A STUDY ON THE PUBLIC HEALTH AND SOCIOECONOMIC IMPACT

of substandard and falsified medical products

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Abbreviations and acronyms

ACT	artemisinin combination therapy
ALRI	acute lower respiratory infection
API	active pharmaceutical ingredient
CFR	case fatality rate
DALY	disability-adjusted life years
GSMS	Global Surveillance and Monitoring System
IOM	Institute of Medicine
LMICs	low- and middle-income countries
NMRA	national medicines regulatory authority
QALY	quality-adjusted life years
VR	vital registration

1 INTRODUCTION AND OVERVIEW

1.1 The need for evidence

The presence of substandard and falsified medical products in countries and their use by patients threatens to undermine progress towards meeting the Sustainable Development Goals. Such products may be of poor quality, unsafe or ineffective, threatening the health of those that take them. The problem of substandard and falsified medical products continues to increase, as globalized manufacturing and distribution systems grow ever more complex. That complexity heightens the risk that production errors will occur, or that medicines will degrade between factory and consumer. Increasing demand for medicines, vaccines and other medical products in almost every country, in addition to poor supply-chain management and the growth of e-commerce also creates opportunities for falsified medicines to be introduced into the supply chain.

Unfortunately, reliable information on the true public health and socioeconomic impacts of substandard and falsified medical products is sparse. A stronger evidence base is needed to help prevent, detect and respond to substandard and falsified medical products, and the public health threat they represent. "The lack of understanding of the public health and economic costs has frustrated efforts at making the argument that investments in strengthening regulatory systems are a good buy and has prevented countries from understanding and acting on the problem in their own settings" *(1)*.

Establishing the magnitude of any disease or public health challenge depends on having clear definitions. In the field of substandard and falsified medical products, such definitions have been lacking. The media, the general public and even some academic researchers have used words such as "fake" and "counterfeit", often interchangeably with other terms. The World Health Organization (WHO) previously used the catch-all term "substandard, spurious, falsely-labelled, falsified and counterfeit medical products", although the various terms were interpreted differently by different Member States *(2)*. Most controversially, the term "counterfeit" was sometimes used in some jurisdictions to refer to medicines that infringed patents or other intellectual property rights.

In 2012, the World Health Assembly established the Member State mechanism to provide oversight, strong commitment and political will from Member States and WHO on this issue from a public health perspective. Intellectual property considerations are explicitly excluded from its mandate and the Member State mechanism works on agreed prioritized activities designed to fill specific data gaps on key technical issues, including the standardization of definitions. In May 2017, the World Health Assembly endorsed the definitions suggested by the Member State mechanism, which are shown in Box 1 *(3)*. Although these definitions are now clear, they have only recently been agreed and comparing studies published before achieving this consensus is not straightforward.

Box 1: WHO definitions of substandard, unregistered/unlicensed and falsified medical products *(3)*

For many years, the response to this important threat to public health was embroiled in a discussion of complex definitions that meant different things to different people. Reflecting this complexity, until May 2017, WHO used the term "substandard/spurious/falsely-labelled/falsified/counterfeit medical products". The WHO Member State mechanism on substandard and falsified medical products was tasked with revising these definitions to ensure that they were based on a public-health perspective, with no account taken of intellectual property concerns. Based on these deliberations, the World Health Assembly, which governs WHO, adopted the following definitions:

Substandard medical products

Also called "out of specification", these are authorized medical products that fail to meet either their quality standards or their specifications, or both.

Unregistered/unlicensed medical products

Medical products that have not undergone evaluation and/or approval by the national or regional regulatory authority for the market in which they are marketed/distributed or used, subject to permitted conditions under national or regional regulation and legislation.

Falsified medical products

Medical products that deliberately/fraudulently misrepresent their identity, composition or source.

Source: Appendix 3 to Annex, World Health Assembly document A70/23, 2017.

1.2 Making the case for attention and investment

To estimate the true impact of substandard and falsified medical products, accurate, reliable and quality data must be systematically gathered and analysed. Therefore, the Member State mechanism commissioned a study on the public health and socioeconomic impact of substandard and falsified medical products to be carried out by the WHO. The study, together with the report on the *WHO Global Surveillance and Monitoring System for substandard and falsified medical products,* represent a comprehensive compilation of data related to substandard and falsified medical products and are a part of a wider approach being developed by WHO and the Member State mechanism to prevent, detect and respond to substandard and falsified medical products. These reports, together with other technical documents published by the Member State mechanism (see Box 2), contribute to the world's evidence base and make the case for the attention of governments and investment in national medicines regulatory agencies to address this challenge.

Box 2: Objectives of the technical documents published by the Member State mechanism *(4)*

- Identification of factors that drive the emergence of substandard and falsified medical products
- Recommendations for health authorities to detect and deal with substandard and falsified medical products
- Developing a national action plan to prevent, detect and respond to substandard and falsified medical products
- Creating a global regulatory focal point network
- Implementing track and trace systems
- Understanding authentication technologies
- Reaching a global common understanding on the definitions of substandard, unregistered/unlicensed and falsified medical products

Source: http://www.who.int/medicines/regulation/ssffc/mechanism/en/

1.3 The study approach

The original objectives of the study, as set by the Member State mechanism, were:

"To provide information and quantify the cost and socioeconomic impact of falsified and substandard medicines and establish the potential costs and benefits of strengthening regulatory systems to secure the health products supply chain. A second objective is to suggest a method that countries can use to assess the extent of the problem domestically based on the experience of the first objective. Policy options for addressing any problems identified at the country level are beyond the scope of this study and the remit of the countries concerned" *(1).*

An Expert Group comprising specialists in public health, medicines regulation and health economics was convened to review existing data sources and the methods most appropriate to gather data about the public health and socioeconomic impact of substandard and falsified medical products. It was acknowledged that fulfilling the original study objectives was not achievable owing to the heterogeneity of data on prevalence, and the absence of empirical information about costs. The scope was further limited to exclude consideration of intellectual property issues and Internet pharmacies, and include data only from the public domain.

To refine the parameters of this study, the Expert Group consulted the WHO team with primary responsibility for this issue. The Substandard and Falsified Medical Products Group leads and coordinates the WHO Global Surveillance and Monitoring System (GSMS), an international system that provides a network of focal points in national medicines regulatory authorities with a platform that allows them to report and exchange information about substandard and falsified medical products.

The report on the *WHO Global Surveillance and Monitoring System for substandard and falsified medical products*, published concurrently with this study, gives a detailed account of the information provided by the GSMS in its first four years of operation. The report uses case studies from around the world to illustrate the forces that drive the trade in these dangerous products, and provides an overview of the systems and actions that are needed to prevent, detect and respond to the threat posed by substandard and falsified medical products. The Expert Group was informed that substandard and falsified medical products from all therapeutic categories are reported from every region, including high-, middle- and low-income countries, and a significant proportion of the cases reported to the GSMS concern antimicrobials, with antimalarials and antibiotics being the most frequently reported medicines. Thus the focus of this study was driven by these public health considerations, particularly in light of the potential link to antimicrobial resistance and drug-resistant infections.

The study entailed a literature review and a review of two impact models. The methods, results and conclusions are elaborated on in the following sections.

2 PART ONE LITERATURE REVIEW

2.1 Methodology

A literature review was carried out through a search of the academic literature, using PubMed and MEDLINE databases. Published papers that reported on field studies or surveys of the quality of medicines were identified. Because papers of interest may have used keywords referring to specific therapeutic areas rather than more general headings, terms describing the products posing a high risk of being substandard or falsified as per the GSMS were added to the search, increasing sensitivity in these areas.

2.1.1 Search strategy

The search was limited to papers published between 1 January 2007 and 31 December 2016. The chosen time frame was sufficiently wide to capture a breadth of papers, but also sufficiently narrow to exclude those that might no longer be relevant. Commentaries and editorials were excluded. The search strategy used is outlined in Box 3.

Box 3: Search strategy

Keywords	Limits
(substandard OR spurious OR falsified OR fake OR counterfeit)	*Date*: 1 January 2007 – 31 December 2016
AND (drug OR medicine OR pharmaceutical OR antibiotic OR anti-infective OR antimicrobial OR antimalarial)	*Publication type*: NOT (comment OR editorial)

Note: The time frame represents the date of publication, not that of data collection. Many papers did not indicate when the samples were collected.

The literature search was conducted for these terms in English. When results returned papers in other languages, they were included for further consideration. The search strategy identified a number of reviews that compiled information about papers potentially within the scope of the study *(5–12)*. Once papers for consideration had been compiled, they were manually screened to see whether they met the inclusion and exclusion criteria listed in Box 4.

Box 4: Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
▪ Paper must have been published between 1 January 2007 and 31 December 2016	▪ Paper includes intellectual property considerations in its classification
▪ Paper or data are available in the public domain	▪ Paper focuses on the validation of testing technologies, rather than on determining the prevalence of substandard and falsified medical products
▪ Paper contains data on the prevalence of substandard and falsified medical products	▪ Samples were procured exclusively from the Internet, or obtained retrospectively following seizures by enforcement authorities or pharmaceutical manufacturers
▪ Although terminology used in the paper may vary, the definitions given for terms used must be stated, and must map on to the WHO working definitions for substandard or falsified medical products	▪ Paper reports only physical inspection of product and/or packaging, with no content analysis
▪ Paper describes methodology, including sampling design and sample size	▪ Paper reports testing on fewer than 10 samples overall
▪ Paper describes the laboratory analysis and reference pharmacopoeia	▪ Paper reports results that had been previously reported elsewhere

2.1.2 Quality evaluation

The papers that remained within the scope of this study following the application of these initial inclusion and exclusion criteria were subjected to a further assessment of quality. In an effort to standardize methods for conducting statistically valid sampling and testing to provide prevalence figures, Newton and colleagues proposed a Medicine Quality Assessment Reporting Guidelines (MEDQUARG) Checklist of items that ought to be included in surveys of medicine quality *(13)*. The review by Almuzaini et al. narrowed the MEDQUARG Checklist down to a twelve-point quality assessment score *(7)*.

The following points were covered by the inclusion criteria determined by the Expert Group to be essential to meet the intended scope of the study:

1. definition of substandard or falsified medicines used mentioned
2. sampling design and sample size calculation described
3. chemical analysis clearly described.

The Expert Group determined that any paper meeting three of the nine additional criteria should be considered of sufficient methodological rigour to be included in further analysis. These nine criteria are as follows:

4. timing and location of study clearly stated
5. type of outlets sampled
6. type and number of dosage units purchased per outlet
7. random sampling used
8. information on who collected the samples (overt versus mystery shoppers)
9. packaging assessment performed
10. statistical analysis described
11. details on method validation
12. chemical analysis performed blinded to packaging.

2.1.3 Analysis of data

The papers reviewed in this study provide data for 88 of the 194 WHO Member States. As far as possible, the data in each of the included papers were disaggregated by country and corresponding sample size. Twenty-eight of the papers reviewed included data on samples collected in more than one country.

The countries were then grouped by World Bank country classification by income level *(14)* (listed in Annex 1). A total of 904 samples (under 2% of the review total) were in multicountry studies that included more than one income category and could be disaggregated. About two thirds of these samples could be attributed to the category “middle income”, which covers both the World Bank categories of lower middle- and upper middle-income countries. Therefore, for the sake of simplicity, all 904 samples from the multicountry studies have been assigned to the middle-income category. This was then used to estimate the aggregate observed failure rates of low and middle income countries by World Bank country classification by income level.

Once the aggregate observed failure rates were established, the total acquisition costs (spending) was estimated by multiplying the relevant rate with an estimate of the corresponding market size, based on available pharmaceutical sales data. BMI Research (Fitch Group) is a research firm that provides macroeconomic, industry and financial market analysis. It gives figures for the total pharmaceutical sales of most world economies.

Because prevalence has been studied in far more detail in low- and middle-income countries (LMICs), this study has only used the pharmaceutical sales data for this group of economies. This method only captures the estimated acquisition costs (spending) of substandard and falsified medical products, not their full range of socioeconomic impacts.

2.2 Results

The search strategy identified 100 published papers which met the inclusion criteria for further consideration. In total, the **100** papers reported on testing of **48 218** samples of medicines collected from **88** countries. In addition, data from one publicly accessible database maintained by United States Pharmacopeia, known as the Medicines Quality Database (MQDB) *(15)*, was included in the review and accounted for 13 909 of the 48 218 samples – about 28.8% of the total. The MQDB collates the results of testing performed under the auspices of a United States funded programme which supports governments in Africa, Asia and Latin America in their efforts to secure the quality of the medical products in the national supply chain. The samples included in the dataset of the present document were collected using non-random methods by regulators between 2007 and 2013.

The original intention of this study was to include vaccines, diagnostic kits and other medical products. Virtually all of the evidence found, however, relates to medicines and therefore this study focuses on medicines. The list of all papers is included in Annex 2.

2.2.1 Distribution by sampling strategy

The sample size varied significantly between studies, ranging between 10 samples to more than 15 000 samples per study. Eighty-five per cent of samples came from survey sizes of over 500, as illustrated in Table 1. Large sample sizes, acquired using appropriate sampling methodology, have much lower variability in their results. However, surveys that include larger sample sizes are more expensive and take longer to complete, which may not be feasible for certain countries or projects.

Table 1: Total samples by survey size

Survey size	Total number of samples included
Less than 50	471
51–100	450
101–500	5 090
More than 500	40 893
Unspecified	1 314
TOTAL	**48 218**

As seen in Table 2, about 77% of all samples were obtained using convenience sampling and about 23% of all samples were obtained using random sampling. Convenience sampling is a "non-probability sampling technique based on the judgement of the survey organizer" and is typically used to utilize resources in the most efficient or risk-based way (e.g. focusing on outlets where the risk of substandard and falsified medicines being found is high) *(16)*. Random sampling is a probability sampling technique that will give reliable estimates (with confidence intervals) of the prevalence of outlets selling substandard and falsified medicines *(16)*. Though this technique is ideal in terms of measuring prevalence, it requires large sample sizes and additional resources, which are not always viable for those conducting surveys.

Table 2: Observed failure rates by sampling strategy

Sampling strategy	Total samples	Failed testing	Percentage failed testing (95% CI)
Random	11 300	2 209	19.5 (18.8–20.3)
Convenience	36 918	2 885	7.8 (7.5–8.1)
TOTAL	**48 218**	**5 094**	

CI: confidence intervals.

It is noteworthy that random sampling of specific products within a given sample frame found a higher observed failure rate than convenience strategies. Further analysis that disaggregates the full sampling methodology, including overt or covert purchase of samples and analytical techniques, is required to understand the difference in these failure rates.

As far as possible, this study aimed to disaggregate samples from different types of outlets or point of surveys. As seen in Table 3, the majority (about 60%) of samples were from a mix of public and private outlets, followed by about 29% of samples coming from only private outlets. Types of pharmaceutical outlets vary greatly both within and between countries, but outlets can generally be classed as public (government) and private (licensed/registered outlets, i.e. registered private for profit and private "not for profit" (nongovernmental organizations (NGOs)) *(16)*.

Table 3: Samples collected by type of outlet/point of survey

Type of outlet/point of survey	Total samples
Public only	64
Private only	14 068
Mixed (public and private)	29 172
Sampling by NMRA at port of entry	4 162
Not stated	752
TOTAL	**48 218**

Samples are unevenly distributed across sampling strategies. Tables 1 to 3 demonstrate the need for careful development of the survey protocol, including the survey size, sampling strategy and types of outlets sampled.

2.2.2 Distribution by analytical technique

As far as possible, the present study standardized the results by scrutinizing the tests and thresholds used in each study, and reclassifying their outcomes according to the currently applicable definitions for "substandard" and "falsified" medical products. The results were compared to the stated reference pharmacopoeia to determine whether the sample was deemed out-of-specification using an appropriate analytical technique. The studies included in the review used various pharmacopoeial standards.

It is worth noting that the samples tested in studies using Minilab[1] were less likely to fail than samples in studies using other methods of analysis, including any high-performance liquid chromatography (HPLC) testing.

Moreover, the thresholds for the percentage of active pharmaceutical ingredient (API) considered "in specification" varied between authors and even between pharmacopoeias: whereas some deemed an API concentration outside the 95% to 105% window as substandard, other national or regional pharmacopoeias sometimes have a wider acceptable API window (for example 85% to 115% for the same product). It was generally not possible to standardize across these differences because most papers give a pass or fail for a given cut-off, rather than the actual percentage of API detected. Table 4 shows how the observed failure rate varies between analytical techniques.

Table 4: Observed failure rates by analytical technique

Testing	Total samples	Failed testing	Percentage failed testing (95% CI)
HPLC	19 809	3 092	15.6 (15.1–16.1)
Minilab™	20 010	1 002	5.0 (4.7–5.3)
Other chemical testing only	4 705	622	13.2 (12.3–14.2)
Spectroscopy/spectronomy only	2 701	349	12.9 (11.7–14.2)
Laboratory methods unspecified	993	29	2.9 (2.0–4.2)
TOTAL	**48 218**	**5 094**	

CI: confidence intervals; HPLC: high performance liquid chromatography.

2.2.3 Distribution across countries by income level

Three quarters of all samples were procured from countries within the middle-income category. LMICs appear disproportionately more than high income countries in the field surveys on the quality of medicines. It should be noted that only 178 samples from high income countries were included; therefore no extrapolation for this group of countries is possible. Table 5 shows how the sample sizes vary between the countries grouped by the World Bank country classification by income level.

Table 5: Distribution by World Bank country classification by income level

World Bank country classification by income level	Number of countries surveyed	Total samples
Low income	19	11 156
Middle income	56	36 884
High income	13	178
TOTAL	**88**	**48 218**

2.2.4 Distribution across therapeutic categories

Studies that focus exclusively on antimalarials, by far the most common among the 100 papers reviewed, provide a combined observed failure rates of 11.8% for substandard and falsified samples. The lowest prevalence of substandard and falsified medicines was recorded in the studies testing multiple classes of medical products, often from multiple regions.

Most of the products tested in "other single categories", as shown in the table 6, were genitourinary and sex hormone drugs, where the specific observed failure rate was very high: 56%. In this same subset, the observed failure rate was also high among 104 antiepileptic medicines tested, with 65% failure. This may help explain the overall high percentage that failed testing.

Table 6 shows the variation in the observed failure rate of substandard or falsified medicines across therapeutic categories.

1 Minilab is a field screening kit using thin layer chromatography and capable of giving semi-quantitative information on the API.

