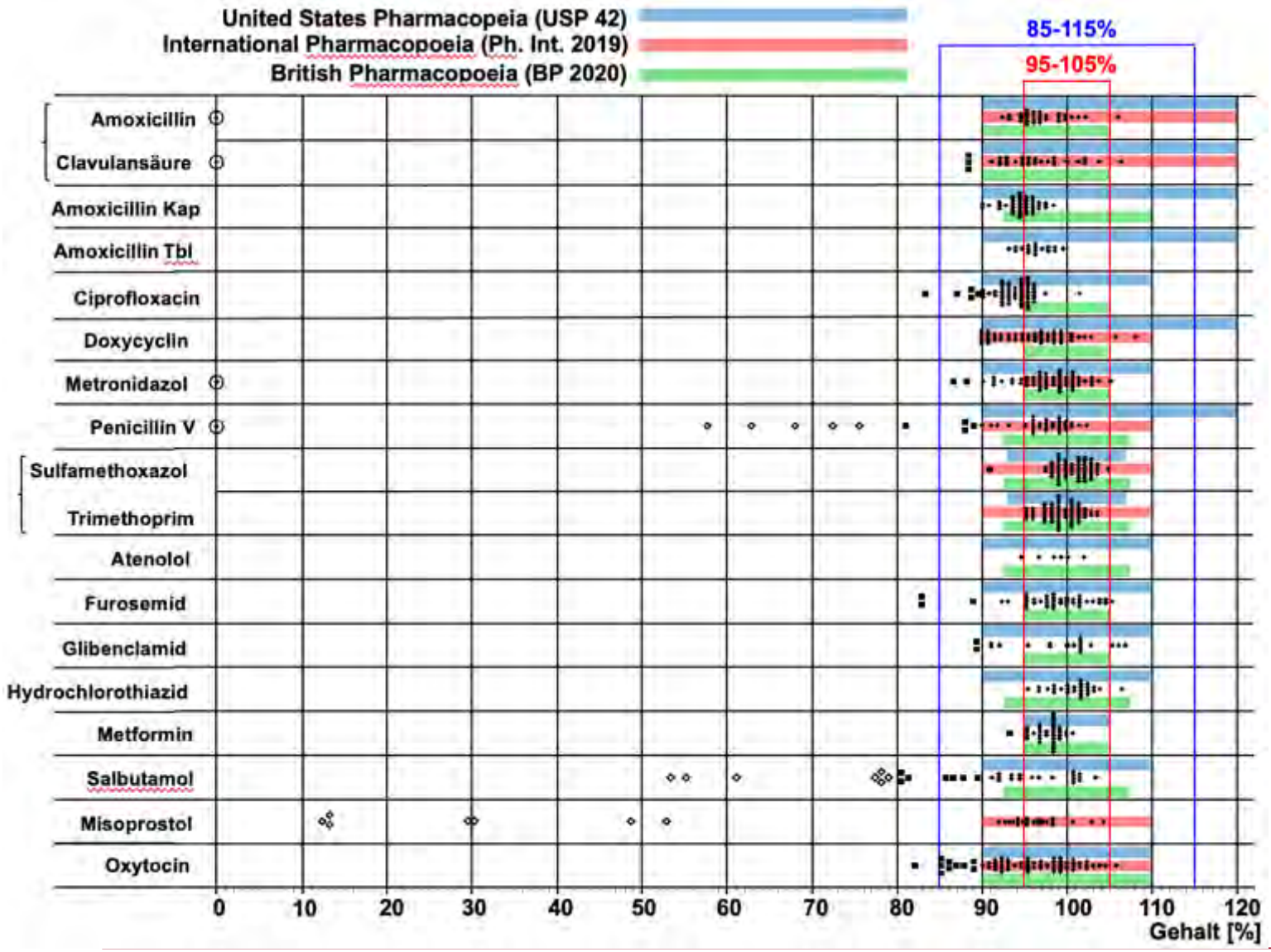
Assay results and tolerance limits



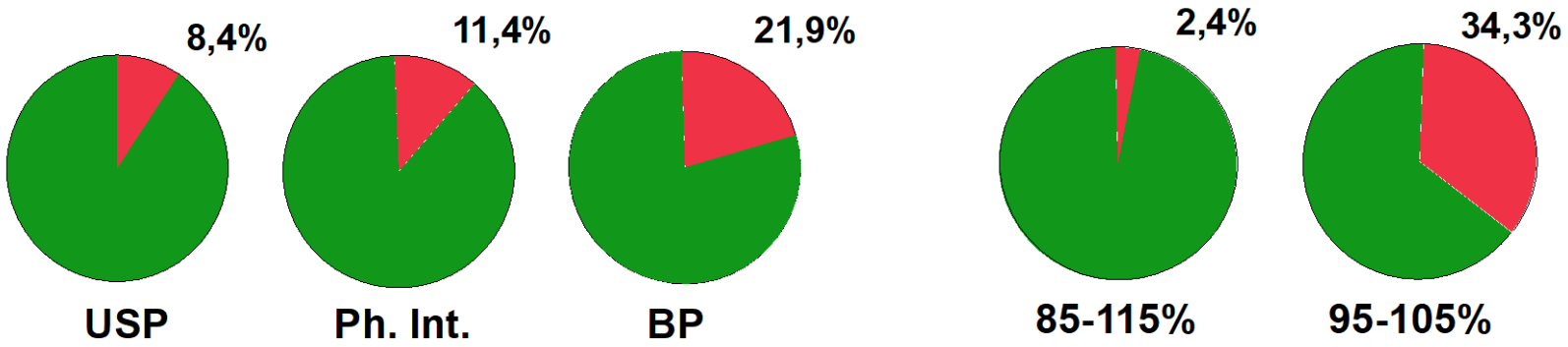
Arbitrary limits used in recent studies:

