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REVIEW

Emerging Antimicrobial Drug Resistance in Africa and Latin America: Search for Reasons

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Abstract: Medicine quality and methods for its assessment play a major role in the effectiveness of therapies and the treatment of many infectious diseases. However, poor-quality and/or falsified products are circulating in huge amounts in many low- and middle-income countries and are one of the major reasons why more and more resistant bacteria emerge. The development of resistance is additionally triggered by a plethora of antibiotic medicines which is easily available through pharmacies and unofficial sources. The uncontrolled overuse of these products is a huge problem not only in single countries but worldwide. In this review, we aim to demonstrate the factors which are involved in an emerging resistance development and how strong regulatory authorities, routine quality control by means of proficiency testing, and post-marketing surveillance as well as training personnel and patients can be combined to curb the problem.

Keywords: medicine quality, falsified, antimicrobial resistance, proficiency testing, post-marketing surveillance, Africa, Latin America

Introduction

Emerging Resistance to Antimicrobial Therapies is a Global Concern

Antimicrobial resistance (AMR) is a growing and severe problem in almost every country of the world. It is estimated that by 2050, approximately 10 million people will die from infections which are due to antibiotic resistant bacteria (ARB).[1] Several reasons can be given, such as the overuse of antibiotics in the clinical and agricultural environment as well as the release of antimicrobial compounds into the ecosystem upon manufacturing, especially in Asian countries where most of the used raw materials are produced.[2] The spread of ARB and the mobility of corresponding antimicrobial resistance genes (ARG) accelerates the dissemination between humans, animals, air, soil, water, and food. However, beside these well-known mechanisms, a poor quality of antibiotics may also have an important impact on the development of resistance, particularly if an antimicrobial drug is underdosed or the tablet does not properly release the active pharmaceutical ingredient (API).

Resistance to common antimicrobial chemotherapy is a globally growing concern which is observed not only in low- and middle-income countries (LMIC) but also in more and more parts of the industrialized world.[3,4] Already in 2011, AMR was declared as "a ticking time bomb (…) for the world" by Prof. Dame Sally Davies, UK Chief Medical Officer, who warned that the "apocalyptic scenario of widespread antimicrobial resistance does not become a reality".[5] A large number of publications thoroughly discussing the problem can be found, e.g., contributions from the UK Government, the European Centre for Disease Prevention and Control in cooperation with the European Medicines Agency, or articles published in scientific journals.[6–8] Careful diagnosis, rational prescription and prevention of antibiotic overuse, and ensuring access to high-quality pharmaceuticals are anticipated within all of them. The latter is of particular interest as

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a huge numbers of patients, particularly in LMICs, are permanently exposed to highly dangerous falsified, substandard, or contaminated medicines.[9,10]

Substandard Medicines

The World Health Organization (WHO) defines substandard products as being "out-of-specification" and "authorized medical products that fail to meet either their quality standards or specification, or both."[11] A great variety of aspects defining "substandard" may appear on the level of the raw API, because it could either contain too many potentially toxic impurities, and/or the drug compound is not stable upon storage. Both result in a lower content than required by international pharmacopeias such as the United States Pharmacopeia (USP), the European Pharmacopoeia (EP), the British Pharmacopoeia (BP), or the International Pharmacopoeia (IP). Table 1 summarizes typical examples of quality deficiencies, illustrating a complex scenario of possible quality failures.

The shelf-life – and thus, eventually the quality and efficacy – of a distinct drug product can also be reduced by long-term chemical reactions and interaction of APIs with excipients used in the finished products (FPs). An even worse situation would be a chemical reaction of the API with highly reactive degradation products of excipients, e.g., hydroperoxides of polyethylene glycols which may oxidize amines.

Furthermore, the incomplete release of the drug from the FP ("dissolution") can also be a critical issue which is often observed in drugs collected in Sub-Saharan Africa: although the tablets actually contain the declared amount of the correct API, only a very low amount or no substance at all is being released from the respective dosage form upon intake.[12,13] Such tablets must be regarded as completely ineffective.

Finally, in many cases, completely different APIs than the declared one(s) have been found, producing severe or even lethal side effects as observed with fever syrups, injectables, pediatrics, or herbal medicine.[14] Those FPs can be regarded as falsified.

Table 1 Quality Attributes Determining the Efficacy and Safety of Medicines

Quality Attribute	Consequence
Concerning API	
No API is present	Underdosing, no effect of therapy
API is present but at a very low level	
Wrong API is present	Intoxication, no effect of therapy, side effects
Concerning impurities	
Known impurities are present at elevated levels	Reduced efficacy due to reduced API content, toxic side effects
Unknown impurities are present	
Concerning visual appearance	
Packaging is falsified	Product could be falsified which is difficult to determine without genuine reference samples
Tablets or capsules have a different appearance	
Concerning release of the API	
Tablets or capsules do not disintegrate	No or reduced therapeutic effect
Chemical reactions between API and excipients	
Degradation due to inappropriate packaging (humidity, light, oxygen)	