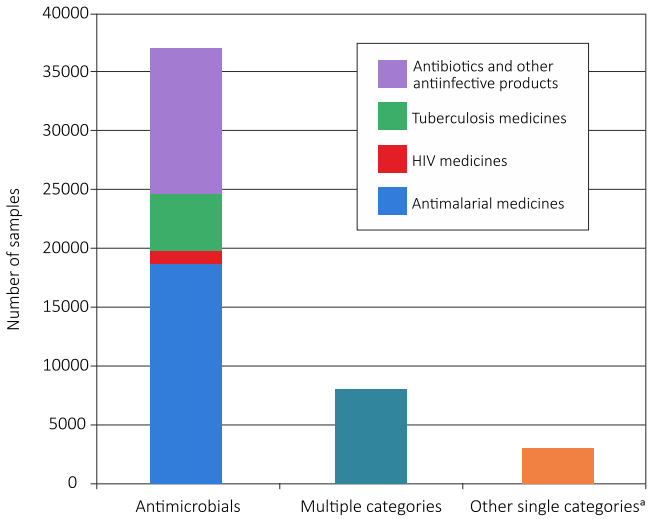
Table 6: Observed failure rates by therapeutic category

Therapeutic category	Total samples	Failed testing	Percentage failed testing (95% CI)
Antimalarial medicines	18 764	2 219	11.8 (11.4–12.3)
Antibiotics and other anti-infective products	12 375	895	7.2 (6.8–7.7)
Multiple categories	8 094	584	7.2 (6.7–7.8)
Tuberculosis medicines	4 920	329	6.7 (6.0–7.4)
Other single categories[a]	3 047	1 024	33.6 (31.9–35.3)
HIV medicines	1 018	43	4.2 (3.1–5.7)
TOTAL	**48 218**	**5 094**	

CI: confidence intervals.
[a] Includes medicines for hypertension, cancer and epilepsy, as well as analgesics, uterotonics and immunosuppressants.

Antimalarials and antibiotics are extremely well represented among the studies: together they account for 64.5% of the samples. The preponderance of these classes of medicines in the studies also reflects important public health concerns, particularly regarding antimicrobial resistance and drug-resistant infections. Fig. 1 highlights the distribution of samples by therapeutic category, showing the high proportion of "antimalarials" and "antibiotics and other anti-infectives".

Fig. 1: Collected samples by therapeutic category, showing the over-representation of antimicrobial products



[a] Includes medicines for hypertension, cancer and epilepsy, as well as analgesics, uterotonics and immunosuppressants.

As previously noted, the sampling strategies used in these studies were rarely representative of all outlets in a country, and never representative of all major therapeutic categories. Specifically, they tended to under-represent public sector outlets, and concentrated on antimicrobials which tend to be at the lower end of the pharmaceutical price range.

2.2.5 Estimated observed failure rate of substandard and falsified medical products

As explained and in section 2.2.3, the observed failure rate estimates can only be applied to LMICs. Furthermore, the data that are systematically available across all reviewed papers and which can be compared on the basis of the disaggregation detailed in section 2.1.3, only allow for an estimate of the observed failure rate, as based on the failure rate of tested samples. Building from Table 5, the aggregate observed failure rate estimates by World Bank country classification by income level for LMICs are detailed in Table 7.

Table 7: Aggregate observed failure rate estimates by World Bank country classification by income level for LMICs

World Bank country classification by income level	Samples tested	Failed samples	Percentage failure rate (95% CI)
Low income countries	11 156	1 166	10.5 (9.9 –11.0)
Middle income countries	36 884	3 906	10.6 (10.3–10.9)

CI: confidence intervals.

- **The aggregate observed failure rate of tested samples of substandard and falsified medicines in low and middle income countries is approximately 10.5%.**

2.2.6 Estimated acquisition costs (spending)

The estimated total pharmaceutical sales published by BMI Research *(17)*, grouped by World Bank country classification by income level is summarized in Table 8.

Table 8: Total pharmaceutical sales (2014), by World Bank country classification by income level

World Bank country classification by income level	Estimated total pharmaceutical sales (US$ billion) (BMI data)
Low income	4.61
Middle income	283.92

One of the aims of this study was to try to estimate the current spending by countries on substandard and falsified products. However, the only publicly available data concerning the estimated total pharmaceutical sales stratified by low and middle income countries are limited: they are not disaggregated by therapeutic class and therefore do not permit accurate estimates of the cost.

However, if one were to use the unweighted combined estimates of market size for low and middle income countries (nearly US$ 300 billion) and the observed failure rates (approximately 10.5%) to calculate possible expenditure by these countries, the resulting total estimate is in the order of US$ 30.5 billion.

If this is even approximately correct, it highlights the urgent need to address this problem. It also highlights the need for better data on expenditure at country level to enable a more accurate estimate of the economic burden on these countries.

2.3 Discussion

The results above depend heavily on the intrinsic nature of the papers reviewed. The following sections discuss some of the limitations that should be considered in conjunction with the results above, and suggests further areas of research. One important limitation of this study was that it was restricted to using information that is in the public domain (for example the market size estimates available in the public domain do not disaggregate the data based on therapeutic categories for all countries). In addition, the literature search was conducted in English, which further limited the pool of data to draw from. There remains a need for standardized methods for producing accurate and meaningful estimates of the impact of substandard and falsified medical products within health systems and across populations.

2.3.1 Impact of the survey methodology on results

"Surveys give snapshots of the medicine quality situation; however, the accuracy, reliability and interpretation of the data obtained depend on the survey design, organization of sample collection and available resources" *(16)*. The representativeness of a sample depends on two things: the sample frame from which products (or, in the case of disease surveillance, patients) are selected; and the method used to choose samples from within that sample frame.

Results can only reliably be extrapolated when the sampling method is random and the sample size sufficiently large. But, importantly, results from random sampling are only representative of the types of sites included in the sample frame. The prevalence of substandard or falsified paracetamol tablets measured in a random sample obtained from dispensaries of public sector hospitals cannot, for example, be extrapolated to sales of paracetamol in pharmacies or street markets. Conversely, even if the sample frame represents all outlets for paracetamol nationally, extrapolation is not possible if products are selected non-randomly from those outlets, for example by choosing cheaper brands to maximize the number of samples collected within the study budget.

"There is an urgent need for data of sufficient sample size with random sampling design to reliably estimate the prevalence of poor-quality medicines" *(18)*. However, it should be recognized that resource limitations may make meeting this goal difficult for researchers.

2.3.2 Impact of varying testing methodologies

Understanding the prevalence (and by extension the likely impact) of substandard and falsified medical products depends not just on how samples are selected, but on what tests are performed. Technologies and tests vary significantly in cost and sophistication as well as function. The choice of tests used will depend on the particular goal of a survey, as well as the financial and technical resources available. If the goal is to assess the health effects of a medicine, tests will focus on API content, as well as the dissolution tests that affect bioavailability. If the goal is to identify substandard medicines in particular, tests may include those for other impurities that can signal degradation. Inspections attempting to identify falsification will place more emphasis on the identity or source of the product, including as indicated on the packaging.

Differences in testing technologies can limit the comparability of studies even when they set out to measure the same thing, such as the presence and concentration of declared API. At the more sophisticated end of the chemical analysis spectrum is HPLC, coupled with mass spectrometry. The infrastructure, equipment and technical skills required to use these techniques are considerable. Certain techniques, such as thin-layer chromatography are more widespread. Some of the other methods used are able to identify the presence or absence of an API, but not to quantify it reliably. It is thus not possible to adjust estimates of the prevalence of medicines which contain too little or too much API for likely biases introduced by different testing technologies.

Technologies developed principally for use in the field are generally more suited to pass/fail screening. The GPHF-Minilab™, for example, is a portable kit that provides guidelines and equipment (including reagents) for quick and reliable testing of 85 APIs, showing whether or not the correct ingredient is present *(19)*. Several reviews of different technologies are listed in the references *(3, 5, 20–22)*. One such review by Kovacs et al. provides a useful summary of the purpose, costs and application of various physical and chemical detection technologies in the field *(21)*. The authors also highlight the critical need for greater capacity for high-volume testing, especially in the countries and regions most at risk.

2.3.3 Impact of uneven distribution of field studies

Substandard and falsified medical products are likely to be unevenly distributed across therapeutic categories and geographical regions. They tend to cluster in areas or situations where risk factors that favour the manufacture or sale of such products are high. A report on the *WHO Global Surveillance and Monitoring System for substandard and falsified medical products,* published together with this study, indicates that this is often when constrained access to safe, affordable, quality products overlaps with poor governance systems, including unethical practice and corruption, and/or weak technical capacity for quality assurance during manufacturing and distribution. This overlap may be suspected in a particular product category or geographical region.

Study developers often take a risk-based approach, choosing to investigate geographical or product areas believed to be vulnerable to substandard and falsified medical products. Particular products may also be the focus of particular interest because of their public health importance or their relevance to disease-specific programmes. In the papers reviewed for the present study, the disease burden of the target population, as well as access to medicines and their public health impact, were frequently cited as factors that contributed to deciding which therapeutic categories to sample. However, data arising from risk-based surveillance cannot be extrapolated to products in other settings. The likely under- or over-representation that can be introduced by this uneven distribution should be considered in the context of this study.

2.3.4 Estimating prevalence of substandard and falsified medical products

The most rigorous way to measure prevalence of substandard and falsified medical products would be to test a random sample of all medical products from a nationally representative sample of outlets – from hospitals to pharmacies, from street markets to the Internet. Information on the overt versus covert nature of the sample collection would also need to be made available. Given the vast size and complexity of the pharmaceutical market, the diversity of products and the expense of laboratory testing, this strategy would not be feasible (or indeed sensible) in most countries or markets.

At this stage, with the available data, it is only possible to provide estimate aggregate observed failure rates of substandard and falsified medical products for LMICs, which might provide inputs for modelling or otherwise inform future work. Since methods are so heterogeneous, it is not possible to perform statistical tests for differences between means. The observed failure rates are calculated as a percentage of samples that failed testing within each category. The authors have chosen to use the total sample size as base number rather than the published paper as a unit of measure, so as to mitigate the effect of varying sizes of the field studies.

2.3.5 Estimating acquisition costs (spending)

The economic impact was estimated only for LMICs from where failure rates have been observed. It is acknowledged that a number of other models that assess the economic impact of substandard and falsified medical products exist. However, these models cannot be applied to LMICs because of the significant difference in income, regulatory frameworks, access to medicines and a multitude of other metrics. It is worth reiterating that one of the main challenges of this document was that prevalence data are mainly available for LMICs that have varying amounts of economic data, and detailed economic data are available for high income countries – for which there are limited data on prevalence.

Data on health system spending on different classes of medicines are available for many countries. Out-of-pocket spending is much less well documented. Although overall figures are available from household survey data in many countries, these very rarely break data down by therapeutic category.

Data are nonetheless available on the prices of medicines slightly higher up the supply chain (before reaching patients) from various data analysis companies. Such data are most often presented in the form of "total pharmaceutical sales" and may in reality reflect the wholesale price of the goods. To estimate acquisition costs (spending) on substandard and falsified medicines, this study has assumed that the prices charged for substandard and falsified medical products are the same as prices charged for a quality-assured alternative. The data on acquisition costs (spending) from BMI Research *(17)* used in this study are publicly available and do not disaggregate estimations by therapeutic category and by country or income level.

2.3.6 Impact of heterogeneous definitions

Many of the papers reviewed for this study use different terminology, or use definitions for the terms "substandard" and "falsified" which do not align with the new WHO definitions. As mentioned previously, a large number of studies, for example, only measure the level of API as a proxy for whether a medical product is out-of-specification. However, it is rarer for researchers to verify the product's source or excipients, and very few have the capacity to determine the root cause for a product not meeting its specifications.

Few studies report authentication of product records with manufacturers. It is therefore possible that many products classified as substandard were in fact falsified. Falsified products that misrepresent their origin, or contain at least some of the correct API, may pass some form of analysis. Although these products are falsified, data to allow for that classification are not typically available, so there is a risk that they would have been misclassified as substandard.

3 PART TWO IMPACT MODELS

As seen in Part 1, field studies on the quality of medical products do not systematically provide detailed information on how far the results for the samples analysed deviate from the expected API content (assay), nor do they systematically test dissolution or disintegration. Data on these parameters are required to better assess the impact on patients' health impact of a decreased availability of the API.

Only one of the papers reviewed for this study described a systematic attempt to estimate the health impact of substandard and falsified medical products on a single disease, malaria *(23)*. Even with more information, the health impact of a given threshold of API is likely to differ across disease categories. That fact, together with the variation in prevalence of substandard and falsified medical products across therapeutic classes, means that rigorous estimates of health impact would require separate modelling for many major diseases – something that has yet to be undertaken. In addition, no broad methodological guidelines exist to help in the task of attributing health impacts to substandard and falsified medical products.

This implies that it is not possible to draw any broad conclusions about the likely health impact of substandard and falsified medical products overall. In an effort to begin to fill this information gap, the Expert Group requested that two models be developed to estimate the health impact of substandard and falsified medical products. The models focused specifically on childhood pneumonia and malaria in sub-Saharan Africa. These models were developed for WHO by the University of Edinburgh (childhood pneumonia model) and the London School of Hygiene and Tropical Medicine (malaria in sub-Saharan Africa model). The full reports on each model are provided in Annexes 3 and 4.

3.1 Model 1: Childhood pneumonia

A team from the University of Edinburgh was commissioned by WHO to investigate the impact of the use of substandard and falsified antibiotics in the treatment of childhood pneumonia. This model provides a first estimation of the potential impact of substandard and falsified antibiotics on mortality from pneumonia among children aged 0 to 5 years.

3.1.1 Introduction

This model considers the potential impact on the treatment of childhood pneumonia,[2] one of the main causes of child mortality globally *(24)* and a major reason for health service utilization *(25)* and the prescription of antibiotics globally.

Lack of high quality data from the majority of LMICs means that first estimates will depend largely on data modelling. The present model builds on existing models for estimating child pneumonia morbidity and mortality globally *(25–27)*, data from large-scale surveys in LMICs, which attempt to estimate the level of use of antibiotics for the treatment of respiratory infections in young children and available data from published review articles on the prevalence of substandard and falsified medicines. These sources of information were used to make a first approximation of the potential impact of substandard and falsified medicines on mortality from childhood pneumonia.

The study objectives were:

- to take estimates from WHO of the prevalence of use of substandard medicines for the treatment of childhood pneumonia and estimate their impact on pneumonia mortality; and
- to provide first rough estimates of the increased mortality, by WHO region and globally, that might be associated with their use.

3.1.2 Methodology

The estimation of the impact of substandard and falsified antibiotics on childhood pneumonia mortality has been approached from a global level and from the level of two broad groups of "industrialized" and "developing" countries and also in two settings – in the hospital and community settings. It is assumed that all children admitted to hospital with severe pneumonia receive antibiotic treatment but that only a fraction of children with severe pneumonia who are not admitted to the hospital receive antibiotic treatment. Finally, three different levels of global prevalence of substandard and falsified antibiotics used for the treatment of childhood pneumonia were considered (1%, 5% and 10%) and it was assumed that these result in an increased case fatality rate (CFR):

2 Pneumonia in this model refers to acute lower respiratory infection in children aged 0–5 years.

i. either a two-fold increase consistent with a reduced antibiotic activity/reduced efficacy of substandard and falsified antibiotics;
ii. or a four-fold increase consistent with a zero antibiotic activity/efficacy of substandard and falsified antibiotics.

The available literature suggests that the first scenario (two-fold increase) is the more plausible. The above model was then used to estimate excess deaths that result from the increased CFR associated with the use of substandard and falsified antibiotics. The estimates considered data for the year 2010.

3.1.3 Results

Table 9 summarizes the findings on excess deaths from severe pneumonia due to substandard and falsified antibiotics at prevalence levels of substandard and falsified antimicrobials of 1%, 5%, and 10% (assuming that use of substandard and falsified medicines results in a two-fold or a four-fold increase in CFR).

Table 9: Findings on excess deaths from severe pneumonia due to substandard and falsified antibiotics in hospital and community settings

Prevalence of substandard and falsified products (%)	**Number of excess deaths in most likely scenario** (two-fold increase in CFR)	**Number of excess deaths in alternative scenario** (four-fold increase in CFR)
1	8 688	18 372
5	37 018	85 438
10	72 430	169 271

Table 9 shows a very wide variation between:

Assuming a two-fold increase in CFR (most likely scenario)

- 8 688 deaths if the prevalence of substandard and falsified antimicrobials is 1% to 72 430 deaths at a prevalence of 10%;
- number of deaths associated with a 1% increase in prevalence of substandard and falsified medicines is 7 082.

Assuming a four-fold increase in CFR (alternative scenario)

- 18 372 deaths at 1% prevalence of substandard and falsified antimicrobials to 169 271 deaths at 10% prevalence;
- number of deaths associated with a 1% increase in prevalence of substandard and falsified medicines is 16 766.

Based on a 10% prevalence of substandard and falsified antibiotics, this model estimates that:

- **Up to 72 430 childhood pneumonia deaths can be attributed to the use of substandard and falsified antibiotics if there is reduced antibiotic activity.**
- **This increases up to 169 271 deaths if substandard and falsified antibiotics have no activity.**

3.1.4 Discussion

This model provides the first rough estimate of the potential impact of substandard and falsified antimicrobials on the treatment of childhood pneumonia, a major cause of antimicrobial prescription and child death globally. Lack of high quality data on the prevalence of the use of substandard and falsified antimicrobials in children globally and on the proportion of young children with pneumonia who are treated with antimicrobials means that it is only possible to provide estimates based on a range of plausible assumptions informed by available published reviews *(7, 10, 12, 28)*.

The full model (see Annex 3) details the limitations of the available data and the modelling approach adopted. The range of explicit parameter levels and the likely direction of bias are provided together with these estimates to promote critical review and guide interpretation. The use of substandard and falsified products has broader health and economic impacts which have not been considered in this exercise. Therefore, **the model estimates are likely to under-represent the true health impact of these products on the treatment of childhood pneumonia**. **This merits priority attention in global and national pneumonia control programmes, since these deaths are avoidable.**

It is further hoped that this work will encourage intensified efforts to gather and report data in a standardized way and the subsequent development of improved estimates.

3.2 Model 2: Malaria in sub-Saharan Africa

A team from the London School of Hygiene and Tropical Medicine was commissioned by WHO to investigate the health and economic cost of substandard and falsified medical products for first-line treatment of uncomplicated *Plasmodium falciparum* malaria in sub-Saharan Africa.

3.2.1 Introduction

The analysis is based on a decision-tree model of febrile illness that follows malaria cases from initial diagnosis and treatment to final health outcome.