85-115%
Kaur *et al.*, PLoS ONE (2015)

95-105%
Antignac *et al.*, Int J Cardiol (2017)

Hauk *et al.*, Am J Trop Med Hyg 2021

Percentage of sample „out of specification“, using different tolerance limits for assay:



Green: „in specification“; red: „out of specification“

- **For the same set of data, percentage out of specification can vary from 2.4 % up to 34.3 %**

→ **This is one reason for the heterogeneity of published prevalance data of substandard and falsified medicines**

→ **Harmonization of tolerance limits in different studies urgently required**

Hauk *et al.*, Am J Trop Med Hyg 2021

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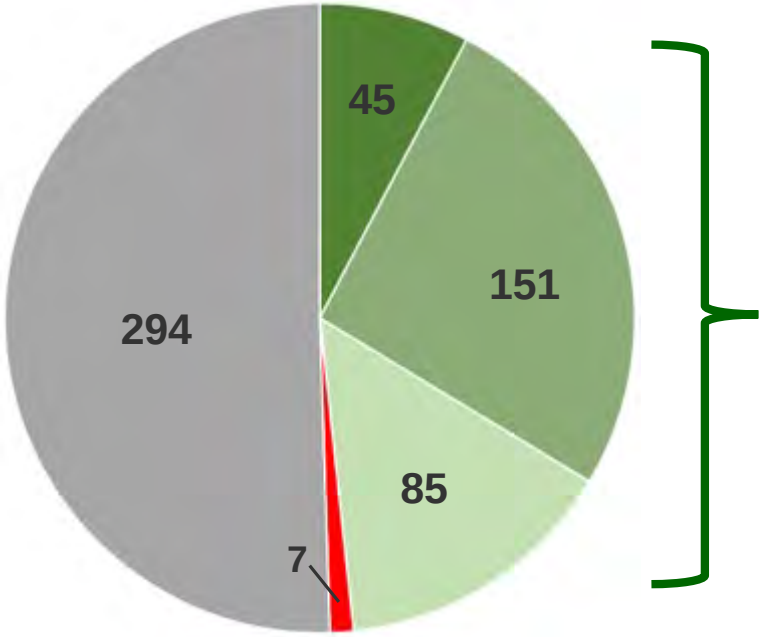
Enquiries to manufacturers and distributors about authenticity of 582 medicine samples



For 288 (49.5 %) of samples, answers on authenticity received

- **281 samples: confirmed as authentic**
- **7 samples: stated to be falsified**
  (all 7 had been compliant in assay and dissolution testing!)

- **Authenticity confirmed by <u>both</u> manufacturer and distributor**
- **Authenticity confirmed by distributor**
- **Authenticity confirmed by manufacturer**
- **Stated to be falsified by manufacturer and/or distributor**
- **No information on authenticity received**

Hauk *et al.*, Am J Trop Med Hyg 2021

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Furosemide 40 mg BP tablets with falsified manufacturing/expiry dates

(all 4 samples had been compliant in assay and dissolution testing!)

Background of label showing expiry date is darker!

	Batch number	Collection site and region in Cameroon		Assay (%)	Mfg. date/ Exp. date	Shelf life
A	FRIH0077	Church health facilities	West	101.8 %	Dez. 2012/ Nov. 2018	**6 years**
B			Littoral	102.7 %		
C			Northwest	100.4 %	Dez. 2015/ Nov. 2019	**4 years**
D			Adamawa	101.0 %		

Falsified

Correct dates for batch FRIH0077 according to manufacturer Micro Labs Ltd. → Dez. 2012/ Nov. 2015 | **3 years**

Hauk *et al.*, Am J Trop Med Hyg 2021

Medicine quality study in Cameroon, DR Congo and Malawi:

Final overall result

Prevalence of:

1) substandard medicines: 15.6 %

(failing in assay and/or dissolution testing)

2) falsified medicines: 1.7 %

(0.6 % no or wrong API;

1.1 % compliant in assay and dissolution testing,

identified only by enquiries to manufacturer)

Similar results published in a review by Sachiko Ozawa *et al.* 2022:

Am. J. Trop. Med. Hyg., 106(6), 2022, pp. 1778–1790
doi:10.4269/ajtmh.21-1123

Prevalence of SF: all LMICs 12.9%
Africa 18.9%

Characterizing Medicine Quality by Active Pharmaceutical Ingredient Levels: A Systematic Review and Meta-Analysis across Low- and Middle-Income Countries

Sachiko Ozawa,[1,2*] Hui-Han Chen,[1] Yi-Fang (Ashley) Lee,[1] Colleen R. Higgins,[1] and Tatenda T. Yemeke[1]

[1]*Division of Practice Advancement and Clinical Education, UNC Eshelman School of Pharmacy, University of North Carolina, Chapel Hill, North Carolina;* [2]*Department of Maternal and Child Health, UNC Gillings School of Global Public Health, University of North Carolina, Chapel Hill, North Carolina*