3.2.2 Methodology

The prevalence of substandard and falsified antimalarials was based on a literature review of studies of antimalarial quality in sub-Saharan Africa using random sampling and published between 2001 and 2016 (10 studies, 17 countries). The proportion of samples with API below 85% was estimated at 7.6% for artemisinin combination therapy (ACT) drugs and 10.4% for other (non-ACT) antimalarials. The analysis modelled the incremental impact of such a prevalence of substandard and falsified antimalarials on treatment effectiveness, by comparing current prevalence against a hypothetical ideal scenario where all antimalarials contained levels of API above 85%. Reductions in efficacy of antimalarial were calculated for the proportion of cases receiving a level of API below 85%. The level of API consumed was calculated as a product of medicine quality and the amount of dose taken (i.e. patient adherence to treatment).

Health impact was measured in terms of deaths and disability-adjusted life years (DALYs) and economic impact in terms of patient and provider costs related to additional treatment and further care due to failure of initial treatment. Results were estimated for a hypothetical cohort of 1 million malaria cases seeking treatment, containing a mix of cases from low transmission (<10% parasitaemia in patients presenting with fever) and high transmission (>10% parasitaemia) settings. Total health and economic impact of substandard and falsified antimalarials in sub-Saharan Africa was also modelled, based on annual malaria case estimates.

Model parameters, including the probability of disease progression for patients not receiving effective treatment and the probability of severe illness leading to death with or without further care, were taken from the available literature. The parameterized base case model gives an overall CFR of 0.79% for malaria cases seeking treatment, and 1.04% for all malaria cases. A "CFR adjusted case" was also calculated, where estimates for disease progression and mortality were adjusted to generate an overall CFR of 0.45% for all malaria cases – consistent with the CFR used by WHO for modelling malaria mortality.

3.2.3 Results

The base case analysis estimated an additional 529 deaths (CFR adjusted case: 230 deaths) per 1 million malaria cases seeking treatment, as a result of the reduced effectiveness of substandard and falsified antimalarials. Drawing on two different sets of annual malaria case estimates (from the World Malaria Report and Clinton Health Access Initiative), the base case analysis estimated that substandard and falsified antimalarials contributed an additional 72 000–267 000 deaths (CFR adjusted case: 31 000–116 000 deaths) annually in sub-Saharan Africa. Total annual economic impact (base case) due to additional treatment-seeking and further care was estimated at between US$ 12.1 million and US$ 44.7 million (CFR adjusted case: US$ 10.4 million and US$ 38.5 million). Table 11 summarizes these findings.

Table 10: Health and economic impact due to reduced effectiveness of substandard and falsified antimalarial products

	Incremental health impact (deaths)		Incremental economic impact (USD 2017)	
	WMR cases	**CHAI cases**	**WMR cases**	**CHAI cases**
Base case	72 000 (40 000 –98 000)	266 906 (147 000 –364 000)	$12 100 000 (6 700 000 –16 500 000)	$44 700 000 (24 800 000 –60 800 000)
CFR adjusted case	31 000 (17 000 –43 000)	116 000 (64 000 –158 000)	$10 400 000 (5 800 000 –14 200 000)	$38 500 000 (21 400 000 –52 400 000)

CFR: case fatality rate. WMR: World Malaria Report; CHAI: Clinton Health Access Initiative.

For both the base case and CFR adjusted case, it is estimated that incremental deaths in sub-Saharan Africa due to substandard and falsified antimalarials comprise:

- **approximately 2.1% to 4.9% of total malaria deaths, or**
- **approximately 3.8% to 8.9% of malaria deaths relating to cases seeking treatment.**

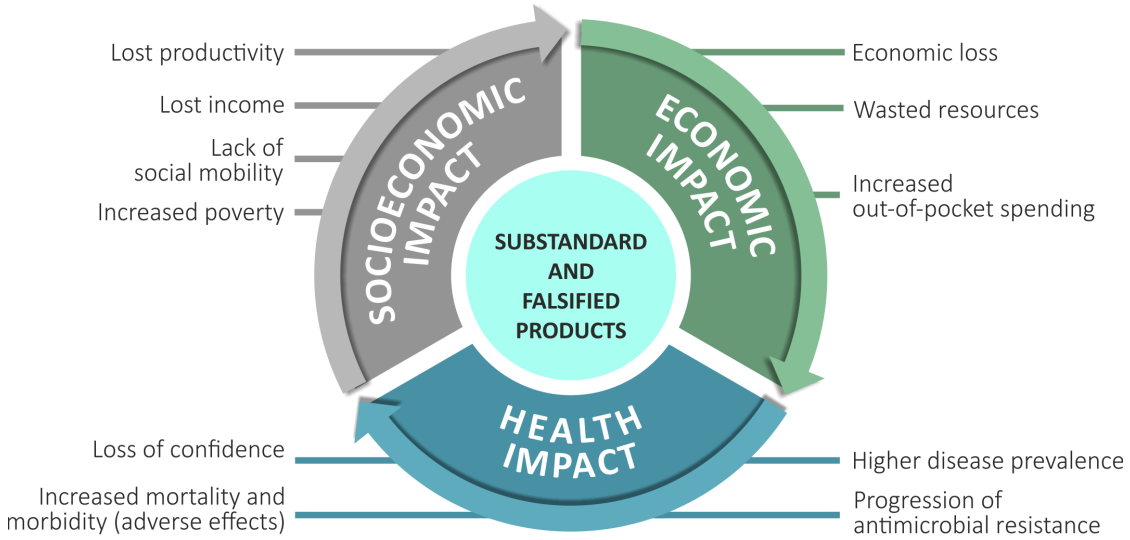
3.2.4 Discussion

The model emphasized considerable uncertainty surrounding the analysis, and cautioned that results should be considered tentative and illustrative only. **Given the limitations of the available data, it is likely that the results of this model under-represent the full health and economic impact of substandard and falsified antimalarial products.** In particular, estimates of prevalence of substandard and falsified antimalarials were based on a limited number of studies that may not be generalizable to the broader sub-Saharan African context. The study did not consider the impact of dissolution, an important but neglected characteristic of drug quality, due to the very limited data available. The impact of adverse drug events relating to substandard and falsified antimalarials was also not modelled for similar reasons. Estimates of economic impact considered incremental provider and patient costs of care sought as a result of treatment failure, but did not include travel costs and economic impact due to lost productivity. There was also considerable uncertainty in the estimates of number of malaria cases in sub-Saharan Africa on which the estimates of the impact of substandard and falsified antimalarials in sub-Saharan Africa as a whole were based. Notwithstanding these limitations, **the model demonstrates that substandard and falsified antimalarials have a substantial impact in both health and economic terms, and will hopefully inform and encourage further research to better understand the nature and impact of substandard and falsified antimalarials in sub-Saharan Africa and elsewhere**.

4 PART THREE KEY AREAS FOR CONSIDERATION

This section lays out some of the key areas that need to be further explored to obtain more precise estimates. This study is presented as an advocacy document, representing the first step towards gaining a better understanding of the public health and socioeconomic impact (summarized in Fig. 2) of substandard and falsified medical products, but there is more to be done.

Fig. 2: Impact of substandard and falsified medical products



4.1 Public health impact

The study aimed to find out what is known about the public health impact of substandard and falsified medical products. To meet this goal, it would be desirable to estimate the proportion of those medical products that may be damaging to health. Health impacts can include death, disability and/or increased illness at the individual level, and have broader implications at the health systems level.

Methods for estimating mortality and morbidity are very well established (for example, years of life lost). The measures that result from application of these methods include the following.

- **Years of life lost:** This is a straightforward measure of mortality attributable to a disease or condition.
- **Quality-adjusted life years (QALYs) and DALYs:** Both QALYs and DALYs provide measures of years of life lived, adjusted for health status. These measures thus combine mortality (years not lived because of a disease) and morbidity (years lived in imperfect health) into a single figure. Although the technicalities differ somewhat, in practice each expresses the inverse of the other measure. QALYs represent years of healthy life gained in the absence of a disease, while DALYs estimate years of healthy life lost in the presence of a disease.

In addition to mortality, morbidity and quality of life measures, there are other metrics for capturing the public health impact of substandard and falsified medicines.

- **Disease prevalence:** Methods for estimating prevalence of most infectious diseases are well established. Although they may differ for each disease, prevalence estimates tend to be based largely on surveillance methods.
- **Antimicrobial resistance:** Although relying on data generated by public health surveillance systems, estimates of antimicrobial resistance are more complex, because they are valid only for particular combinations of drugs and pathogens. After case studies, the best measurements linking substandard and falsified medicines to antimicrobial resistance therefore come from mathematical models. The utility of these models, however, depends entirely on the robustness of their assumptions and the quality of the input data *(29)*. For this reason, such models often focus on very narrow therapeutic categories and target populations.

These methods and metrics are difficult to use because medical products may be substandard or falsified for many different reasons, including irregularities relating to identity, composition or source, all of which may have very different implications for public health. It is therefore necessary to have enough information to make plausible assumptions about the distribution of those specific shortcomings within the broader category of substandard and falsified medical products.

4.1.1 Mortality and morbidity

Any product containing a dangerous contaminant (including dangerously high levels of the expected API) will pose an immediate hazard to the individual taking it. Patients may also die, or suffer a longer bout of disease, if their condition goes untreated because the "medicine" they take contains no API, or the API is at subtherapeutic concentrations. However, the thresholds at which subtherapeutic products become threatening to health are not well established, and are likely to differ across products. When prophylactics (for example vaccines) are either substandard or falsified, they may leave people unprotected against future disease.

4.1.2 Disease prevalence

When infectious diseases are not prevented because prophylactic products are substandard or falsified, or when infections are not cured or controlled, disease prevalence is likely to rise. A larger pool of infected people increases opportunities for onward transmission, increasing the risk to wider populations: in today's globalized world, where microbes travel long distances with their human hosts, this implies a rapid spread of diseases to non-endemic regions.

An antimalarial or emergency contraceptive, for example, that looks visually identical to the authorized product but is composed of potato or corn starch, may not cause a toxic reaction, but it will fail to treat malaria or prevent conception. Health systems that have regulatory capacity gaps, including pharmacovigilance and postmarket surveillance, may experience a delay or outright failure in picking up signals of unexpected lack of efficacy. Although not all such cases can be attributed to substandard or falsified medicines, they can result in neglected epidemiological incidents that contribute to increased prevalence of disease.

4.1.3 Antimicrobial resistance

Antimicrobial resistance is driven in part by pathogens being exposed to subtherapeutic doses of treatments, which may be due to administration of substandard and falsified antimicrobials. In many cases the levels of the API are so low or non-existent that the treatment will be ineffective. Antimicrobial resistance happens most effectively where the concentration of API is high enough to kill a proportion of susceptible pathogens significant enough to confer a reproductive advantage on mutant variants, while not being high enough to wipe out the mutant variants effectively – a range known as the "mutant selection window" *(30, 31)*. It is not clear exactly what range of concentrations of API fall within the mutant selection window, which is likely to vary between pathogens, individual patients and by product. The remaining pool of microbes, some of which may include mutations that confer resistance against the drug used, face less competition and are able to reproduce more rapidly. Colonies of pathogens resistant to the drug in question may thus be established, and onward spread is facilitated. People who develop resistant infections because of substandard and falsified medicines in one country can easily travel to another country and pass on the mutant infection.

Efforts at quantifying the link between substandard and falsified medicines and antimicrobial resistance have been both anecdotal and statistical, although predominantly focused on research on antimalarials. Based on field surveys, for example, Dondorp and colleagues have shown that 53% of antimalarials sampled in south-east Asia contained incorrect levels of the API *(31)*. "Poor-quality antimalarial drugs lead to drug resistance and inadequate treatment, which pose an urgent threat to vulnerable populations and jeopardise progress and investments in combating malaria" *(9)*.

In another study, Lubell and colleagues modelled the human and economic costs associated with resistance to antimalarial treatments at more than 116 000 deaths a year *(32)*.[3] Moreover, although antimalarial and antibiotic medicines are often quite inexpensive relative to other classes of medicine, they are sold in vast quantities, through a very wide variety of outlets.

Finally, high levels of antibiotic resistance also increase the danger when treating noncommunicable diseases such as cancer, and when performing routine surgery – cases where antibiotics are used prophylactically.

3 These findings are also supported by clinical data. The WorldWide Antimalarial Resistance Network (WWARN), for example, amalgamates and analyses data from thousands of malaria patients worldwide, and has found that subtherapeutic doses were associated with significantly longer parasite clearance times, greater rates of parasitic re-emergence and increased prevalence of resistance in ***Plasmodium falciparum*** malaria *(11)*.

4.1.4 Loss of confidence

A further potential effect of substandard and falsified medical products is the loss of public confidence in medication and in health systems. Where doubts about the quality of medicines lead people to stay away from particular health facilities, refuse vaccination for their children or fail to take treatment as prescribed, their health may suffer.

Substandard or falsified medical products can moreover contribute to an erosion of trust if patients and households develop a suspicion or mistrust of health professionals, the health system and even other public institutions. This can result, for example, in patients forgoing treatment altogether or even seeking alternative treatment from unregulated outlets and/or care providers. Various stakeholders, from academics to policy-makers, have highlighted this as a significant consequence for health systems *(5, 18, 33)*. Much of the evidence has been based on studies or patient surveys and there is a need for standardized methods for producing accurate and meaningful estimates of the impact of substandard and falsified medical products in this context.

4.2 Socioeconomic impact

While data on prevalence are scattered and incomplete, studies on health and economic impacts are virtually non-existent. The most important information gap in this area relates to attribution. Health economists have no shortage of robust methods by which to estimate the cost and economic impact of a disease, or the savings that might accrue from an intervention. To use those methods, however, they must be able to attribute a health outcome to a pathogen or risk factor. In this case, the "risk factor" is an out-of-specification medical product. While a body of work around pharmacokinetics may provide useful indications about the health impacts of subtherapeutic dosing, further work would be needed to fully understand its health implications and would differ from one treatment to another.

Two measures of the direct cost of substandard and falsified medical products are important. The first is the amount of money *spent* on such products by individuals and health systems. The other is the amount of money *forfeited* by manufacturers (and other actors in the supply chain) because patients or suppliers have bought products that are not quality-assured. Although the measures are similar, they are not the inverse of one another. Each raises rather different measurement challenges. Regardless of the cost of production of substandard and falsified medical products, the price to the purchaser is required to precisely calculate economic impact.[4] However, the price of any given medical product at point of care, at the very end of the supply chain, varies greatly between and within countries.

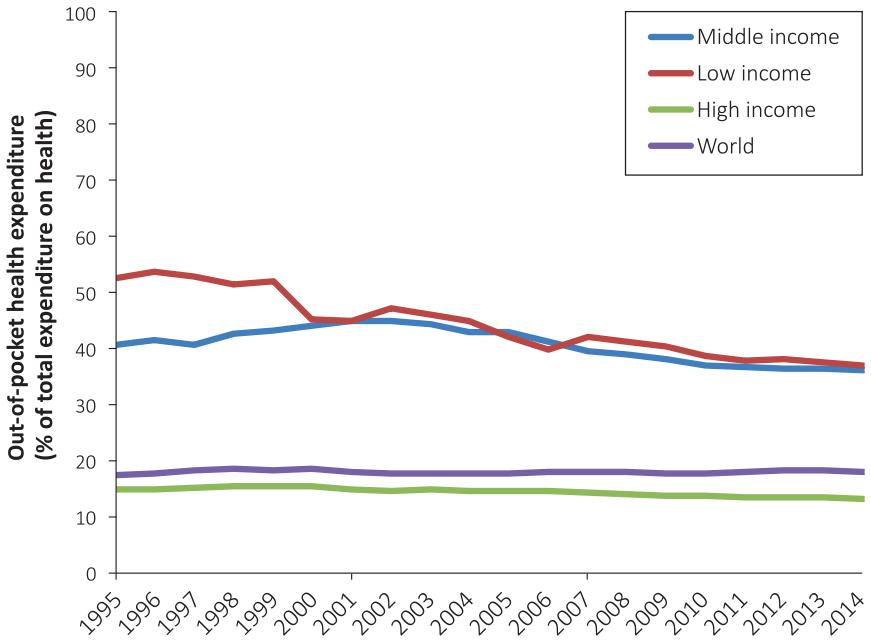
4.2.1 Individual and household costs

The most direct cost of substandard and falsified medical products to patients and their families is the money they spend on medical products that cause harm, or that do not work. Products that are toxic, or that fail to cure or prevent further disease, will certainly represent a wasted financial outlay. Toxicity, treatment failure, or infection resulting from failed prophylaxis may also lead to extra spending on health services and new medical products.

Estimating direct costs at the household level thus requires information on the likely health impact of poor production, degradation and falsification for each class of drug, as described above. This has to be combined with information on the price of medicines in each category and the proportion of substandard or falsified medical products that have been paid for out of family budgets. This varies greatly by country. Health insurance and other systems to achieve universal health coverage are well established in many high income countries, reducing health spending from family budgets (termed "out-of-pocket" spending). Such systems are also expanding rapidly in several middle income countries, as well as a few low income countries. That has led to a moderate drop in the percentage of out-of-pocket spending. The drop has been most marked in low income countries, as Fig. 3 shows. But in LMICs, individuals and families still shoulder the highest burden of spending on health – accounting for around 37% of spending, compared with 14% in high income countries *(34)*. If the analysis is restricted to spending on medicines alone, the proportion spent by households is higher, since medicines make up a higher proportion of household expenditure on health than they do national expenditure.

4 How manufacturers set prices is complex and is influenced by a range of other factors, including scale of production, commercial setting, market size, patent status, type of medicines and consumer behaviour, among others.

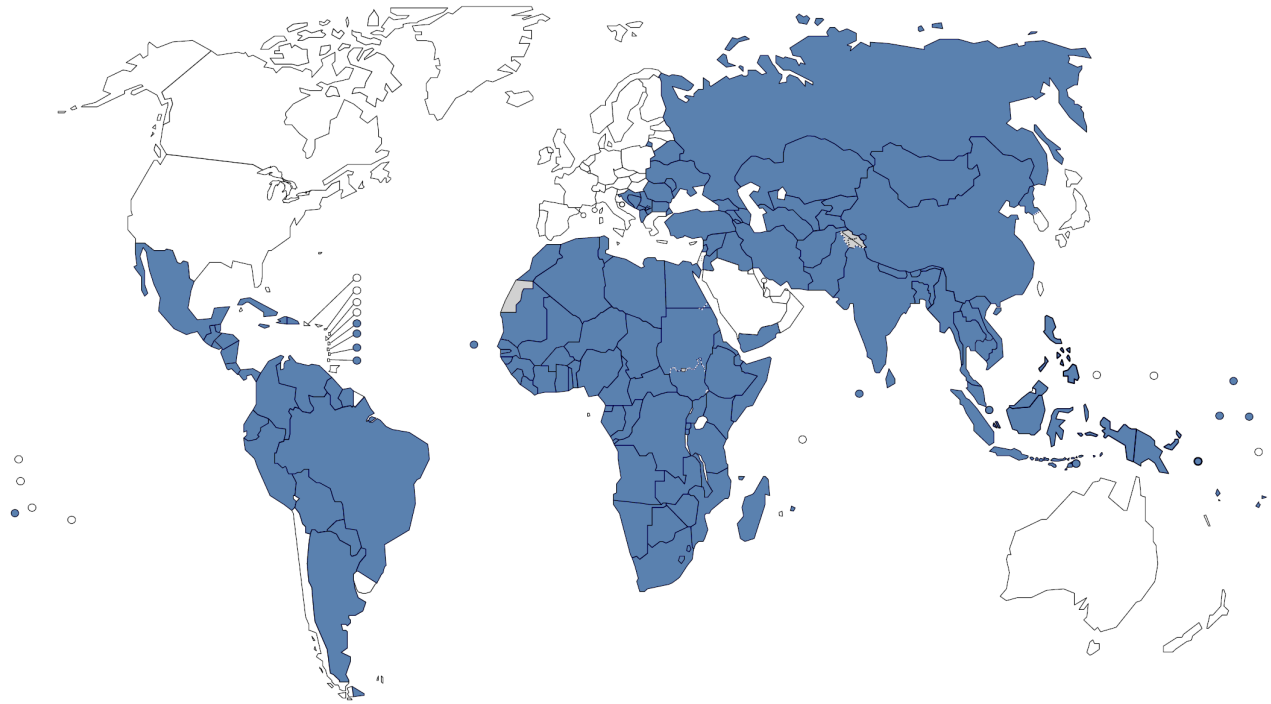
Fig. 3: Out-of-pocket spending as a percentage of total expenditure on health, by World Bank country classification by income level



Source: World Bank *(34)*

In their study, Niens and colleagues found that seeking access to medicines could pose a significant risk of impoverishment in low and middle income countries *(35)*. As seen in Figure 3, this risk spans across multiple regions of the world and affects 84% of the world's population *(14, 34)*.

Fig. 4: Geographical distribution of low and middle income countries by World Bank country classification by income level, showing where 84% of the world's population lives



Source: World Bank *(14, 34)*

4.2.2 Health systems costs

Those medical products that are not paid for from out of household budgets usually represent costs to the health system, including to providers of health insurance. Health systems and insurers thus bear some of the costs of substandard or falsified medical products that cause treatment or prophylactic failure or toxicity.

Additional testing, treatment and care absorbs money, staff and infrastructure across the health system, further straining resources that are often already overstretched. When incidents involving substandard and falsified medical products cause public alarm that undermines the use of cost-effective programmes such as those for vaccination, the effect is multiplied *(36, 37)*.

Adverse effects (including lack of efficacy) caused by substandard and falsified medical products may lead to additional spending on repeat treatment with quality-assured medicines, as well as to extra health care costs associated with adverse reactions or infections that would not have occurred had the original product been safe and effective. Since drug-resistant pathogens are often suspected in cases of treatment failure, those costs may include payment for susceptibility tests as well as the cost of expensive higher-order classes of antimicrobials.

In the case of infectious diseases, health systems may also have to bear costs associated with higher disease prevalence due to the additional transmission resulting from treatment failure. Where substandard or falsified medicines contain subtherapeutic doses of antimicrobials that contribute to the spread of drug-resistant infections, those costs too will be borne by the health system. This can lead to even further costs, particularly if new therapies are required. Wertheimer and Norris provide the example of resistance to first-line antimalarial treatments necessitating the development of new, probably more expensive, alternatives *(36)*. Where resources are stretched, their irrational use carries an opportunity cost, with potential consequences for the health of other people. In addition, where the product in question is an antimicrobial, switching to another medicine may lead to the unnecessary use of classes of antimicrobial that ought to be used very sparingly, to avoid development of resistance and preserve effectiveness *(38)*.

4.2.3 Socioeconomic costs

All of the health outcomes discussed in the previous section (for example treatment failures, exposure to disease, death or prolonged illness) carry costs for patients and their families and in turn, put strains on the broader health systems. In addition to their public health impact, substandard and falsified medical products can have a socioeconomic impact.

Although many direct and indirect socioeconomic costs are associated with substandard and falsified medicines, these costs are difficult to measure. In particular, there are challenges in identifying and quantifying all the social costs, which can be pervasive and indirect. To accurately measure the socioeconomic impact would require, for example, a quantification of the effects that substandard and falsified medicines would have on economic and social development. This includes gross national income, life expectancy, literacy, levels of employment, social mobility, and how trust is negotiated between the patient or the household and health systems, among others. It would also be helpful to be able to compare the cost of optimal treatment versus suboptimal treatment that is directly attributable to the use of substandard and falsified medicines and data on the following indirect costs:

– lost income because of prolonged illness or death, travel expenses to access health care resulting from toxicity or treatment failure, and funeral expenses;

– lost productivity costs to patients and households of seeking additional medical care, during the recovery period or as a result of premature death *(39)*.

Patients can also incur costs of further treatment, diagnostics or outpatient visits. This can include payment for laboratory tests, supplementary scans and other diagnostics. Costs may also be associated with additional medical treatment that would be needed following adverse events or lack of improvement as a result of using substandard or falsified medical products. If the use of substandard and falsified medical products leads to additional time off work, the effect may be felt by businesses and the wider economy as well as by individuals and their families. This may, in turn, lead patients into a vicious cycle of poor health and poverty.

5 CONCLUSION

The impact of substandard and falsified medical products is important to understand and is summarized in Box 5 (adapted from Newton et al. *(18)*).

Box 5: Impact of substandard and falsified medical products

Health impact
• adverse effects (for example toxicity or lack of efficacy) from incorrect active ingredients
• failure to cure or prevent future disease, increasing mortality, morbidity and the prevalence of disease
• progression of antimicrobial resistance and drug-resistant infections
• loss of confidence in health care professionals, health programmes and health systems
Economic impact
• increased out-of-pocket and health system spending on health care
• economic loss for patients, their families, health systems and manufacturers (and other actors in the supply chain) of quality medical products
• waste of human effort and financial outlay across the health system, further straining resources, staff and infrastructure
• increased burden for health care professionals, national medicine regulatory authorities, law enforcement and criminal justice systems
Socioeconomic impact
• lost income due to prolonged illness or death
• lost productivity costs to patients and households when seeking additional medical care, the effects of which are felt by businesses and the wider economy
• lack of social mobility and increased poverty

Quantifying the public health and socioeconomic impact of substandard and falsified medical products is possible, but it needs consistent use of guidelines to reduce variability. Studies may use different definitions and sampling and testing strategies even when they are investigating similar therapeutic categories. Information that would allow for better comparison (for example sampling characteristics, or providing more details on API concentrations) is often not reported. Just as the problem of substandard and falsified medical products may be diminished by greater and more effective application of standards in production and supply chain management, the problem of the evidence base might be diminished by increased use of standards in data collection, analysis and reporting.

Besides being based on clear definitions, robust estimates of the prevalence of disease, behaviours or products depend largely on two factors: sampling that is representative of wider populations or markets, and testing that has a known sensitivity and specificity. Some relevant standards already exist – for sampling and reporting, for example – and others, including those on testing methods, are under development. The consistent use of guidelines and other technical documents, such as those listed in Box 6 should, over time, reduce variability, so that further studies contribute to more consistent and comparable data globally. The use of these technical documents is to be encouraged; however, they can only be used if the resources to support data collection and analysis are available.

Box 6: WHO guidelines and technical documents

Subject
The definitions of substandard, falsified and unregistered/unlicensed medical products
Draft guidance on testing of suspected falsified medical products
Testing of suspect substandard and falsified medicines

There must be consistent data and strategic information gathering. This study has illuminated some of the important information gaps that impede our ability to understand the exact nature and extent of the threat posed by substandard and falsified medical products. Annex 5, adapted from Pisani *(29)*, outlines the main data sources identified by this study and also lists data sources that were excluded, including because the data were not always publicly available and/or they included intellectual property considerations. All have advantages and disadvantages, including in terms of resources required, and all are most useful when used in combination. Potentially rich data sources, however, exist within national, regional and sectoral systems which could, with appropriate safeguards, be used to enrich our understanding of the magnitude, distribution and impact of substandard and falsified medical products. Data routinely recorded by national regulatory authorities could, if shared within appropriate partnerships, help identify patterns and trends regionally and globally. Postmarket surveillance systems maintained by regulatory and health authorities, global health bodies and the pharmaceutical industry could contribute information that would increase understanding about prevalence. Customs seizures provide a potential entry point for risk-based surveillance that has a public health focus. Pharmacovigilance systems may also provide useful information in terms of health impact of substandard and falsified medical products.

In this study, the exclusion of studies that tested samples acquired only over the Internet may also have reduced representation for those countries where Internet purchases are widespread. For example, in high income countries, this may under-represent prevalence and costs in the large United States market, where consumers bear a higher burden of out-of-pocket spending on medicines than their counterparts in most European Union countries, and where the use of Internet pharmacies that can introduce vulnerabilities to the supply chain is well-developed *(5, 40)*. The public health concern with online pharmacies is clear, particularly as many have been found to sell medicines that are unapproved, contain the wrong concentration or no API, and sometimes have toxic ingredients *(40)*. The absence of advice from a health practitioner, such as a physician or pharmacist, leading to patient self-diagnosis and self-medication, introduces additional risks of adverse events. These include overdosing, drug interactions and administration of the wrong medication and/or dose. Despite efforts to regulate online pharmacies, they pose unique challenges, ranging from jurisdictional concerns to the difficulty in tracking physical locations *(40, 41)*. The full spectrum of e-commerce of medical products, ranging from Internet pharmacies to smartphone applications through to social media and business to business platforms, requires detailed understanding which can only be achieved by targeted research. These sources may contribute to national and global estimations over time, but it is clear that more primary data collection will be necessary.

Box 7 lists areas in which it would be useful to gather data to enable a more complete, accurate and representative picture to be built up of the health and economic impact of substandard and falsified medical products.

Box 7: Data to better understand health and economic impact

To construct estimates of the health impact of substandard and falsified medical products the following data would be useful:

- reliable estimates of the prevalence of substandard and falsified medical products, by product type, geographical distribution and level of active ingredient;
- reliable estimates of the burden of disease and health service utilization, by geographical distribution;
- estimates of the effect of subtherapeutic dosing on morbidity, mortality and (for anti-infectives) antimicrobial resistance, for each drug/disease pairing.

Estimates of the economic impact of substandard and falsified medical products will be based largely on these health impact estimates, but will require additional information, including:

- publicly available estimates of out-of-pocket and health system spending on health care, appropriately disaggregated by disease and geographical region;
- estimates of income lost to death or increased morbidity;
- estimates of the economic impact of increased antimicrobial resistance on health systems;
- estimates of the costs to regulators and industry of product recalls and other expenses associated with substandard production or falsification of medical products.

It is well recognized that investing in public health generates cost-effective health outcomes and contributes to wider sustainability, with economic, social and environmental benefits *(42)*. Taken in conjunction with the report on the *WHO Global Surveillance and Monitoring System for substandard and falsified medical products*, it is hoped that these two studies will provide the impetus to make a compelling case for mainstreaming the prevention, detection and response to substandard and falsified medical products as a "good buy" for health.

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Annex 1: World Bank country classification by income level

ECONOMY	INCOME GROUP
Afghanistan	Low income
Albania	Upper middle income
Algeria	Upper middle income
American Samoa	Upper middle income
Andorra	High income
Angola	Lower middle income
Antigua and Barbuda	High income
Argentina	Upper middle income
Armenia	Lower middle income
Aruba	High income
Australia	High income
Austria	High income
Azerbaijan	Upper middle income
Bahamas, The	High income
Bahrain	High income
Bangladesh	Lower middle income
Barbados	High income
Belarus	Upper middle income
Belgium	High income
Belize	Upper middle income
Benin	Low income
Bermuda	High income
Bhutan	Lower middle income
Bolivia	Lower middle income
Bosnia and Herzegovina	Upper middle income
Botswana	Upper middle income
Brazil	Upper middle income
British Virgin Islands	High income
Brunei Darussalam	High income
Bulgaria	Upper middle income
Burkina Faso	Low income
Burundi	Low income

ECONOMY	INCOME GROUP
Cabo Verde	Lower middle income
Cambodia	Lower middle income
Cameroon	Lower middle income
Canada	High income
Cayman Islands	High income
Central African Republic	Low income
Chad	Low income
Channel Islands	High income
Chile	High income
China	Upper middle income
Colombia	Upper middle income
Comoros	Low income
Congo, Dem. Rep.	Low income
Congo, Rep.	Lower middle income
Costa Rica	Upper middle income
Côte d'Ivoire	Lower middle income
Croatia	Upper middle income
Cuba	Upper middle income
Curaçao	High income
Cyprus	High income
Czech Republic	High income
Denmark	High income
Djibouti	Lower middle income
Dominica	Upper middle income
Dominican Republic	Upper middle income
Ecuador	Upper middle income
Egypt, Arab Rep.	Lower middle income
El Salvador	Lower middle income
Equatorial Guinea	Upper middle income
Eritrea	Low income
Estonia	High income
Ethiopia	Low income

ECONOMY	INCOME GROUP
Faroe Islands	High income
Fiji	Upper middle income
Finland	High income
France	High income
French Polynesia	High income
Gabon	Upper middle income
Gambia, The	Low income
Georgia	Lower middle income
Germany	High income
Ghana	Lower middle income
Gibraltar	High income
Greece	High income
Greenland	High income
Grenada	Upper middle income
Guam	High income
Guatemala	Lower middle income
Guinea	Low income
Guinea-Bissau	Low income
Guyana	Upper middle income
Haiti	Low income
Honduras	Lower middle income
Hong Kong SAR, China	High income
Hungary	High income
Iceland	High income
India	Lower middle income
Indonesia	Lower middle income
Iran, Islamic Rep.	Upper middle income
Iraq	Upper middle income
Ireland	High income
Isle of Man	High income
Israel	High income
Italy	High income
Jamaica	Upper middle income
Japan	High income
Jordan	Lower middle income
Kazakhstan	Upper middle income
Kenya	Lower middle income
Kiribati	Lower middle income
Korea, Dem. People's Rep.	Low income
Korea, Rep.	High income
Kosovo	Lower middle income
Kuwait	High income

ECONOMY	INCOME GROUP
Kyrgyz Republic	Lower middle income
Lao PDR	Lower middle income
Latvia	High income
Lebanon	Upper middle income
Lesotho	Lower middle income
Liberia	Low income
Libya	Upper middle income
Liechtenstein	High income
Lithuania	High income
Luxembourg	High income
Macao SAR, China	High income
Macedonia, FYR	Upper middle income
Madagascar	Low income
Malawi	Low income
Malaysia	Upper middle income
Maldives	Upper middle income
Mali	Low income
Malta	High income
Marshall Islands	Upper middle income
Mauritania	Lower middle income
Mauritius	Upper middle income
Mexico	Upper middle income
Micronesia, Fed. Sts.	Lower middle income
Moldova	Lower middle income
Monaco	High income
Mongolia	Lower middle income
Montenegro	Upper middle income
Morocco	Lower middle income
Mozambique	Low income
Myanmar	Lower middle income
Namibia	Upper middle income
Nauru	Upper middle income
Nepal	Low income
Netherlands	High income
New Caledonia	High income
New Zealand	High income
Nicaragua	Lower middle income
Niger	Low income
Nigeria	Lower middle income
Northern Mariana Islands	High income
Norway	High income
Oman	High income

ECONOMY	INCOME GROUP
Pakistan	Lower middle income
Palau	High income
Panama	Upper middle income
Papua New Guinea	Lower middle income
Paraguay	Upper middle income
Peru	Upper middle income
Philippines	Lower middle income
Poland	High income
Portugal	High income
Puerto Rico	High income
Qatar	High income
Romania	Upper middle income
Russian Federation	Upper middle income
Rwanda	Low income
Samoa	Upper middle income
San Marino	High income
São Tomé and Principe	Lower middle income
Saudi Arabia	High income
Senegal	Low income
Serbia	Upper middle income
Seychelles	High income
Sierra Leone	Low income
Singapore	High income
Sint Maarten (Dutch part)	High income
Slovak Republic	High income
Slovenia	High income
Solomon Islands	Lower middle income
Somalia	Low income
South Africa	Upper middle income
South Sudan	Low income
Spain	High income
Sri Lanka	Lower middle income
St. Kitts and Nevis	High income
St. Lucia	Upper middle income
St. Martin (French part)	High income
St. Vincent and the Grenadines	Upper middle income
Sudan	Lower middle income
Suriname	Upper middle income
Swaziland	Lower middle income
Sweden	High income
Switzerland	High income
Syrian Arab Republic	Lower middle income
Taiwan, China	High income
Tajikistan	Lower middle income
Tanzania	Low income
Thailand	Upper middle income
Timor-Leste	Lower middle income
Togo	Low income
Tonga	Upper middle income
Trinidad and Tobago	High income
Tunisia	Lower middle income
Turkey	Upper middle income
Turkmenistan	Upper middle income
Turks and Caicos Islands	High income
Tuvalu	Upper middle income
Uganda	Low income
Ukraine	Lower middle income
United Arab Emirates	High income
United Kingdom	High income
United States	High income
Uruguay	High income
Uzbekistan	Lower middle income
Vanuatu	Lower middle income
Venezuela, RB	Upper middle income
Vietnam	Lower middle income
Virgin Islands (U.S.)	High income
West Bank and Gaza	Lower middle income
Yemen, Rep.	Lower middle income
Zambia	Lower middle income
Zimbabwe	Low income

Source: World Bank. How does the World Bank classify countries? Washington (DC): World Bank; 2016 (https://datahelpdesk.worldbank.org/knowledgebase/articles/378834-how-does-the-world-bank-classify-countries).

Annex 2: List of papers included

Notes:

The paper published by Hajjou et al. cites the Medicine Quality Database (MQDB) as a source of the data analysed in this study. For more granular analysis, the authors of this study directly used the data from the MQDB from 2007 to 2013.

There are four papers published by Bate et al. which have been counted as one because they relate to a continuous field survey.