Literature analysis of 100 studies

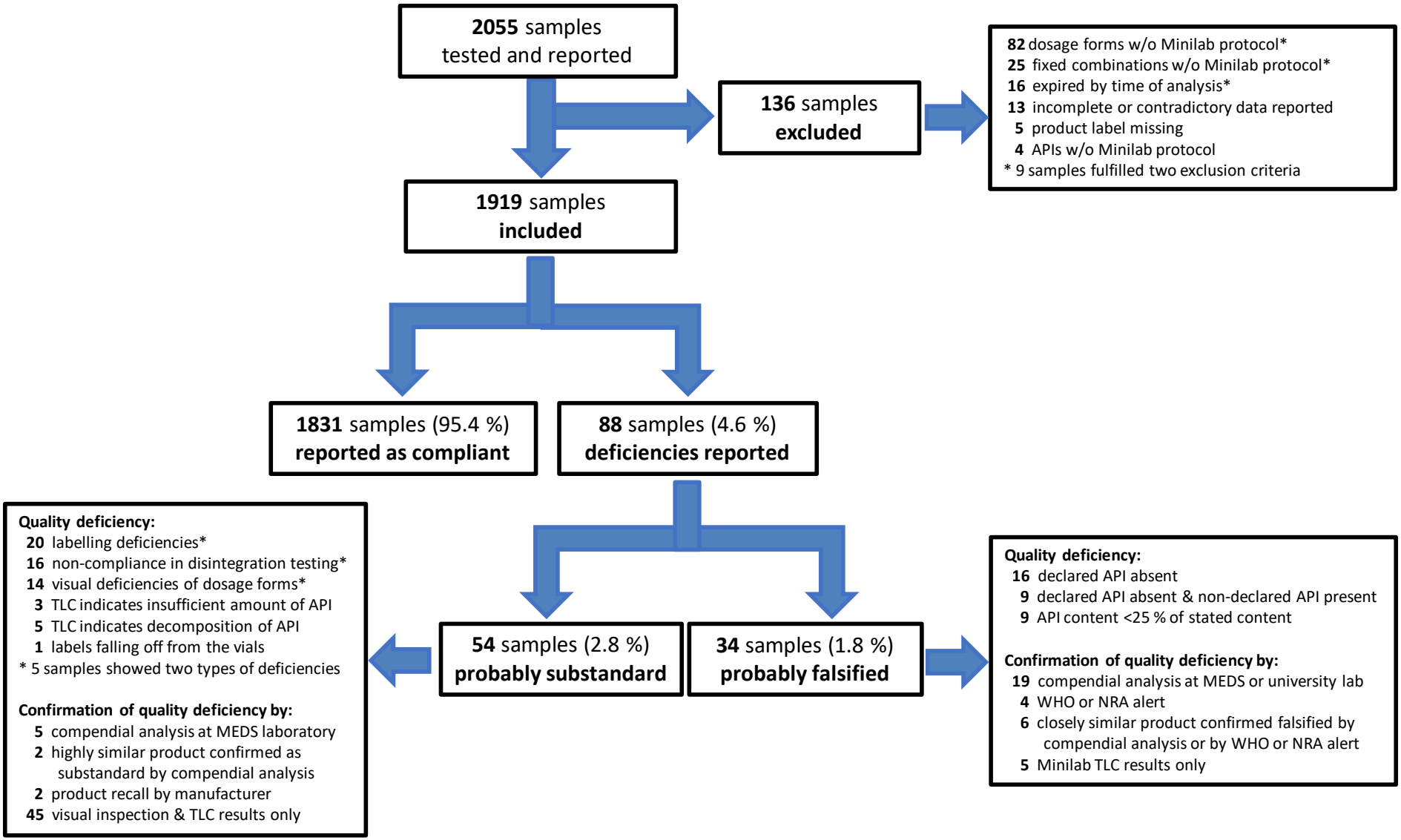
in the years 2007-2016,

selected for scientific quality

→ Prevalence of substandard and falsified medicines in low- and middle income countries = 10.5 %