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Annex 3: Model 1 – Childhood pneumonia, University of Edinburgh

Impact of substandard and falsified medicines in the treatment of childhood pneumonia: a first estimation of the potential impact on mortality

Introduction

The health impact of substandard and falsified medical products is generally accepted as important but is difficult to quantify in terms of disease burden that can be attributed to this cause. Available published data suggest that low- and middle-income countries (LMICs) are particularly affected. The lack of plausible and evidence-based estimates of attributable burden hinders efforts to raise awareness of this problem and advocate for appropriate priority to be given to tackling it. There is, therefore, a need for transparent and data-driven estimates of the attributable disease burden. Lack of high quality data from the majority of LMICs means that first estimates will depend largely on data modelling. It is important, however, that such modelling makes its assumptions and approaches explicit to enable them to be subject to peer review. Furthermore, estimates are presented with uncertainty ranges to reflect the limited data. It is hoped this study will serve as a basis for subsequent improved estimates and will incentivize investment to obtain improved data from more countries.

A first step will be to develop estimates of disease burden (globally and by region) associated with this problem that can serve as a basis for subsequent economic modelling which assesses health costs. This report considers the potential impact of substandard and falsified medicines on the treatment of childhood pneumonia, one of the main causes of child mortality globally *(1)* and a major reason for health service utilization *(2)*, and on the prescription of antibiotics globally. The report utilizes existing modelling conducted by the University of Edinburgh for estimating morbidity and mortality from childhood pneumonia globally *(2–4)*. The model uses data from large-scale surveys in LMICs, which attempt to estimate the level of use of antibiotics for the treatment of respiratory infections in young children and available data from published review articles on the prevalence of substandard and falsified medicines in order to make a first approximation of the potential impact of substandard and falsified medicines on mortality from childhood pneumonia. The study objectives were therefore:

1. to take estimates from WHO of the prevalence of use of substandard medicines for the treatment of childhood pneumonia and estimate their impact on pneumonia mortality;
2. to provide first rough estimates of the increased mortality by WHO region and globally that might be associated with their use.

Methods

Owing to the lack of data, this study has approached this question at a global level and at the level of two broad groups of "industrialized" and "developing" countries. It is possible to express the results by WHO region but uncertainties increase within more stratified groups since very few data are available to identify the pattern of variation of prevalence of substandard and falsified antibiotics across these regions.

Global burden of childhood (0–5 year) acute lower respiratory infection (ALRI)[1]

It is assumed that all child pneumonia deaths come from **severe** pneumonia cases.

The number of deaths, number of severe cases of pneumonia and case fatality ratio (CFR) of severe pneumonia cases globally in young children was estimated. This was done globally and separately for industrialized and developing countries and also in two settings – in the hospital and community settings *(2)*.

It is assumed that all children admitted to hospital with severe pneumonia receive antibiotic treatment but that only a percentage of children with severe pneumonia who are not admitted to hospital receive antibiotic treatment (and it is assumed that this percentage is the same as the Demographic and Health Surveys (DHS)/Multiple Indicator Cluster Surveys (MICS) indicator from large-scale representative population surveys on the percentage of cases of suspected pneumonia in children that report receiving antibiotic treatment).

1 ALRI is referred to hereafter as "pneumonia".

Three different levels of global prevalence of substandard and falsified antibiotics used for the treatment of childhood pneumonia are considered (1%, 5%, and 10%) and it is assumed that these result in an increased CFR (either a two-fold increase consistent with a reduced antibiotic activity/reduced efficacy of substandard and falsified antibiotics or a four-fold increase consistent with a zero antibiotic activity/efficacy of substandard and falsified antibiotics) against childhood pneumonia. The available literature suggests that the former scenario is the more plausible. These assumptions were applied separately in industrialized and developing country regions and in hospital and community settings to the number of severe pneumonia cases and the CFRs that were estimated in each of these groups. Estimates were then made of the number of excess deaths that result due to this increased CFR associated with the use of substandard and falsified antibiotics. The steps followed were:

Estimate 1. The **global number of deaths from pneumonia in young children in 2010** globally and by WHO region was estimated.

- Globally, this is 1.4 (1.19–1.64) million (from *(1)*).
- For methods see Appendix note 1.

Estimate 2. The **global number of severe pneumonia cases in young children in 2010** globally and by WHO region was estimated.

- This is 19.2 (15.6–23.8) million (based on *(5)*).
- For methods see Appendix note 2.

Estimate 3. The **global number of *hospitalized* severe pneumonia cases in young children in 2010** globally and by WHO region was estimated. We assume **all** these children are given antibiotic treatment.

- This is 11.9 (10.3–13.9) million (from *(2)*).
- For methods see Appendix note 3.

Estimate 4. The **CFR in hospitalized cases of severe pneumonia cases in young children in 2010** globally and by WHO region was estimated.

- This is 2.1% (1.4–3.1%) (from *(2)*)
- For methods see Appendix note 4.

Estimate 5. The **global number of pneumonia deaths which occur in hospital** in young children globally and by WHO region was calculated.

- This is given by [estimate 3 x estimate 4]

From these estimates the following was *inferred*:

Estimate 6. The **global number of deaths from pneumonia in young children in 2010** which do not reach hospital: globally and by WHO region.

- Globally, this is 1.13 (1.03–1.19) million
- This is given by [estimate 1 – estimate 5]

Estimate 7. the **global number of severe pneumonia cases in young children in 2010 which do not reach hospital**: globally and by WHO region**.**

- Globally, this is 7.3 (5.3–9.9) million
- This is given by [estimate 2 – estimate 3]

Estimate 8. the **global number of severe pneumonia cases in young children in 2010 which do not reach hospital and who receive/do not receive antibiotic treatment**: globally and by WHO region.

- We assume that only a percentage of these children who do not reach hospital are given antibiotic treatment.
- For industrialized countries we assume that this is 90%.
- For developing countries, the percentage of children that receive treatment is based on a median from all DHS/MICS data estimates of percentage “suspected pneumonia” reported to have received antibiotic treatment (and assuming that this would be the same for severe pneumonia).
- For methods see Appendix note 5.
- Thus we have generated estimates of the number of severe pneumonia cases in the community that do and do not receive antibiotic treatment (separately for industrialized and developing countries).
- *Note*: there are data on this parameter from many developing countries so they could be used to vary estimates by region in a future revision.

Estimates of the prevalence of substandard and falsified antibiotics (for the treatment of severe pneumonia in young children) and their level of activity

Prevalence of substandard and falsified antibiotics

There are insufficient reliable large-scale population-based data on the prevalence of substandard and falsified antibiotics (which are used for the treatment of childhood pneumonia) in individual countries or regions of the world to serve as a good parameter data for a modelling exercise. It was therefore decided to consider a range of likely scenarios. According to WHO, up to 10% of the drugs worldwide are falsified *(6)*. Fifty per cent of the cases reported involved antibiotics and 78% were from developing countries *(6)*. Three possible scenarios have been developed based on this information.

- **Global prevalences of substandard and falsified antibiotics of 1%, 5% and 10% as a range** within which the true value may lie.
- *Note*: these values could be changed to others that are considered to be more plausible.

Impact of substandard and falsified antibiotics on treatment efficacy for childhood pneumonia

There are no large-scale representative data on the **pharmaceutical activity of circulating substandard and falsified antibiotics** (used for the treatment of childhood pneumonia) nor are there data on the **impact of a reduced level of activity on treatment efficacy in childhood pneumonia.** This applies not only to reduced activity due to reduced active ingredient, but also taking into account an unknown level of change in treatment to an alternative active agent when the child does not respond to initial treatment with a substandard or falsified antibiotic. Thus, there are insufficient data to serve as good parameter data for a modelling exercise. We have selected scenarios based on the possible impact of substandard and falsified antibiotics on the CFR for severe childhood pneumonia.

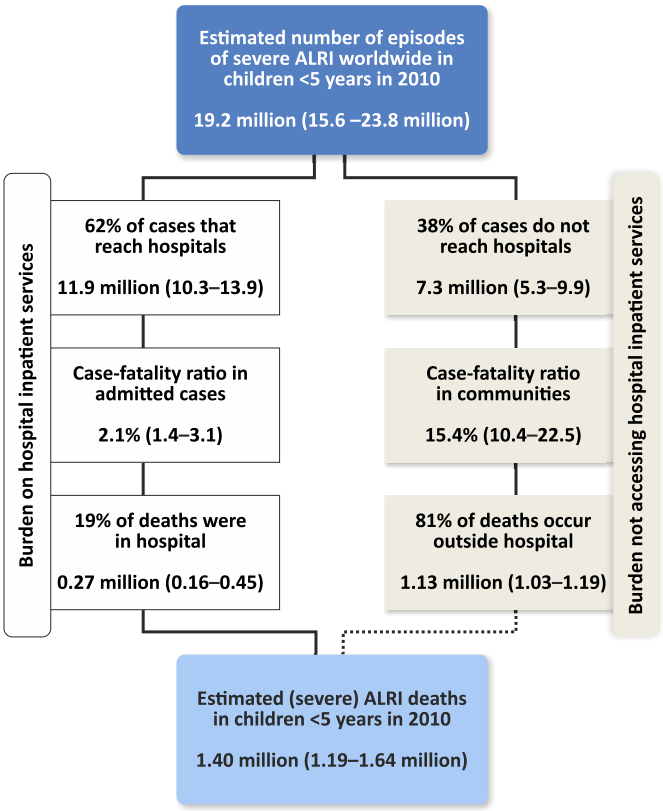
- The following settings have been considered:
  - severe pneumonia cases admitted to hospital in developing countries;
  - severe pneumonia cases not admitted to hospital in developing countries (community management only);
  - severe pneumonia cases admitted to hospital in industrialized countries;
  - severe pneumonia cases not admitted to hospital in industrialized countries (assumed to be zero).

- Within these settings it has been assumed that the use of substandard and falsified antibiotics is associated with either:
  - *a two-fold increase in the CFR* (which is found in each of these four settings) consistent with a reduced activity/ reduced efficacy for the treatment of childhood pneumonia;
  - *a four-fold increase in the CFR* (which is found in each of these four settings) consistent with zero activity/no efficacy for the treatment of childhood pneumonia.

- *Note*: these could be changed to other values if those were considered to be more plausible or more consistent with published data (now or in the future as more data become available).

Fig. A3.1 (from *(2)*) summarizes the parameter estimates for estimates 1–7 in the year 2010. This shows the numbers of cases of severe pneumonia treated in hospital and in the community and their CFRs (for both industrialized and developing countries).

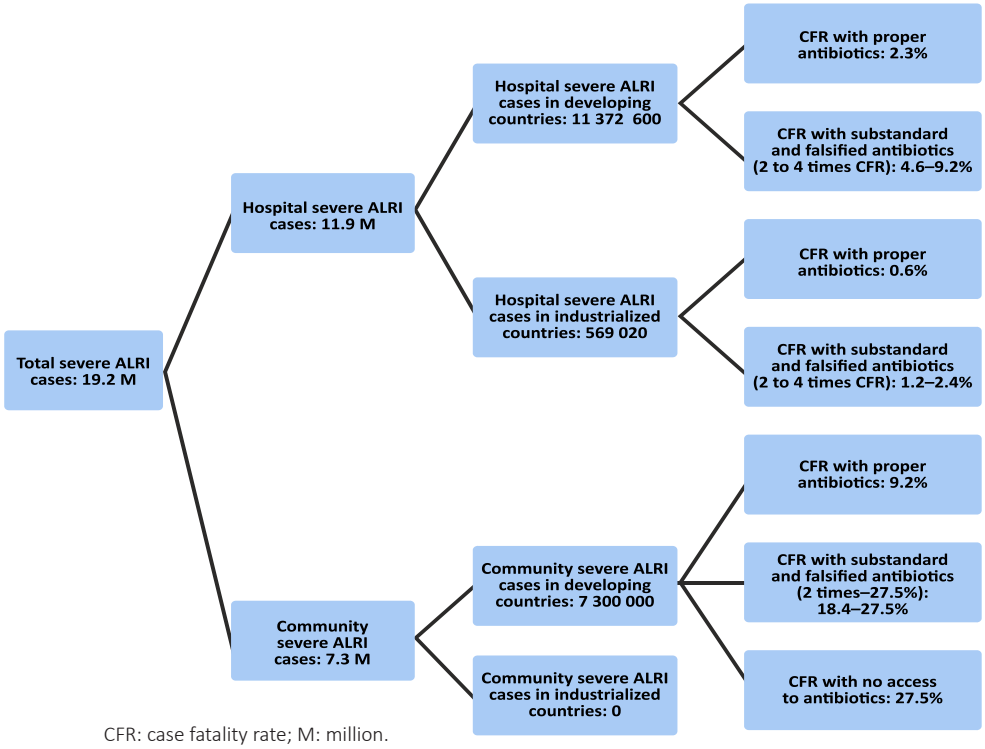
Fig. A3.1: Parameter estimates for acute lower respiratory infection (ALRI) in 2010 (adapted from *(2)*)



ALRI: acute lower respiratory infection.

The framework shown in Fig. A3.2 considers scenarios in which the use of substandard and falsified antibiotics increases the CFR (in each industrialized country, developing country and hospital or community setting) compared to "true" antibiotic treatment.

Fig. A3.2: Framework for estimation of impact of substandard and falsified antibiotics on childhood pneumonia treatment outcomes.



CFR: case fatality rate; M: million.

Note: Currently it is assumed that the prevalence of substandard and falsified antibiotics is 0% and scenarios in which prevalence of substandard and falsified medicines is 1, 5 or 10% are considered to give some indication of the likely magnitude of the impact. However, it is possible to assume a current level of 1, 5 or 10% and then estimate how much lower the number of deaths would be if this was reduced to 0% (or a lower prevalence level).

Results

Table A3.1 summarizes the findings on excess deaths from severe pneumonia due to substandard and falsified antibiotics at prevalence levels of 1%, 5% and 10% (assuming that substandard and falsified antibiotics results in a two- or four-fold increase in CFR). Globally, this shows a very wide variation from:

Assuming a two-fold increase in CFR (most likely scenario)

- From 8688 deaths at 1% prevalence of substandard and falsified antimicrobials to 72 430 deaths at 10% prevalence.
- Number of deaths associated with a 1% increase in prevalence of substandard and falsified antibiotics is 7082.

Assuming a four-fold increase in CFR (alternative scenario)

- From 18 372 deaths at a 1% prevalence of substandard and falsified antibiotics to 169 271 deaths at a 10% prevalence.
- Number of deaths associated with a 1% increase in prevalence of substandard and falsified antibiotics is 16 766.

Table A3.1: Excess deaths from severe ALRI due to substandard and falsified antibiotics (hospitals and community)[a]

All countries		
Prevalence of substandard and falsified medicines (percentage)	**Excess deaths (two-fold increase in CFR)**	**Excess deaths (four-fold increase in CFR)**
1	8 688	18 372
5	37 018	85 438
10	72 430	169 271

ALRI: acute lower respiratory infection; CFR: case fatality rate.

[a] For methods see Appendix note 6.

For a more direct comparison with the estimates of the model on substandard and falsified malaria treatments (Annex 4), equivalent estimates just for the WHO African Region are provided in Table A2.2. The findings are expressed as the number of deaths associated with substandard and falsified medicines per 1% increase in prevalence of such medicines in the WHO African Region.

Table A3.2: Excess deaths from severe ALRI due to substandard and falsified medicines in the WHO African Region (hospitals and community)

Prevalence of substandard and falsified medicines (percentage)	Excess deaths (two-fold increase in CFR)	Excess deaths (four-fold increase in CFR)
1	2 253	5 784
5	10 241	27 893
10	20 225	55 528

ALRI: acute lower respiratory infection; CFR: case fatality rate.

The estimated number of deaths in the WHO African Region associated with a 1% increase in prevalence of substandard and falsified medicines is 1 997 (two-fold increase in CFR) or 5 527 (at four-fold increase in CFR).

The Excel file (available on the WHO substandard and falsified medical products website) shows details of the calculations which led to the estimates of:

- The Excel calculation for *global* excess deaths in **hospitalized severe pneumonia cases** (for 1%, 5% and 10% prevalence of substandard and falsified medicines, where CFR increases by two- or four-fold) globally; (and for developing countries and industrialized countries)
- The Excel calculation for excess deaths in **non hospitalized severe pneumonia cases** (for 1%, 5% and 10% prevalence of substandard and falsified medicines, by whether there has been access to antibiotic treatment, and where CFR increases by two- or four-fold for developing countries

- The Excel calculation for *global* overall excess deaths in severe pneumonia cases (for 1%, 5% and 10% prevalence of substandard and falsified medicines and where CFR increases by 2 or 4 fold
- The Excel calculation for *African Region* excess deaths in **hospitalised severe pneumonia cases** (for 1%, 5% and 10% prevalence of substandard and falsified medicines, where CFR increases by 2 or 4 fold) globally;
- The Excel calculation for *African Region* excess deaths in **non hospitalised severe pneumonia cases** (for 1%, 5% and 10% prevalence of substandard and falsified medicines, by whether there has been access to antibiotic treatment, and where CFR increases by two- or four-fold
- The Excel calculation for *African Region* overall excess deaths in severe pneumonia cases (for 1%, 5% and 10% prevalence of substandard and falsified medicines and where CFR increases by two- or four-fold

The spreadsheet can be re-run for alternate parameter settings now or when new data become available to update these parameter estimates.

Discussion

Need for estimates of health impact of substandard and falsified medicines

The lack of estimates of the health impact associated with the use of substandard and falsified antimicrobials has limited efforts to raise awareness of this problem and hindered efforts to determine the priority that should be given to tackling it. This report provides a first estimate of the potential impact of substandard and falsified antimicrobials on the treatment of childhood pneumonia, a major cause of antimicrobial prescription and child death globally. Lack of high quality data on the prevalence of the use of substandard and falsified antimicrobials in the treatment of children globally and on the proportion of young children with pneumonia who are treated with antimicrobials means that it is only possible to provide estimates based on a range of plausible assumptions informed by available published reviews *(6–9)*. Limitations of the available data, range of explicit parameter levels and the likely direction of bias are presented together with these estimates to promote critical review and guide interpretation. It is hoped that these estimates will encourage improved data collection from more countries, increased reporting, and the subsequent development of improved estimates.

Estimated impact of the use of substandard and falsified antimicrobials for the treatment of childhood pneumonia

Based on a broad plausible range of prevalence of the use of substandard and falsified antimicrobials for the treatment of childhood pneumonia globally, the estimates from this analysis suggest that:

- 8 688 childhood pneumonia deaths can be attributed to the use of substandard and falsified antimicrobials (based on a prevalence of substandard and falsified antimicrobials of 1%).
  - The number of deaths increases to 18 372 if it is assumed that substandard and falsified antibiotics have no activity.
- 37 018 childhood pneumonia deaths can be attributed to the use of substandard and falsified antimicrobials (based on a prevalence of substandard and falsified antimicrobials of 5%).
  - The number of deaths increases to 85 438 if it is assumed that substandard and falsified antibiotics have no activity.
- 72 430 childhood pneumonia deaths can be attributed to the use of substandard and falsified antimicrobials (based on a prevalence of substandard and falsified antimicrobials of of 10%).
  - The number of deaths increases to 169 271 if it is assumed that substandard and falsified antibiotics are assumed to have no activity.

Thus, if the assumptions made in these estimates are correct, the use of substandard and falsified antimicrobials may be associated with a substantial number of child deaths globally. These represent a variable proportion of all child pneumonia deaths depending on the prevalence of substandard and falsified antimicrobials (0.6% at 1% prevalence; 2.6% at 5% prevalence; 5.2% at 10% prevalence).

- This increases to (1.3% at 1% prevalence of substandard and falsified antimicrobials; 5% at 5% prevalence and 12.1% at 10% prevalence) of all child pneumonia deaths.

Limitations of the childhood pneumonia model

There are a number of important limitations relating to the available data and the modelling approach adopted.

Mortality estimates

These are described by Liu et al. *(1)* and Theodoratou et al. *(4)*. Briefly, the main limitations are due to the following.

- The scarcity of vital registration (VR) data – medically certified VR data were only available for about 3% of deaths of children aged under 5 years *(1)*. This lack of data is particularly evident in sub-Saharan Africa.
- The relatively limited availability of verbal autopsy studies and their imperfect validity for the identification of deaths from childhood pneumonia due to known misclassification errors *(1)*.
- Data on model covariates not being complete and resulting in the potential for model biases in the relationship between deaths from childhood pneumonia and explanatory variables *(1, 10)*.

Estimates of severe pneumonia and hospitalized severe pneumonia episodes

- These are limited by the relatively small number of high-quality data points from LMICs and by the variable case definitions across studies.

Estimates of the use of antimicrobials for the treatment of children presenting with pneumonia globally

- This is not well known. The best available data, which are reported from large-scale surveys in many LMICs, are from the MEASURE Demographic and Health Surveys and the United Nations Children's Fund (UNICEF) Multiple Intervention Cluster Surveys *(11)*. However, the denominator for these population-based surveys is reported episodes of suspected pneumonia rather than true pneumonia. Since many of these episodes may not represent true pneumonia *(11)* it is possible that this treatment indicator under-represents the true proportion of children with pneumonia that are treated with antimicrobials and this in turn will result in the model tending to *under-represent* the number of deaths from childhood pneumonia that could be averted by the reduction of the use of substandard and falsified antimicrobials.
- In the absence of separate data on antimicrobial use in neonates with pneumonia we have made estimates for the 0–59-month age group, assuming no difference in antimicrobial use or effectiveness of antimicrobials for the treatment of pneumonia in the 0–1-month and 1–59-month age groups. This assumption is not likely to be correct. A (likely) lower level of antimicrobial use in 0–1-month-olds than in children aged 1–59 months and a (likely) lower effectiveness of antimicrobial treatment in this age group will result in the model tending to over-represent the number of deaths from childhood pneumonia that could be averted by the reduction of the use of substandard and falsified antimicrobials.

Current model estimating impact of the use of substandard and falsified antimicrobials

There are insufficient data from which to estimate global, regional and national estimates of the use of substandard and falsified antimicrobials. Available data do not come from studies in which systematic samples were taken from known populations at risk or from carefully documented sampling of large-scale (regional or national) stores of antimicrobials which are then subject to testing for antimicrobial activity. Data are also not reported routinely by age group so as to identify data relevant to children. Thus, a (wide) range of plausible estimates (1–10% prevalence of substandard and falsified antimicrobials) applied to all settings was used in this exercise, based on published reviews of the use of substandard and falsified antimicrobials. This is clearly a major simplification of the true picture but there were insufficient data to make valid distinctions between settings in terms of prevalence of substandard and falsified antimicrobials. It was assumed that substandard and falsified antimicrobials might result in two- or four-fold increases in CFR (consistent with reduced or no activity), but this is based on a range of plausible values and not on published data.

WHO initiatives to promote more complete reporting of significant instances of wide-scale use of substandard and falsified medicines globally should improve the evidence base over time. Furthermore, WHO's advocacy for the importance of this issue may result in greater investment in research studies to describe the scale of this problem globally. However, it is not yet possible to make precise estimates of the health impact associated with this problem. This model therefore provides a first rough estimate of the possible scale of this problem as it relates to childhood pneumonia based on a range of plausible scenarios and making explicit the many limitations of the available data and of the models employed.

The use of substandard and falsified products has broader health and economic impacts that have not been considered in this exercise, for example, indirect impacts due to erosion of public trust in health services *(12)* and to promotion of antimicrobial resistance *(7)*. Thus our modelled estimates will *under-represent* the true health impact of these products on the treatment of childhood pneumonia.

Future research

There is a need for data on the prevalence of use of substandard and falsified antimicrobials from large-scale studies with carefully documented random or systematic sampling followed by testing for antimicrobial activity. Adoption of standard definitions that can be applied in most settings would help ensure international comparability of data. Results should be reported by type and class of antibiotic and/or by indication for treatment. Studies to identify risk factors associated with high prevalence of substandard and falsified medicines could enable data on these covariates to be gathered and used to model variability in the prevalence of substandard and falsified medical products in different countries or settings (rather than using common estimates for all countries, owing to lack of data, as in this exercise).

Conclusions

The estimated impact of substandard and falsified antimicrobials on deaths from childhood pneumonia suggests that this could represent a modest but important percentage of all child pneumonia deaths. These merit priority attention in global and national pneumonia control programmes since these deaths are avoidable and the use of substandard and falsified antibiotics will undermine public confidence in the health system. There may be countries or regions in which the use of substandard and falsified antimicrobials may exceed these modelled prevalence levels and in which a higher priority for the issue within child pneumonia control programmes may be appropriate. A true estimate of the health impact of this problem will require an overview of its impact on a much broader range of health problems and related treatment practices. In aggregate the use of substandard and falsified medical products could result in substantial health impacts. This might merit priority attention in

the form of a cross-cutting control programme with links to a range of specific disease control programmes. In this context, attention to actions to control the use of substandard and falsified antimicrobials in the treatment of childhood pneumonia would be one important aspect.

Action on this problem will first require intensified efforts to gather and report data on instances of large-scale substandard and falsified antimicrobial use so that the true scale of this problem can be estimated and improved impact models can be developed. It is important that these data are gathered in a standard format which includes details of a denominator base (so that prevalence rate can be assessed), information on the level of activity of the substandard and falsified product, the range of indications for its use and the age group distribution of the people who were prescribed the product. Provisional estimates from this modelling exercise suggest that action on this problem merits further investment to continue to estimate the prevalence of use of substandard and falsified medical products, the scale of the related health impact and regional and national variations.

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Appendix: Childhood pneumonia

SOURCE OF ESTIMATES IN FIGURE A3.1

Appendix Note 1

Estimation of child pneumonia mortality

Detailed descriptions of the input data and statistical methods applied for the estimation of child pneumonia mortality estimates have been published previously *(1, 3)*. In brief, the distributions of child mortality for all causes of death were estimated separately for neonates and children aged 1–59 months. Based on data availability and quality, one of various methods was applied. First, vital registration data reported to WHO for countries with an adequate vital registration system (>80% coverage of vital events with high-quality data) was used. Second, for countries with low rates of under-5 mortality, but inadequate vital registration data, a vital registration data-based multi-cause model was used, applying a multinomial logistic regression framework. Third, for countries with high under-5 mortality, a verbal autopsy data-based multi-cause model was used, applying a multinomial logistic regression framework similar to that used for countries with low mortality and inadequate vital registration data. For India, a state-level verbal autopsy data-based multi-cause model was developed with only Indian subnational verbal autopsy data for children aged 1–59 months, and that used the global verbal autopsy model described above for neonates. For China, data for child mortality by cause from Chinese literature was applied to develop single-cause model-based estimates (5). Once the proportional distribution of child mortality by cause was estimated for each country-year, these estimates were applied to the annual numbers of deaths in children aged 1–59 months and neonates as estimated by the United Nations Inter-Agency Group for Child Mortality Estimation (UN-IGME). We then aggregated these results to obtain regional and global estimates for the overall under-5 age group.

Appendix Note 2

Estimation of number of child severe pneumonia cases

- See *(2)*

Appendix Note 3

Estimation of number of cases of hospitalization of children with severe pneumonia

- See *(2)*

Appendix Note 4

Estimation of CFR in hospitalized severe pneumonia cases

- See *(2)*

Appendix Note 5

Estimation of the global number of severe pneumonia cases in young children in 2010 which do not reach hospital and who receive/do not receive antibiotic treatment:

- The prevalence of access to antibiotics was obtained from UNICEF's Global databases (Update: SOWC 2013). These data are based on the MICS and DHS studies (Question "Antibiotic treatment for suspected pneumonia – Percentage of children under age 5 years with *suspected* pneumonia (cough and fast or difficult breathing due to a problem in the chest) in the two weeks preceding the survey who received antibiotics"). Data are available for 76 countries. For low mortality countries (under 5 mortality rate ≤25/1000 live births in 2013), we could assume access to antibiotics to be 90%.

Appendix note 6

To calculate the excess from severe ALRI due to *SF* in Africa (community) we did as follows:

1. AFR severe hospitalized cases = 3 014 000 *(2)*
2. AFR CFR in these cases =3.9% *(2)*
3. Infer the AFR hospital deaths = 117 546 deaths
4. All AFR ALRI deaths (from CHERG) = 603 840 *(1)*
5. Non hospital deaths (4–3) = 486 294
6. All severe ALRI cases = 4 298 171 *(5)*
7. Non hospital severe ALRI cases (6-1) = 1 284 171
8. Non hospital overall CFR (5/7) = 37.87%
9. AFR access to antibiotics = 41%
10. AFR non hospital CFR for antibiotics = 15.6% (4 times CFR in hospital with treatment)
11. AFR non hospital CFR for no antibiotics = 53.6% (to fit the overall envelope of deaths in AFR community)

Annex 4: Model 2 – Malaria, London School of Hygiene and Tropical Medicine

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Prepared for: **World Health Organization**

Final Report : 2 May 2016 (revised September 2017)

Note: The report has been converted from PowerPoint slides to publishable format.

Contents

Introduction

The London School of Hygiene and Tropical Medicine (LSHTM) was engaged by the World Health Organization to model the health and economic cost of substandard and falsified (SF) drugs for firstline treatment of uncomplicated Plasmodium falciparum malaria in sub-Saharan Africa (SSA).

The analysis was conducted by comparing two options: **Real World scenario**: based on an assessment of current levels of substandard and falsified antimalarial drugs; and an **Ideal Antimalarial Quality** scenario, where all antimalarials contain acceptable active pharmaceutical ingredient (API) (defined here as 85 –115% API).[1]

The report considers:

- health impact: measured in terms of deaths and disability adjusted life years (DALYs); and
- economic cost: patient and provider costs related to additional treatment seeking and further care due to failure of initial treatment.

1 The International Pharmacopoeia states an acceptable range of 90–110% API for artemisinin-based antimalarials. Similar to recent, large-scale studies (e.g. ACT Consortium & IMPACT2 2015, Kaur et al. 2015), a more conservative range of 85–115% API was adopted for this analysis.

Results were estimated for a hypothetical cohort of 1 million malaria cases seeking treatment, containing a mix of low transmission (<10% parasitaemia in patients presenting with fever) and high transmission (>10% parasitaemia in patients presenting with fever) cases. Total health and economic impact of SF in SSA was also modelled, based on annual malaria case estimates.

Methods

Methodological challenges

A number of key challenges were identified in conducting the analysis. We list these below, and summarize our approach to tackling each one.

Table A4.1 Methodological challenges

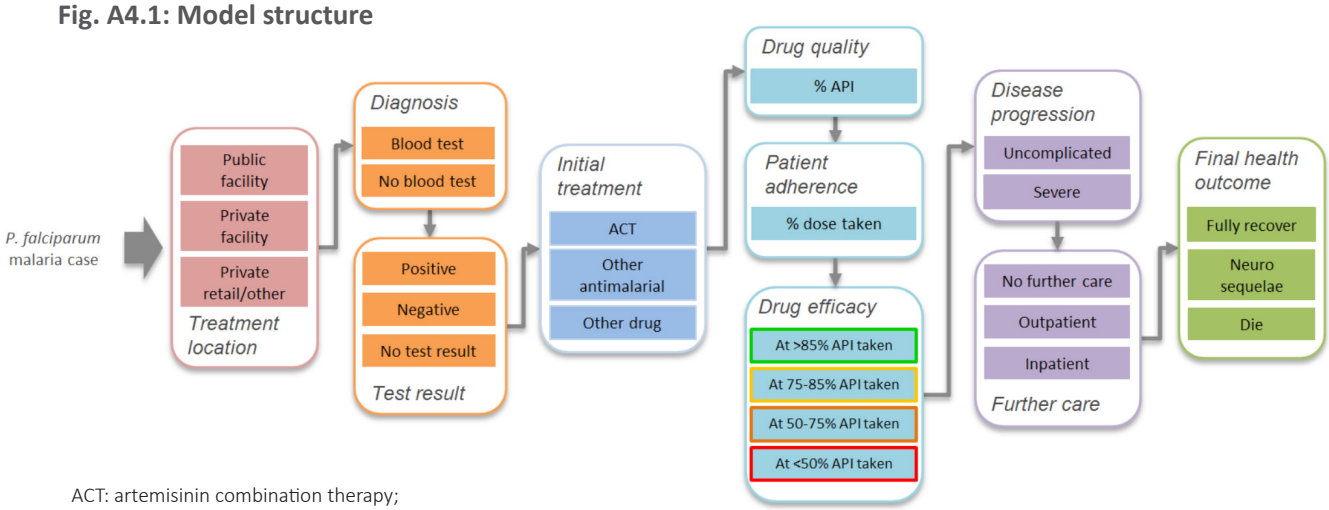
Challenges	Approach
Lack of empirical data on link between drug quality and treatment failure/health outcomes (e.g. deaths).	Model impact of drug quality on a cohort of malaria patients using a decision – tree model of febrile illness
Not all antimalarials outside therapeutic range are ineffective. Drug effectiveness decreases with the amount of API consumed (including both drug quality and patient adherence).	Estimate reductions in effectiveness based on API consumed.
Higher transmission settings lead to increased immunity, which affects the likelihood of progression to severe disease and death.	Define two broad transmission strata (low and high), with differing parameters for disease progression and death.
High degree of uncertainty across many parameters.	Conduct various types of sensitivity analysis to investigate impact of individual parameters.

API: active pharmaceutical ingredient.

Model structure

- Based on a decision–tree model of febrile illness. Follows *P. falciparum* malaria case from initial presentation (public facility, private facility, private retail/other) to final health outcome.
- Drug quality parameters differ between the “real world” and “ideal antimalarial quality” options. All other parameters are the same between these two scenarios.

Fig. A4.1: Model structure



ACT: artemisinin combination therapy;
API: active pharmaceutical ingredient.

Inputs and assumptions

Drug quality

- Model parameters for drug quality were based on a literature review of antimalarial quality studies provided by WHO (PubMed and MEDLINE databases) and cross-referenced with the WorldWide Antimalarial Resistance Network (WWARN) Antimalarial Quality Surveyor.[2]
- Screened studies based on inclusion criteria:
  - sub-Saharan Africa;
  - publication date between 2001 and 2016; and
  - "Random survey" collection type (i.e. excluding convenience surveys, case reports, etc).
- Search results: we identified 10 papers, covering 17 countries. Seven papers reported on ACTs, and 7 on non-ACT antimalarials. Five papers concerned medicines obtained from the private sector and 5 were mixed (public and private) studies.
- All papers reported proportion of "failed" samples (outside therapeutic range – e.g. 85–115% API). Average failure rates were separately calculated for ACT and non-ACT antimalarials, as the weighted average of failure rates for individual drug types reported for each study.[3]
- Seven papers reported whether failures were above or below the API range. The remaining papers only reported whether failures were outside the range. For these papers, the proportion of failures that were <85% API were interpolated from the other seven studies.

2 www.warn.org/about-us/medicine-quality.
3 For ACTs, where % API was reported for both the artemisinin and the partner drug, a failure was recorded if either drug was outside the API range.

Table A4.2: Artemisinin combination therapy (ACT) quality studies

First author	Publication year	Country	Sector	Type of facilities	Number of samples	% outside API range	% below API range
ACT Consortium Drug Quality Project Team	2015	United Republic of Tanzania	Private	Retail outlets	1 281[a]	8.7%	5.1%
Affum	2013	Ghana	Private	Chemical sales outlets	16	6.3%	6.3%
Kaur	2015	Nigeria	Mix	Pharmacies, patent medicine vendors, public facilities	2 640[b]	7.8%	7.8%
Nyarko	2013	Ghana	Private	Pharmacies	9	66.7%	55.6%
Visser	2015	Gabon	Private	Pharmacies	338	0.3%	0.3%
WHO	2009	Various	Mix	Public/private wholesale & retail outlets; informal sector	105[c]	9.8%	9.8%[d]
WHO	2011	Various	Mix	Public/private wholesale & retail outlets; informal sector	112	7.6%	7.6%
Median							**7.6%**

[a] These findings are also supported by clinical data. The WorldWide Antimalarial Resistance Network (WWARN), for example, amalgamates and analyses
[b] Excluding samples collected by convenience sampling.
[c] Excluding 'Central' distribution: importers, central medical store, manufacturers, NGO central stores.
[d] % below API range interpolated from other studies.

Table A4.3: ACT quality studies[a]

First author	Publication year	Country	Sector	Type of facilities	Number of samples	% outside API range	% below API range
Kaur	2008	United Republic of Tanzania	Private	Retail outlets	301	12.0%	10.4%[b]
Kaur	2015	Nigeria	Mix	Pharmacies, patent medicine vendors, public facilities	188[c]	8.0%	6.9%
Onwujekwe	2009	Nigeria	Mix	Public and private providers	225	26.7%	23.1%[b]
Sawadogo	2011	Various	Mix	Various (pharmacies, stores, suppliers, medical centres, peddlers)	18[d]	27.8%	11.1%
Visser	2015	Gabon	Private	Pharmacies	94	1.1%	1.1%
WHO	2009	Various	Mix	Public/private wholesale & retail outlets; informal sector	80[e]	18.8%	16.3%[a,b]
WHO	2011	Various	Mix	Public/private wholesale & retail outlets; informal sector	94	2.1%	2.1%
Median							**10.4%**

[a] Range excludes lowest and highest values of the seven studies.
[b] % below API range interpolated from other studies.
[c] Including artemisinin monotherapy. Excluding samples collected by convenience sampling.
[d] Excluding non-retail distribution (e.g. wholesalers).
[e] Excluding 'Central' distribution: importers, central medical store, manufacturers, NGO central stores.