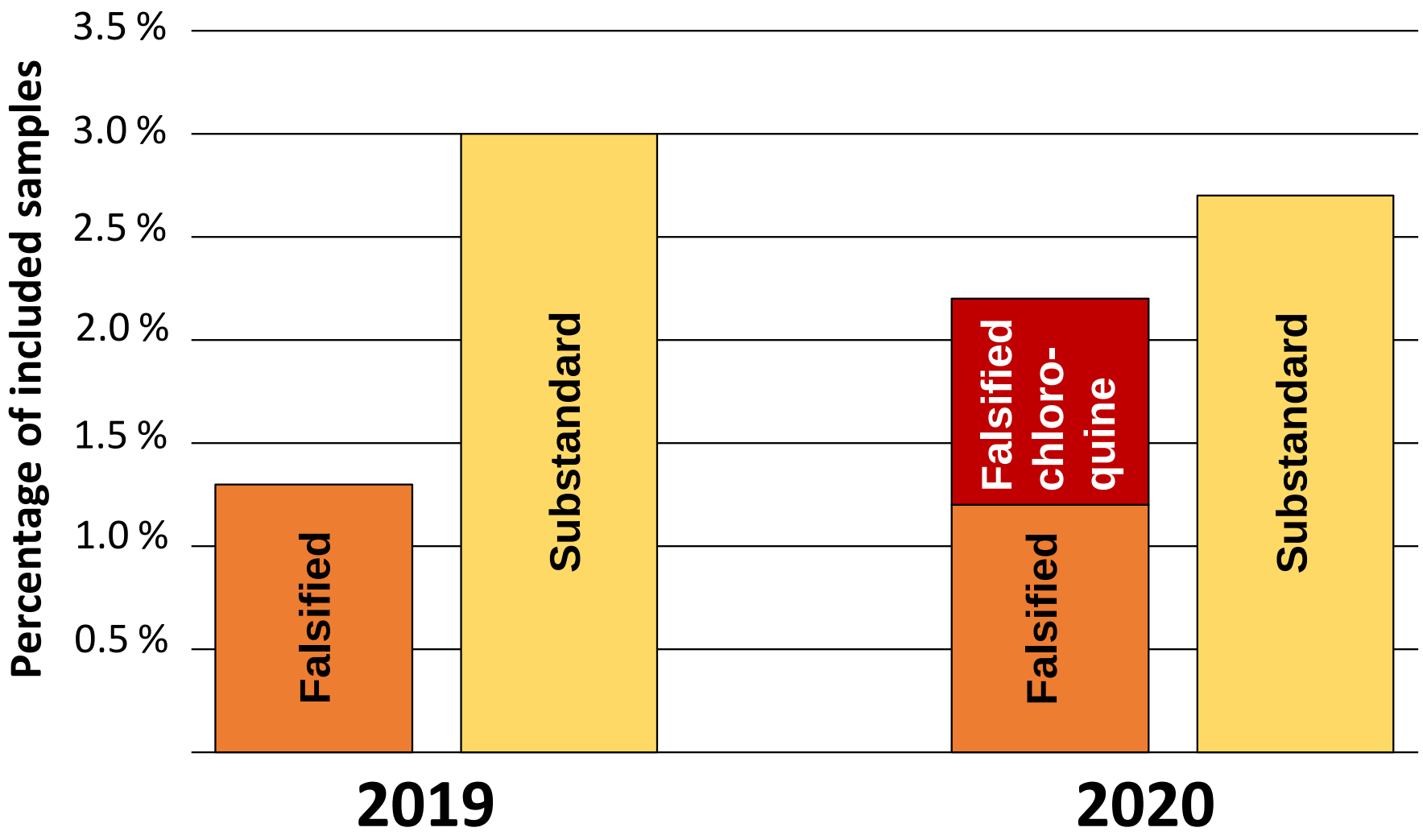
Surveillance for substandard and falsified medicines 2019 & 2020 using the GPHF Minilab

Gesa Gnegel *et al.*, Scientific Reports 2022



Surveillance for substandard and falsified medicines 2019 & 2020 using the GPHF Minilab:

Change of prevalence of SF medicines during the COVID-19 pandemic

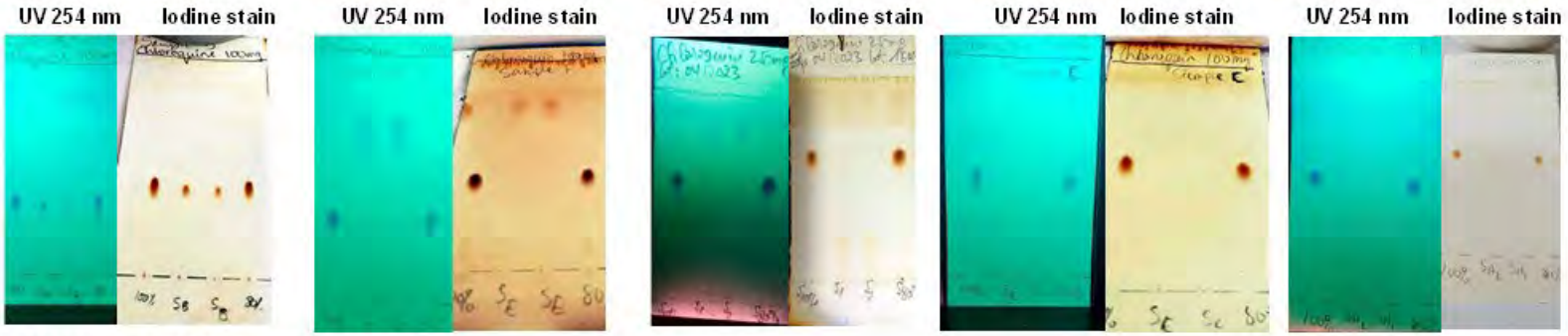


Falsified chloroquine tablets during the COVID-19 pandemic

Gesa Gnegel *et al.*, Am J Trop Med Hyg 2020

Sample photos

GPHF Minilab Detection
Cameroon & DR Congo



HPLC/MS analysis
Tübingen University

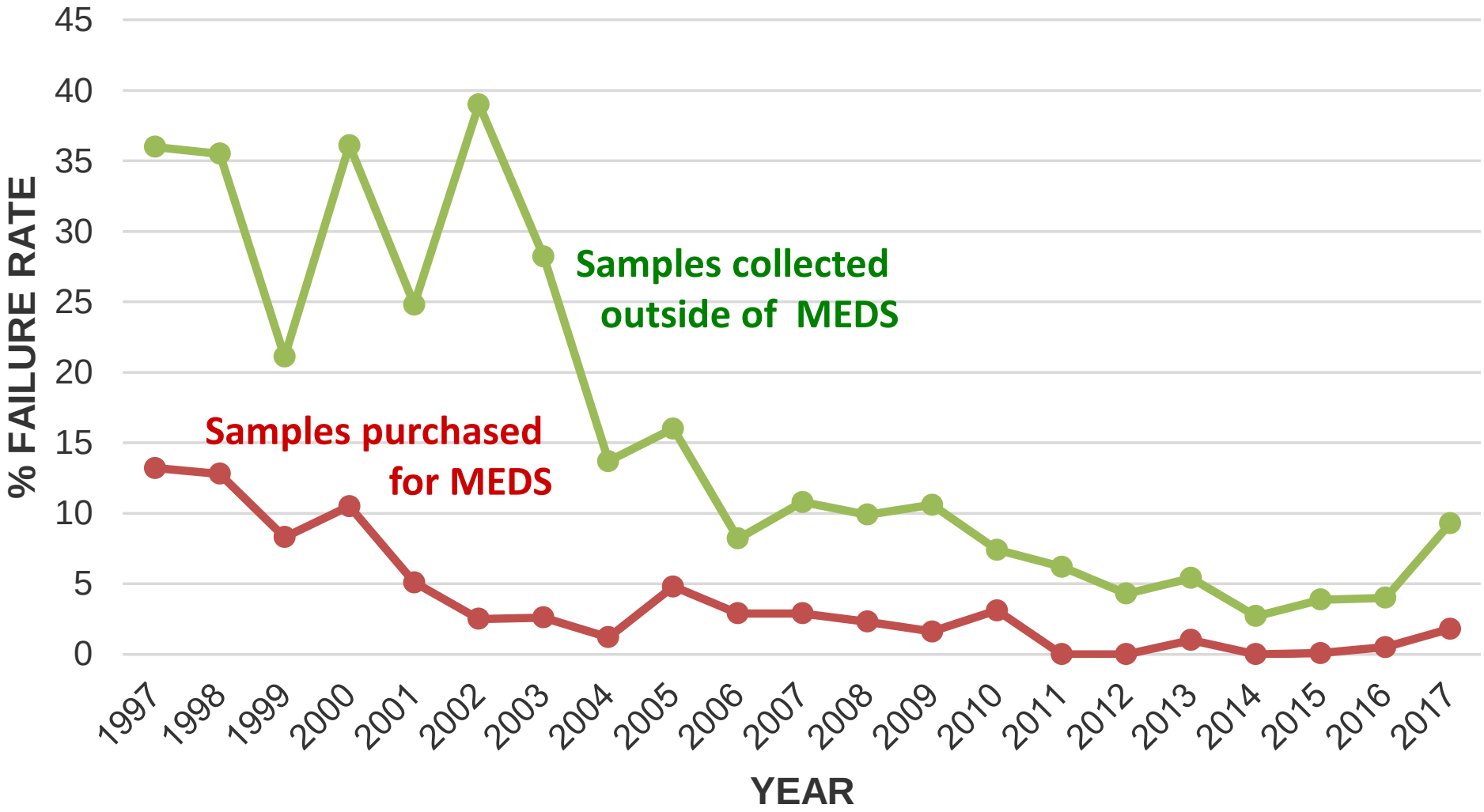
Chloroquine (CQ) amount declared:

100 mg CQ phosphate	100 mg CQ phosphate	250 mg CQ	100 mg CQ phosphate	250 mg CQ phosphate

Active principles detected:

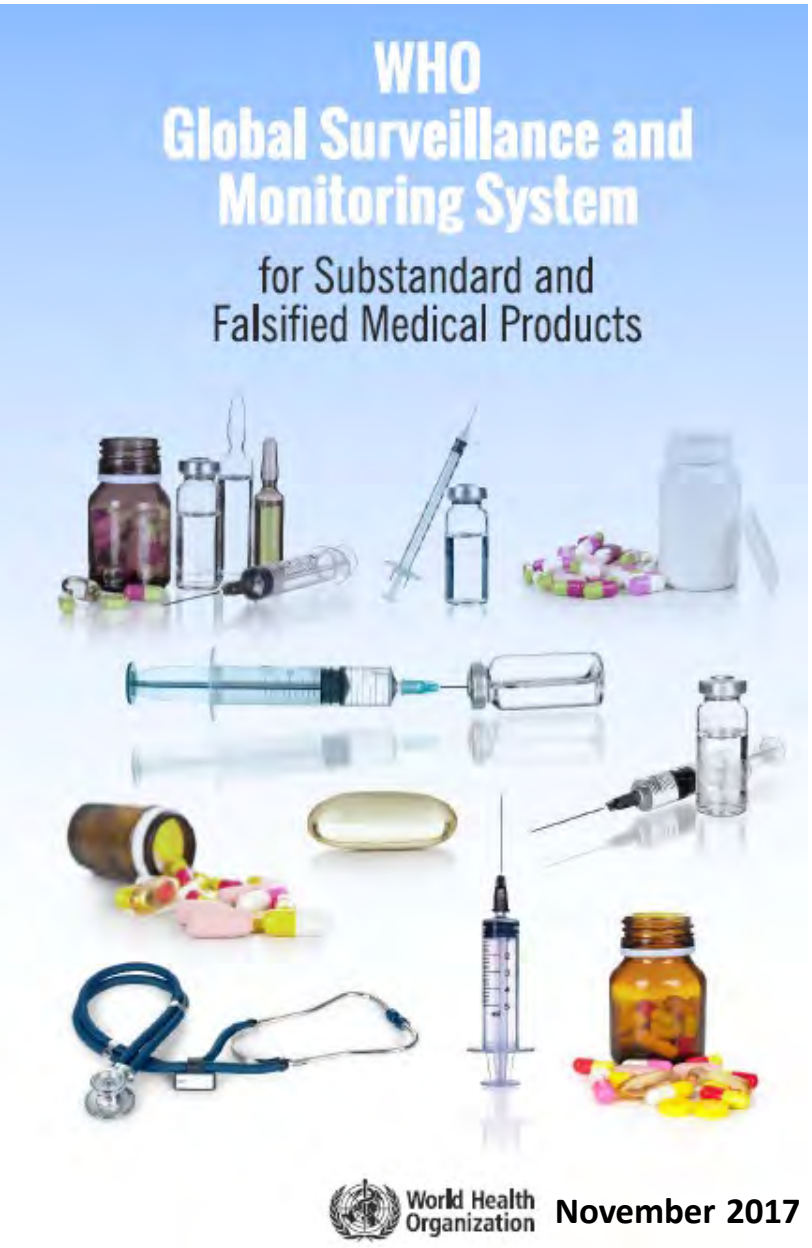
21.7 mg CQ phosphate	no CQ 35.7 mg paracetamol	no CQ 126.5 mg metronidazole	no CQ 14.1 mg metronidazole	no CQ 1.6 mg paracetamol 14.6 mg metronidazole