Impact on drug efficacy

- Efficacy of good quality ACT and other (non-ACT) antimalarials estimated from SSA studies reported by WWARN Explorer.[4]
- Reductions in efficacy due to insufficient API were estimated based on API category,[5] for low and high transmission settings.
- Distribution of failed drugs by API category was estimated based on two large studies that provide such a distribution: ACT Consortium Drug Quality Project Team and IMPACT2 Study Team 2015 *(1)* and Kaur et al 2015 *(2)*.[6]

4 www.wwarn.org/tracking-resistance/wwarn-explorer
5 See description of API categories.
6 Distribution for *(2)* provided from additional analysis of data provided in supplementary materials.

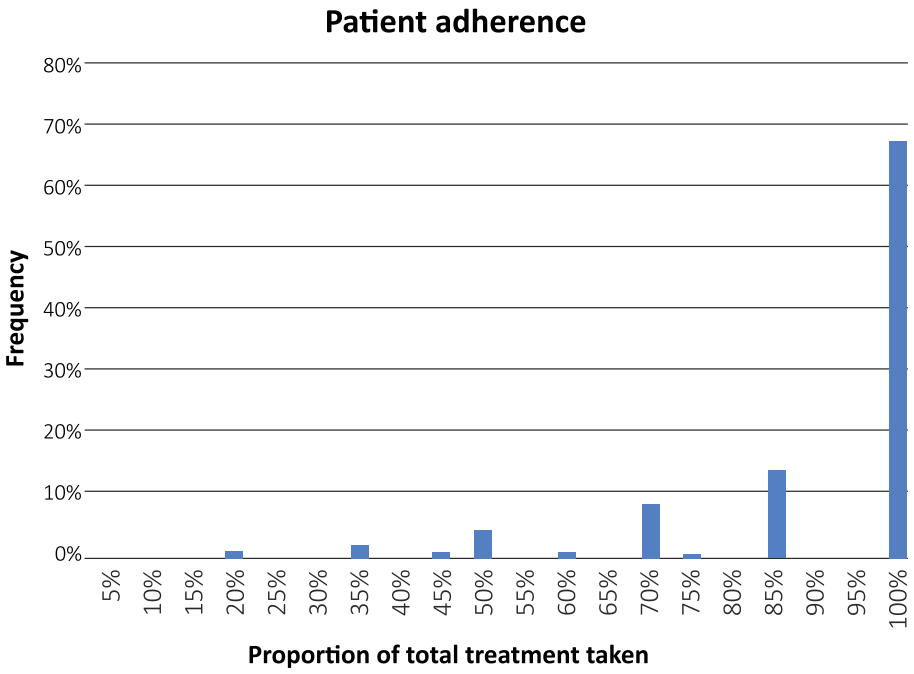
Table A4.4: Estimates of efficacy of ACT and non-ACT medicines by % API category

% API present	Low transmission			High transmission		
	Reduction in efficacy	ACT efficacy	Other antimalarial efficacy	Reduction in efficacy	ACT efficacy	Other antimalarial efficacy
>85%	–	98.6%	78.0%	–	98.6%	78.0%
75-85%	30%	69.0%	54.6%	25%	74.0%	58.5%
50-75%	60%	39.4%	31.2%	50%	49.3%	39.0%
<50%	100%	0.0%	0.0%	100%	0.0%	0.0%

Patient adherence

- As well as drug quality, the amount of API consumed is also determined by the dose taken. This is affected by patient adherence to treatment.
- Adherence adapted from additional analysis of adherence data in *(6)* (United Republic of Tanzania, artemether-lumefantrine), which gives a distribution of patients by the number of pills taken.

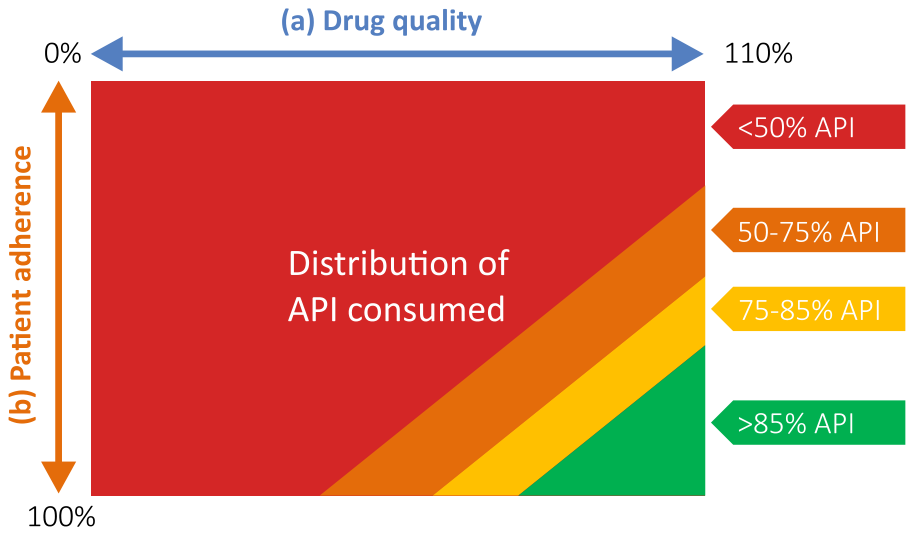
Fig. A4.2: Distribution of "proportion of total treatment taken" based on Bruxvoort et al. 2015 *(6)*



Treatment effectiveness

The proportion API consumed is calculated as the product of: (a) API distribution due to drug quality, and (b) the dose taken due to adherence.

Fig. A4.3: Calculation of distribution of API consumed



Treatment effectiveness is calculated by applying relevant efficacy reductions to the API categories in the above matrix.

Table A4.5 compares mean ACT and non-ACT effectiveness for "real world" and "ideal antimalarial quality" options.

Table A4.5: mean ACT and non-ACT effectiveness

	Real World	Ideal antimalarial quality
Mean ACT effectiveness		
Low transmission	75.1%	80.3%
High transmission	76.9%	82.0%
Mean non-ACT effectiveness		
Low transmission	60.5%	63.5%
High transmission	62.3%	64.9%

Other key inputs and assumptions

Table A4.6: Summary of additional model inputs and assumptions

Parameter	Value	Source
Age	Under 5 years of age: 45% Over 5 years of age: 55%	Assumptions based on review of literature[a]
Treatment location	Public facility: 25% Private facility: 10% Private retail/other: 65%	
Blood test	Public/private facility: 60% tested, 40% not tested Private retail/other: no testing	
Initial antimalarial treatment	Low transmission: 90% with positive test, 20% with negative test, 80% with no test High transmission: 80% with positive test, 20% with negative test, 70% with no test	
Test accuracy	Sensitivity: 95%	Adapted from RDT sensitivity (systematic review): *(7)*
Progression to severe disease (where no/unsuccessful treatment)	Low transmission setting: 30% (under 5 years), 18% (over 5 years) High transmission setting: 10% (under 5 years), 2% (over 5 years) Assumes rate of progression to severe disease where treatment is not successful is the same as progression without treatment.	Adapted from *(8)*
Further care (where no/unsucessful treatment)[b]	Uncomplicated: 48% outpatient, 52% no further care Severe: 75% inpatient, 25% no further care	Uncomplicated: *(9)* Severe: assumption
Case fatality rate (severe disease) with no further care	Low transmission: 73% (under 5 years), 70% (over 5 years) High transmission: 60% (under 5 years), 45% (over 5 years)	*(8)*
Case fatality rate (severe disease) with further (inpatient) care	Low/high transmission: 10%	Adapted from *(9,10)*
Probability of neurological sequelae (severe disease)	Under 5 years of age: 3.5% Over 5 years of age: 1.5%	*(9)*

Parameter	Value	Source
Cost of further care, per case treated (US$ 2017)[c]	Outpatient visit: $3.95 Inpatient visit: dies $19.00, recovers $23.87	WHO-CHOICE (median of Kenya, Nigeria, Uganda, United Republic of Tanzania); *(9,10)*; International drug price indicator guide 2014
Disability–adjusted life years (DALYs)	Under 5 years: life expectancy at 1-4 years (62.5 years) Over 5 years: life expectancy at 25-29 years (43.4 years) Discounted years of life lost (per death): 28.22 (under 5 years), 24.3 (over 5 years) Discounted years of life lived with a disability (per neurological sequelae case): 15.30 (under 5 years), 13.1 (over 5 years)	Consistent with standard DALY methodology; without age weights. Life expectancy (LE): WHO life tables, Africa, 2015 (mean of male & female LE). Discounted at 3% per annum. Neurological sequelae disability weight: *(11)* ("Motor plus cognitive impairments: severe") (0.542)
Proportion of malaria cases in the cohort that are in low/high transmission settings	10% of total cases in low transmission setting (remaining 90% of cases in high transmission setting)	*(12)*

[a] In practice, there is considerable variance in treatment seeking, testing, and initial treatment in different settings. These assumptions represent a stylised case.
[b] Probability of receiving further outpatient care (if uncomplicated malaria) or inpatient care (if severe malaria).
[c] Provider and patient cost (i.e. regardless of any fees charged).

Limitations

- Substandard and falsified antimalarial data are based on a limited number of studies, which may not be generalizable to the broader SSA context. Insufficient data are currently available to estimate drug quality for the public and private sector separately. Note that there are very limited data on dissolution – an important but neglected characteristic of drug quality.
- Proportion of "failed" drugs in different API categories (<50%, 50–75%, 75–85%) is based on only two studies. Large studies with available data on API distribution are very limited.
- Adherence to treatment is assumed to be the same for ACT and other (non-ACT) antimalarials, though the data are based on a study involving 3–day fixed dose treatment (artemether-lumefantrine) only; adherence to single dose and non-fixed dose treatment is likely to differ.
- Impact of adverse drug events relating to poor quality antimalarials has not been modelled.
- There is considerable of uncertainty around key parameters (e.g. disease progression with no/failed treatment, case fatality rates, malaria cases receiving treatment) and results are sensitive to such uncertainty. Estimates of health and economic impact are best estimates within a wide range.

- Economic impact only considers incremental provider and patient costs due to care sought for treatment failure. Travel costs and economic impact due to lost productivity are not considered.
- **Given the large amount of uncertainty, results should be considered tentative and illustrative only.**

Results base-case

The first present results for our base case analysis, and secondly present a "CFR adjusted case", with model parameters adjusted to fit WHO case fatality estimates. For both cases, we first present health impact, followed by economic impact.

Health impact

Table A4.7: Health impact (base case)

	Receive initial antimalarial treatment	Initial antimalarial treatment fails[a]	Treated malaria becomes severe[a]	Health impact for malaria cases receiving initial antimalarial treatment[a]	
				Deaths	DALYs
Ideal antimalarial quality	724 130	179 836	13 698	3 156	91 825
Real world[b]	724 130	210 191 (196 679 –221 120)	15 995 (14 966 –16 826)	3 685 (3 448 –3 876)	107 209 (100 309 –112 779)
Difference[c]	**–**	**30 356 (16 844 –41 284)**	**2 296 (1 267 –3 128)**	**529 (291 –720)**	**15 384 (8 484 –20 953)**

[a] Figures in the table are only for those cases receiving an antimalarial.

- Incremental health impact (base case) of Real World compared with Ideal Antimalarial Quality, per million malaria cases seeking treatment, is estimated at 529 deaths (range 291–720) and 15 384 DALYs (range 8 484–20 953).
- Note that estimates of health impact shown above are only for cases receiving an antimalarial. Total real world malaria health impact, including cases not receiving an antimalarial, is estimated at 302 000 DALYs per million cases, which equates to an overall case fatality rate for malaria cases seeking treatment of 0.79%, and for all malaria cases of 1.04%.

Economic impact

- Economic cost (base case) for a hypothetical cohort of 1 million malaria cases seeking treatment (assuming 90% of cohort are in high transmission settings and 72% of cohort receive an antimalarial).

Table A4.8: Economic impact (base case)

	Further care cost (USD 2017)[a]		
	Outpatient	Inpatient	Total
Ideal antimalarial quality	286 000	240 000	526 000
Real world[b]	334 000 (313 000 –351 000)	280 000 (262 000 –295 000)	615 000 (575 000 –646 000)
Difference[b]	**48 000** **(27 000 –66 000)**	**40 000** **(22 000 –55 000)**	**89 000** **(49 000 –120 000)**

[a] Figures in the table are only for those cases receiving an antimalarial (rounded to nearest US dollar).
[b] Value ranges reflect the minimum and maximum ranges for the proportion of ACT and non-ACT antimalarials below API range.

- Incremental economic impact (base case) of Real World compared with Ideal Antimalarial Quality, per million malaria cases seeking treatment, is estimated at $89 000 (range 49 000–120 000).

Results CFR adjusted case

- Based on the assumptions in the base case scenario, the "real world" CFR (all malaria cases) is 1.04%. This is substantially higher than the CFR of 0.45% used by WHO in modelling of malaria mortality *(13)*.
- An alternative scenario (CFR adjusted case) is provided, with the following assumptions adjusted to fit the "real world" CFR to the 0.45% WHO rate.

Table A4.9: Parameters adjusted for CFR adjusted case

Parameter	Value (base case)[a]	Value (CFR adjusted case)
Progression to severe disease (where no/successful treatment)	Low transmission setting: 30% (under 5 years), 18% (over 5 years)	Low transmission setting: 20% (under 5 years), 12% (over 5 years)
	High transmission setting: 10% (under 5 years), 2% (over 5 years)	High transmission setting: 7% (under 5 years), 1% (over 5 years)
Case fatality rate (severe disease) with no further care	Low transmission: 73% (under 5 years), 70% (over 5 years)	Low transmission: 48% (under 5 years), 46% (over 5 years)
	High transmission: 60% (under 5 years), 45% (over 5 years)	High transmission: 40% (under 5 years), 30% (over 5 years)
Case fatality rate (severe disease) with further (inpatient) care	Low/high transmission: 10%	Low/high transmission: 7%

[a] See previous base case assumptions.

Health impact (CFR adjusted case)

- Health impact (CFR adjusted case) for a hypothetical cohort of 1 million malaria cases seeking treatment (assuming 90% of cohort are in high transmission settings and 72% of cohort receive an antimalarial).

Table A4.10: Health impact (CFR adjusted case)

	Receive initial antimalarial treatment	Initial antimalarial treatment fails[a]	Treated malaria becomes severe[a]	Health impact for malaria cases receiving initial antimalarial treatment[a]	
				Deaths	DALYs
Ideal Antimalarial Quality	724 130	179 836	9 027	1 371	41 239
Real world[b]	724 130	210 191	10 541	1 600	48 149
		(196 697–221 120)	(9 862–11 088)	(1 497–1 683)	(45 050–50 650)
Difference[c]	**–**	**30 356**	**1 513**	**230**	**6 909**
		(16 844–41 284)	**(835–2 061)**	**(127–313)**	**(3 811–9 411)**

[a] Figures in the table are only for those cases receiving an antimalarial.
[b] Value ranges reflect the minimum and maximum ranges for the proportion of ACT and non-ACT antimalarials below API range.
[c] Including cases seeking treatment but not receiving an antimalarial, and cases not receiving treatment (for which it is assumed that no antimalarial is received).

- Incremental health impact (CFR adjusted case) of "real world" compared with "ideal antimalarial quality" per million malaria cases seeking treatment, is estimated at 230 deaths (range 127–313) and 6,909 DALYs (range 3 811–9 411).
- Estimates of health impact shown above are only for cases receiving an antimalarial. Total "real world" malaria health impact, including cases not receiving an antimalarial[7], is estimated at 136 000 DALYs per million cases, which equates to the 0.45% case fatality rate used by WHO.

7 Including cases seeking treatment but not receiving an antimalarial, and cases not receiving treatment (for which it is assumed that no antimalarial is received).

Economic impact (CFR adjusted case)

- Economic cost of further care (CFR adjusted case) for a hypothetical cohort of 1 million malaria cases seeking treatment (assuming 90% of cohort are in high transmission settings and 72% of cohort receive an antimalarial).

Table A4.11: Economic impact (CFR adjusted case)

	Further care cost (USD 2017)[a]		
	Outpatient	Inpatient	Total
Ideal antimalarial quality	294 000	159 000	453 000
Real world[b]	343 000 (321 000–361 000)	186 000 (174 000–196 000)	530 000 (496 000–557 000)
Difference[c]	**50 000 (28 000–67 000)**	**27 000 (15 000–36 000)**	**76 000 (42 000–104 000)**

[a] Figures in the table are only for those cases receiving an antimalarial (rounded to nearest US dollar).
[b] Value ranges reflect the minimum and maximum ranges for the proportion of ACT and non-ACT antimalarials below API range.
[c] Lower bound of CFR adjusted case with WMR case estimates, and upper bound of base case with CHAI case estimates, respectively.

- Incremental economic impact (base case) of "real world" compared with "ideal antimalarial quality" per million malaria cases seeking treatment, is estimated at US$76 000 (range 42 000–104 000).

Sensitivity analysis

- There is a high level of uncertainty of many model parameters. Univariate sensitivity analysis has been conducted to investigate sensitivity of the health and economic impact relating to selected parameters.