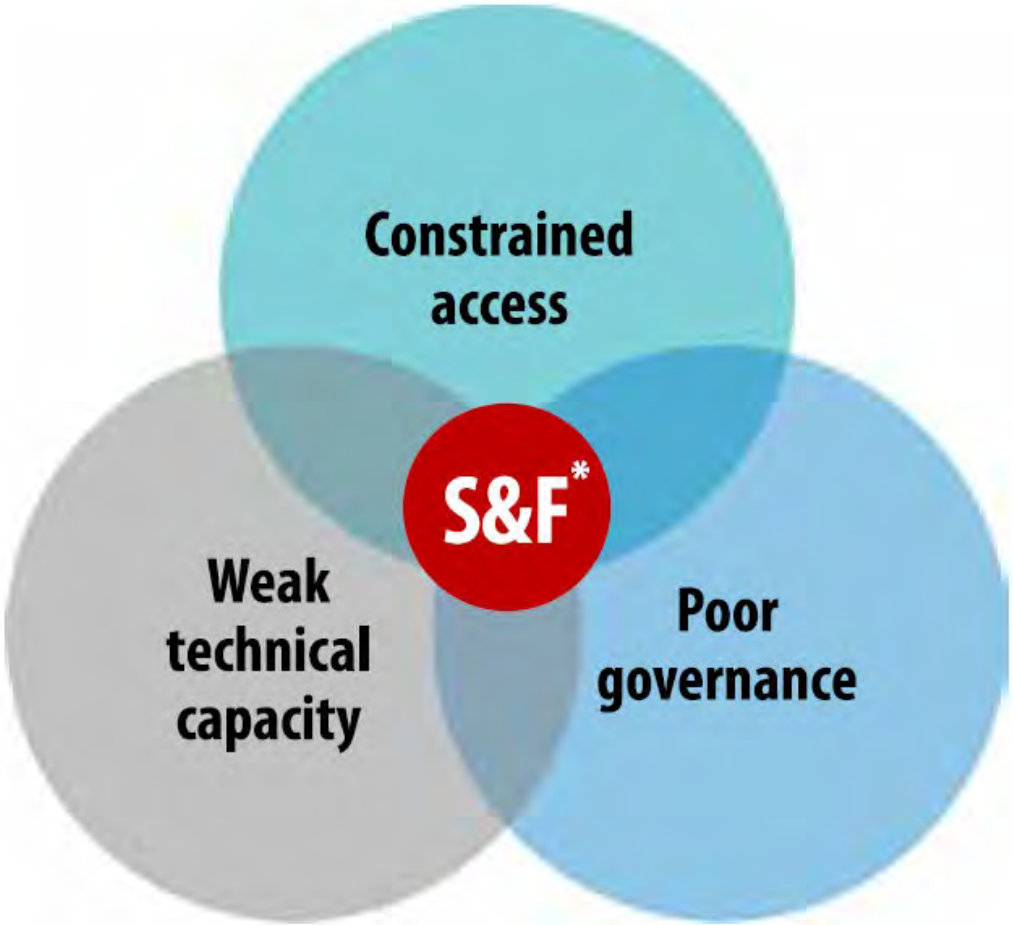
Fighting substandard and falsified medicines:
Success is possible!



Percentage of poor-quality medicines detected in the laboratory of the Mission for Essential Drugs and Supplies (MEDS), Nairobi

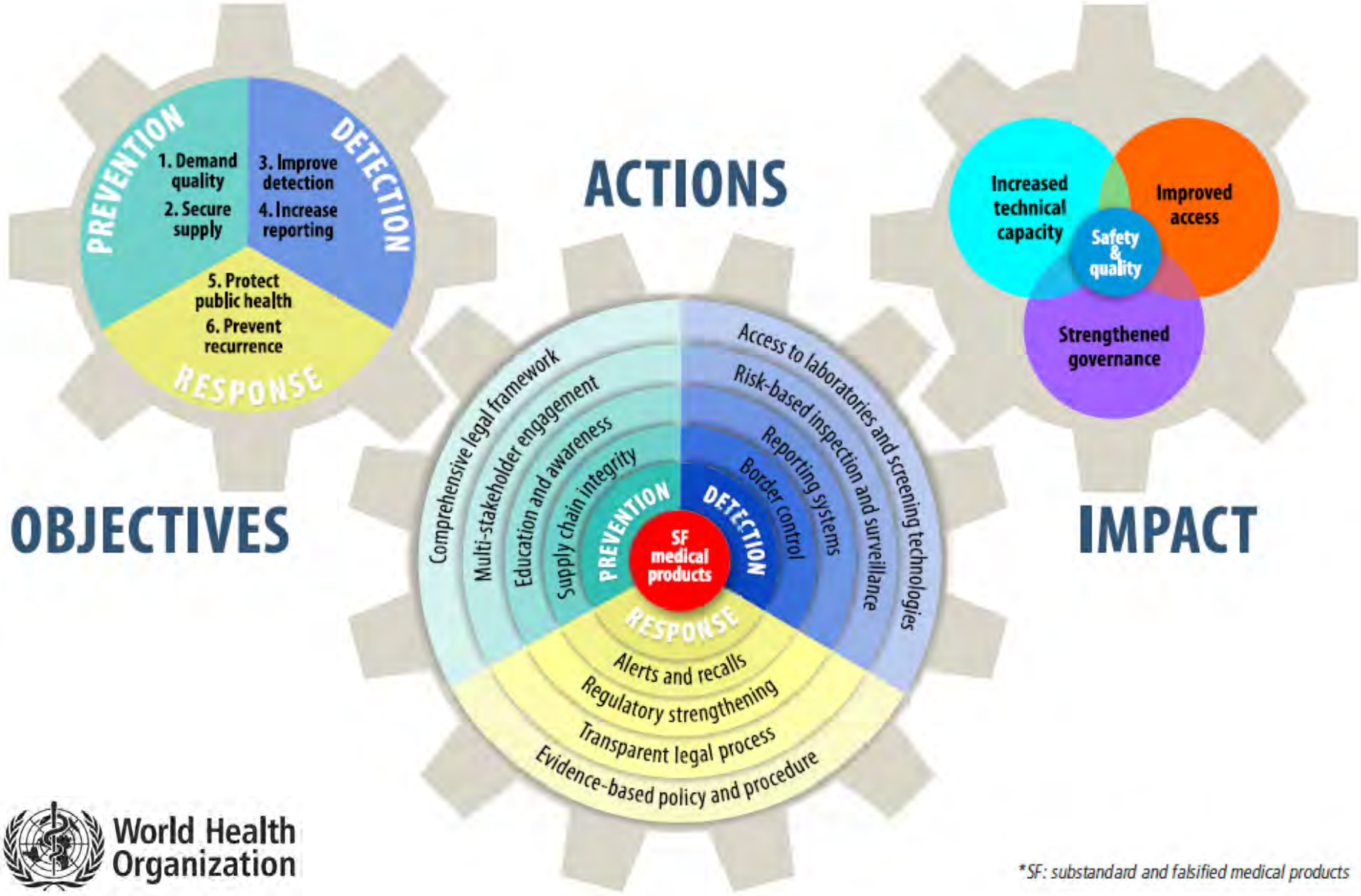
Substandard and falsified medical products: Causes