Table A4.12: Parameters varied in the sensitivity analysis

Parameter	Best estimate	Min value	Max value	Source for range
Antimalarial drugs <85% API (Real World option)	ACT: 7.6% Other antimalarial: 10.4%	ACT: 5.1% Other antimalarial: 2.1%	ACT: 9.8% Other antimalarial: 16.3%	See analysis above
Efficacy reduction (75–85% API)	Low transmission: 30% High transmission: 25%	Low transmission: 15% High transmission: 10%	Low transmission: 45% High transmission: 40%	Assumption
Efficacy reduction (50–75% API)	Low transmission: 60% High transmission: 50%	Low transmission: 45% High transmission: 35%	Low transmission: 75% High transmission: 65%	Assumption
% receiving antimalarial (no blood test)	Low transmission: 80% High transmission: 70%	50%	90%	Assumption
% receiving antimalarial (positive blood test)	Low transmission: 90% High transmission: 80%	60%	100%	Assumption
% antimalarial that is ACT (no blood test)	57%	35%	80%	Assumption
% antimalarial that is ACT (positive blood test)	75%	50%	100%	Assumption
Progression to severe disease (where no/unsuccessful treatment)[a]	**Base case:** Low transmission: 30% (<5 yrs), 18% (>5 yrs) High transmission: 10% (<5 yrs), 2% (>5 yrs) **CFR adjusted case:** Low transmission: 20% (<5 yrs), 12% (>5 yrs) High transmission: 7% (<5 yrs), 1% (>5 yrs)	Low transmission: 10% (<5 yrs), 5% (>5 yrs) High transmission: 5% (<5 yrs), 0% (>5 yrs)	Low transmission: 90% (<5 yrs), 50% (>5 yrs) High transmission: 60% (<5 yrs), 15% (>5 yrs)	Adapted from *(8)*
% severe cases receiving further inpatient care	75%	40%	88%	Assumption, *(9)*
% uncomplicated cases (with no/unsuccessful treatment) receiving further outpatient care	48%	19%	88%	*(9)*

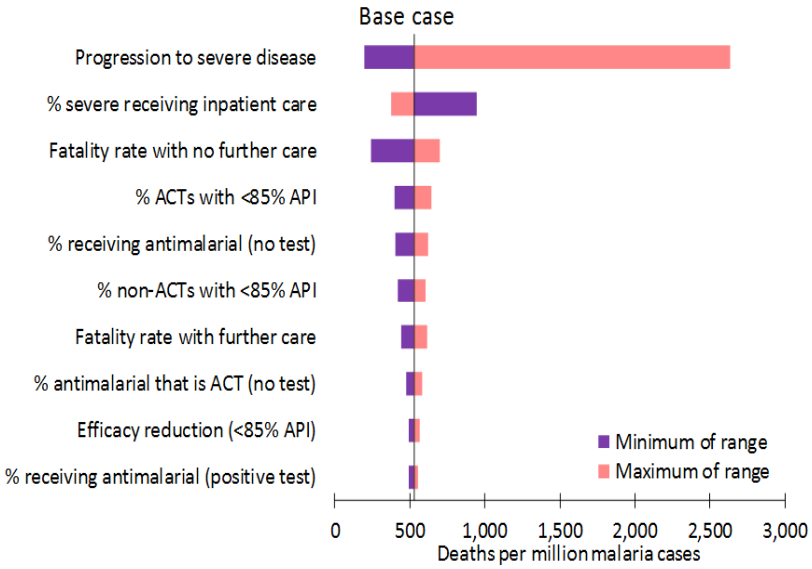
Parameter	Best estimate	Min value	Max value	Source for range
Case fatality rate (severe disease) with no further care[b]	**Base case:** Low transmission: 73% (<5 yrs), 70% (>5 yrs) High transmission: 60% (<5 yrs), 45% (>5 yrs) **CFR adjusted case:** Low transmission: 48% (<5 yrs), 53% (>5 yrs) High transmission: 40% (<5 yrs), 30% (>5 yrs)	Low transmission: 25% (<5 yrs), 5% (>5 yrs) High transmission: 10% (<5 yrs), 5% (>5 yrs)	Low transmission: 95% High transmission: 90% (<5 yrs), 95% (>5 yrs)	Adapted from *(8)*
Case fatality rate (severe disease) with further care[b]	**Base case:** 10% **CFR adjusted case:** 7%	5%	15%	(9, 10); assumption
Cost of further inpatient care, per case treated (USD 2017)[c]	US$ 3.95	US$ 2.27	US$ 7.57	WHO-CHOICE; assumption
Cost of further outpatient care, per case treated (USD 2017)[d]	Dies: US$ 19.00 Recovers: US$ 23.87	Dies: US$ 13.33 Recovers: US$ 16.82	Dies: US$ 42.22 Recovers: US$ 49.39	WHO-CHOICE; assumption

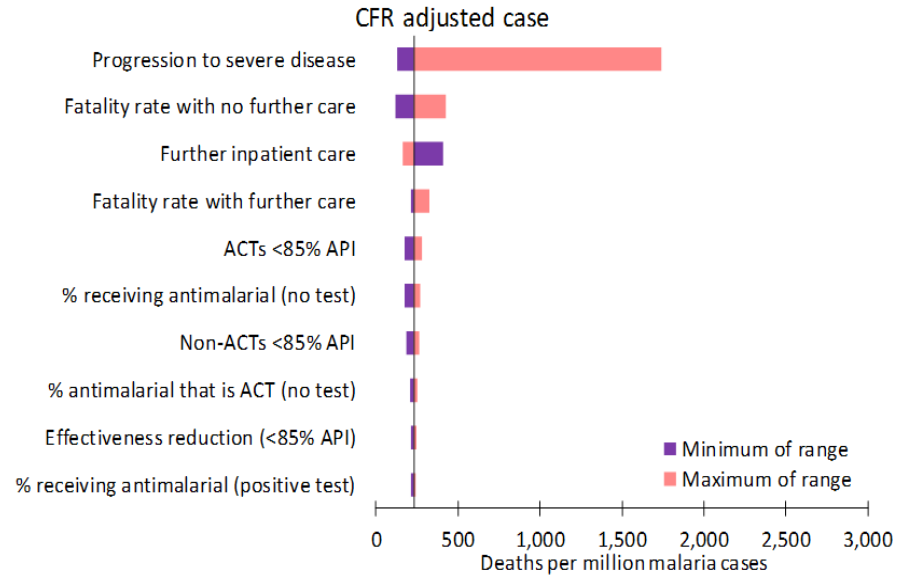
[a] Including cases seeking treatment but not receiving an antimalarial, and cases not receiving treatment (for which it is assumed that no antimalarial is received).
[b] Minimum and maximum values apply to both base case and CFR adjusted case.
[c] Provider and patient cost (i.e. regardless of any fees charged).
[d] Proportion of annual fevers receiving an antimalarial derived from 2016 data provided by Clinton Health Access Initiative (see footnote below).

Sensitivity analysis results

Sensitivity of incremental health impact (deaths) by individual parameter (base and CFR adjusted cases):

Fig. A4.4: Sensitivity analysis – incremental health impact (deaths) for (a) Base Case and (b) CFR adjusted analyses



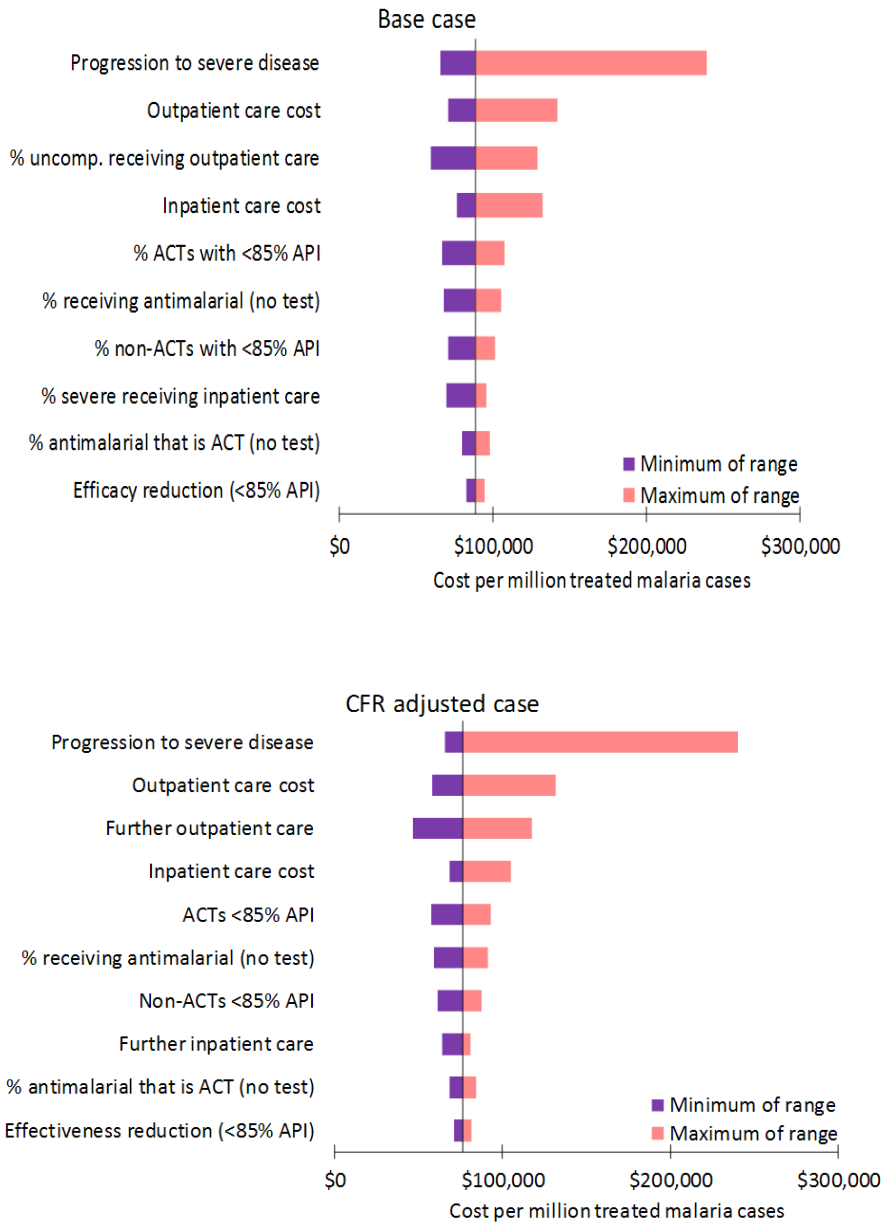


- Likelihood of progression to severe disease (with no/failed treatment) is the most sensitive parameter in both base case and CFR adjusted case (119–2 638 and 131–1739 deaths per million malaria cases seeking treatment, respectively).
- Further inpatient care and the fatality rate with no further care are the next most sensitive parameters in both cases.

Sensitivity analysis results

Sensitivity of incremental economic impact (USD) to variation in individual parameter (base and CFR adjusted cases):

Fig A4.5: Sensitivity analysis - incremental economic impact (deaths) for (a) Base Case and (b) CFR adjusted analyses



- Likelihood of progression to severe disease (with no/failed treatment) is the most sensitive parameter in both base case and CFR adjusted case (US$66,000–US$239,000 and US$66,000–US$240,000 per million malaria cases seeking treatment, respectively).
- Outpatient care cost and the likelihood of receiving further outpatient care for uncomplicated illness are the next most sensitive parameters in both cases.

Estimating the Sub-Saharan Africa-wide health and economic impact

In addition to estimating health and economic impact for a hypothetical cohort of 1 million malaria cases seeking treatment, we also estimate the health and economic impact for the whole of sub-Saharan Africa (SSA). This required an estimate of total annual fevers receiving an antimalarial in SSA for which we used two different methods:

1. **World Malaria Report (WMR) estimated annual malaria cases (14)**
   - 190 million *P. falciparum malaria* cases estimated for African Region (2015)
   - 99 million (52%) of these cases receive an antimalarial.[8]
2. **Clinton Health Access Initiative (CHAI) estimated annual fevers**[9]
   - 4.63 billion annual fevers in SSA
   - 3.17 billion with fever seek treatment
   - 505 million with fever seeking treatment are *P. falciparum* malaria cases[10]
   - 366 million malaria cases receive an antimalarial.

SSA-wide impact

- The results from the base case and CFR adjusted case are applied to the estimated cases receiving an antimalarial (WMR and CHAI methods) to estimate annual incremental health and economic impact of substandard and falsified medicines in SSA.
- Value ranges reflect the minimum and maximum ranges for the proportion of ACT and non-ACT antimalarials below the 85% API range (5.1-9.8% and 2.1-16.3%, respectively).

Table A4.13: Estimated incremental health and economic impact for sub-Saharan Africa

	Incremental health impact (deaths)		Incremental economic impact (USD 2017)	
	WMR cases	CHAI cases	WMR cases	CHAI cases
Base case	72 000 (40 000–98 000)	266 906 (147 000–364 000)	12 100 000 (6 700 000–16 500 000)	44 700 000 (24 800 000–60 800 000)
CFR adjusted case	31 000 (17 000–43 000)	116 000 (64 000–158 000)	10 400 000 (5 800 000–14 200 000)	38 500 000 (21 400 000–52 400 000)

CFR: case fatality rate; CHAI: Clinton Health Access Initiative; WMR: World Malaria Report.

Due to substantial parameter uncertainty, results show wide ranges for estimates of incremental health and economic impact. Incremental health impact estimates range from **17 000 and 364 000 deaths**. Incremental economic impact estimates range from **US$ 5.8 million to US$60.8 million**.[11]

8 Proportion of annual fevers receiving an antimalarial derived from 2016 data provided by Clinton Health Access Initiative (see footnote below).

9 Based on analysis (annual fevers, fevers seeking treatment, antimalarial use, and P. falciparum infections receiving an antimalarial) from Clinton Health Access Initiative (12)

10 Calculated by multiplying annual fevers in each administrative region by the region's estimated P. falciparum parasite rate amongst the febrile population. Parasite positivity rates are based on 2010 data and therefore malaria cases may be overstated in areas where prevalence has declined since 2010.

11 Lower bound of CFR adjusted case with WMR case estimates, and upper bound of base case with CHAI case estimates, respectively.

Conclusion

There is a large degree of uncertainty around key parameters, leading to estimates of incremental health and economic impact within wide ranges.

Nevertheless, this modelling demonstrates that substandard and falsified antimalarials have a substantial impact in both health and economic terms. For both the base case and CFR adjusted case, it is estimated that incremental deaths in SSA due to substandard and falsified antimalarials comprise approximately **2.1% to 4.9% of total malaria deaths**,[12] or approximately **3.8% to 8.9% of malaria deaths relating to cases seeking treatment**.[13]

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Appendix: Antimalarial quality studies

First author	Title	Journal	Publication year	Country	Antimalarial group	Sector
ACT Consortium Druq Quality Project Team	Quality of Artemisinin-Containing Antimalarials in Tanzania's Private Sector—Results from a Nationally Representative Outlet Survey	Am J Trop Med Hyg	2015	United Republic of Tanzania	ACT	Private
Kaur, H	Quality of Artemisinin-Based Combination Formulations for Malaria Treatment: Prevalence and Risk Factors for Poor Quality Medicines in Public Facilities and Private Sector Drug Outlets in Enugu, Nigeria	PLoS ONE	2015	Nigeria	ACT, Other	Mix
Affum, AO	A pilot study on quality of artesunate and amodiaquine tablets used in the fishing community of Tema, Ghana	Malaria Journal	2013	Ghana	ACT	Private
Kaur, H	A Nationwide Survey of the Quality of Antimalarials in Retail Outlets in Tanzania	PLoS ONE	2008	United Republic of Tanzania	ACT	Private
Luke, A	Evaluation of the Quality of Artemether/Lumefantrine, Sulphadoxine/Pyrimethamine and Quinine Sulphate Tablets in Public and private Health Institutions in Lusaka District	University of Zambia (PhD thesis)	2012	Zambia	ACT, Other	Mix
Nyarko, EA	Quality Assessment of Artemether/ Lumefantrine Tablets Sampled from Pharmacies in Accra, Using the MVHimagePCv8.exe Color Software	Phamacology & Pharmacy	2013	Ghana	ACT	Mix
Onwujekwe, O	Quality of anti-malarial drugs provided by public and private healthcare providers in south-east Nigeria	Malaria Journal	2009	Nigeria	Other	Mix
Sawadogo, CW	Quality of chloroquine tablets available in Africa	Ann Trop Med Parasitol	2011	Various	Other	Mix
Visser, BJ	Assessing the quality of antimalarial drugs from Gabonese pharmacies using the MiniLab®: a field study	Malaria Journal	2015	Gabon	ACT, Other	Private

First author	Title	Journal	Publication year	Country	Antimalarial group	Sector
WHO	Survey of the Quality of Selected Antimalarial Medicines Circulating in Madagascar, Senegal, and Uganda	(Report)	2009	Various	ACT, Other	Mix
WHO	Survey of the quality of selected antimalarial medicines circulating in six countries of sub-Saharan Africa	(Report)	2011	Various	ACT, Other	Mix

Annex 5: Sources of data on substandard and falsified medicines[14]

Data source	Description	Strengths	Limitations
Population-, market- or threshold-based surveillance	Systematic representative or random sampling and testing of medical products within a market	Most rigorous methodology for sampling and testing to determine prevalence of substandard and falsified medical products	Demands significant resources (time, human, financial, technical); not suited for urgent public health response
Risk-based surveillance	Convenience sampling focused on selected geographical regions, therapeutic categories or outlets	Needs based (adaptable to particular geographical or therapeutic context); cost-effective; feasible; can provide approximate snapshot of prevalence	May overstate magnitude of the problem (*ex ante* bias of researcher); may miss other regions and/or therapeutic categories of public health concern
Case reporting	Database of reported medical products submitted by trained national focal points; maintained by reliable organizations (for example regulatory authorities or WHO)	Data available in real time; standardized reporting format; public health action possible; valuable for advocacy	Relies on focal point reporting; may lead to over-representation of falsified medicines versus substandard medicines (as most incidents are not discovered because of adverse events or by laboratory testing, but rather overt falsification of packaging or product); only confirmed cases are made public
Open access databases	Database of incidents/reports that are publicly accessible; typically maintained by organizations focused on selective regions and/or therapeutic categories	Open access; reports may contain detailed case data and/or laboratory data on samples that pass or fail quality control	Value of data limited to regions or therapeutic category; methodologies are not harmonized; results may be based on screening tests of limited sensitivity
Closed-access databases Not included in this study	*Database of incidents/reports that are not publicly accessible; typically maintained by organizations representing multinational pharmaceutical companies*	*Includes confidential industry reports; mainly valuable for pharmaceutical companies for sharing information on vulnerabilities, incidents, best practices*	*Only aggregate data may be publicly available; emphasis on limited medical products; definition may not focus on public health (i.e. includes violations of intellectual property rights)*
Seizures Not included in this study	*Periodic reports of random or systematic seizure operations by customs, regulatory or enforcement authorities*	*Valuable for awareness; identifying and addressing gaps across supply chains; includes data on online pharmacies*	*Only aggregate data may be publicly available; may lead to over-representation of falsified over substandard medicines; definition may not focus on public health (i.e. includes violations of intellectual property rights)*

14 Pisani E. Antimicrobial resistance: What does medicine quality have to do with it? 2015 (http://apps.who.int/medicinedocs/documents/s22186en/s22186en.pdf, accessed 11 November 2017)

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