*S&F : substandard and falsified medical products

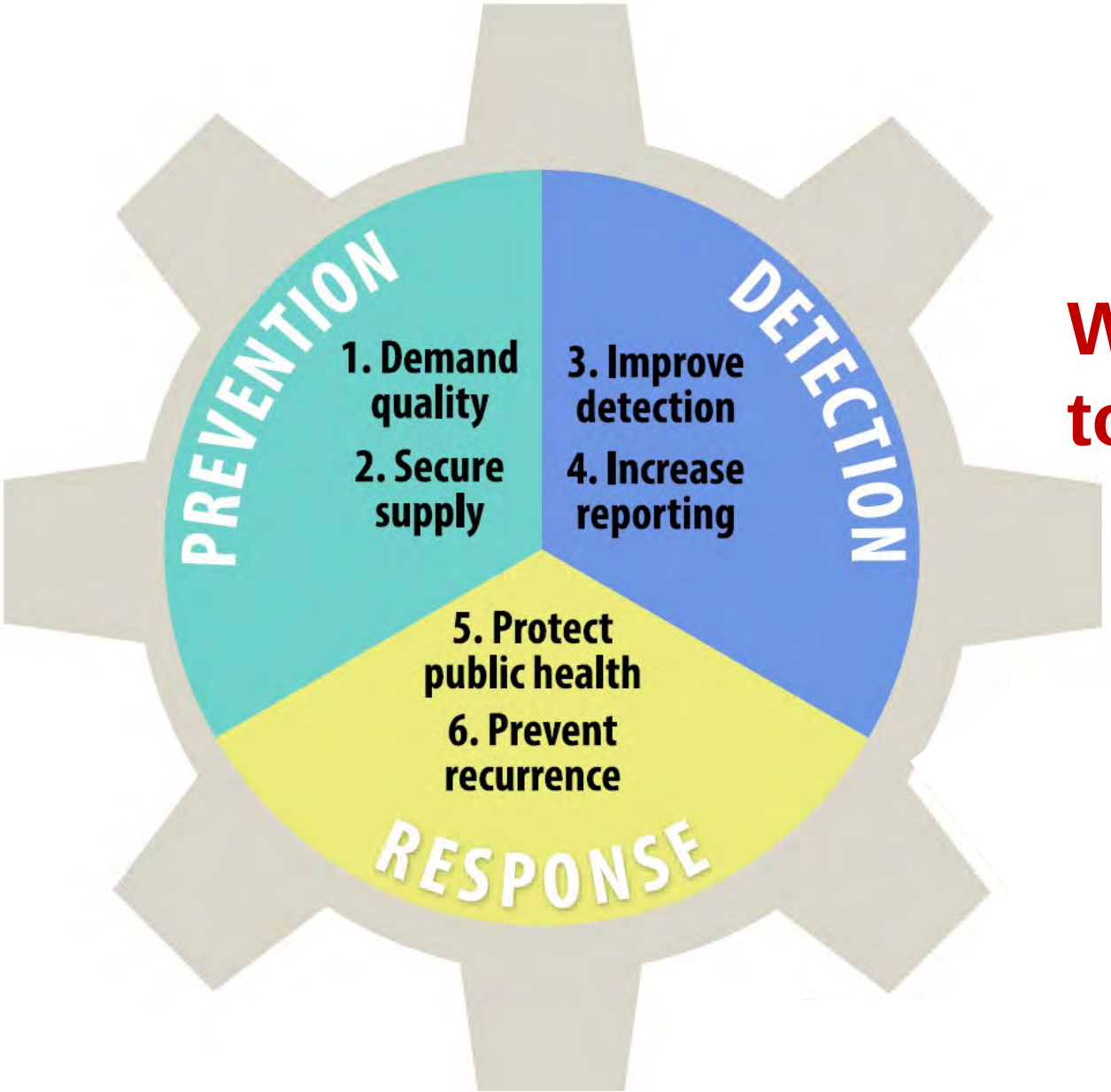
Substandard and falsified medical products: Solutions



World Health Organization

*SF: substandard and falsified medical products

Prevention – Detection - Response



What can we do to improve:

- **prevention**
- **detection**
- **response**

World Health Organization

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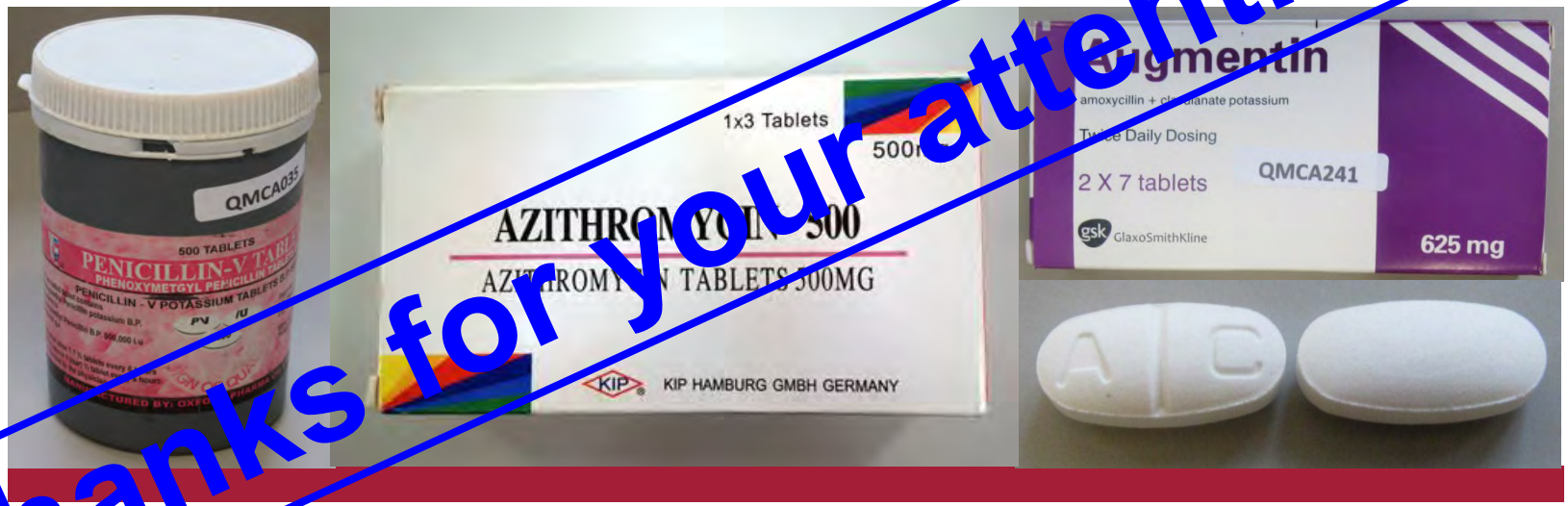
Faculty of Science
Pharmaceutical Institute



Thanks for your attention!

Substandard and Falsified Medicines in Sub-Saharan Africa

Prevalence and Prevention / Detection / Response

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