Methods for Detecting Poor-Quality Medicine

Routine evaluation of medicine quality is a proven course of action for ensuring efficacy and safety, not only in the field of chemotherapeutics. A broad spectrum of sensitive analytical technologies is available which allows the qualitative and quantitative evaluation of raw materials and the respective FPs.[15,16] However, not all methods are suitable for routine use in LMICs: the limited applicability of modern state-of-the-art instrumentation and the growing complexity of pharmacopoeial methods poses significant challenges to local testing laboratories and eventually obstructs embracive testing activities.[17,18]

Enabling routine medicine quality control in resource-limited settings has been piloted by inventing and implementing simple, stand-alone mobile testing kits such as the "GPHF Minilab®." It makes use of simple thin-layer chromatographic tests and has rapidly gained wide acceptance as a risk-based screening tool in tiered approaches for more than 100 APIs and/or finished products, especially antibiotics and antiviral drugs. Despite being an undoubtedly helpful invention for quickly identifying grossly substandard samples, its validity has become questionable, and accuracy as well as reproducibility have been discussed several times.[19]

Portable instruments based on vibrational spectroscopy (near infrared, Raman) have additionally gained recent attention and are considered to be ideal techniques for rapid qualitative determinations "in the field" because no further equipment or chemicals are required and the methods are non-destructive. However, the extracted information is limited and for example not suitable for determining the impurity profile of a sample.[20]

Assessing the most important quality attributes of APIs and FPs, i.e., assaying the content and determining and quantifying impurities, can be done by various methods. The one still considered as the gold standard in pharmaceutical analysis is high performance liquid chromatography (HPLC). It allows the separation and quantification of the respective compounds and is being applied in almost all contemporary monographs of the major pharmacopoeias. Nevertheless, it is difficult to routinely implement HPLC in the majority of LMICs because HPLC systems are highly sensitive, expensive devices which demand a sophisticated laboratory setup. Insufficient infrastructural variables such as inadequate power supply, difficult availability of consumables, expensive prices for spare parts, missing air conditioning, or lacking technical support services make it very tedious to install and operate such apparatus on a routine basis. It can also be used for determining the disintegration and dissolution profile according to the major pharmacopeias (paddle method, etc.) which are critical parameters as described before. Various solutions have been presented so far.[21] Developing simple and very robust methods which can be run even on quite simple equipment is a concept which was anticipated before, e.g., for enabling the quality analysis of common antimalarial medicines.[22,23]

Qualification of Laboratories and Establishment of Standards

To overcome the challenges and limitations of quality control, the WHO is continuously establishing and expanding a network of so-called "WHO Prequalified Laboratories", and almost 60 institutions from different countries worldwide had already been identified as compliant as of September 2020.[24] An interesting feature of this system is the publication of "WHO Prequalified Active Pharmaceutical Ingredients" and "WHO Prequalified Medicinal Products" which have been evaluated, approved, and certified according to WHO standards.[25]

Annex 1 in "Good practices for pharmaceutical quality control laboratories" published by the WHO provides basic requirements for the quality management system (QMS) "External Quality Assurance Assessment Scheme" in order to produce more reliable results.[26,27] Table 2 summarizes the requirements prescribed by the WHO guidelines for good manufacturing practices together with the requirements of the International Standard ISO/IEC 17025:2006.[28,29]

Proficiency Testing

Ensuring the performance of quality control laboratories is possible through proficiency testing (PT) which is the mechanism of assessing a laboratory's ability to competently perform specific tests and/or measurements according to previously set standards. It supplements a laboratory's own internal quality control procedure by providing an additional, independent, and unbiased external audit of their testing capability and provides laboratories with a basis for continuous improvement of the respective procedures and protocols.[29] During PT, the organizer prepares and sends blinded samples to laboratories that have agreed or registered to participate and which conduct analysis according to the testing scheme. Results of all laboratories are

Table 2 Summary of Key Requirements for Quality Control Laboratories According to the WHO

Infrastructure	• Facilities must be of a suitable size, construction, and location, as well as equipped with adequate instruments and equipment, including work benches, work stations, and fume hoods. • Separate and dedicated unit or equipment with appropriate environmental conditions. • Storage and retrieval of all documents. • Equipment, instruments, and other devices should be designed, constructed, adapted, located, calibrated, qualified, verified, and maintained as required by the operations to be carried out. • Equipment should be purchased from an agent capable of providing full technical support and maintenance. • All should meet the laboratory's requirements and comply with the relevant standard specifications.
Personnel	• Sufficient personnel with respective education, training, technical knowledge, and experience for their assigned functions (e.g., a graduate in pharmacy, analytical chemistry, microbiology or other relevant skills). • Technical management should ensure the competence of all personnel in operation of specific equipment, instruments, or other devices who are performing tests, calibrations, validations, or verifications. • All personnel should be permanently employed or under contract and have the ability to adequately perform the tasks assigned to them. • Technical staff should be available qualified at diploma level. • A quality manager should be available.
Organization	• The laboratory should be an entity that is legally authorized to function and operate to meet the requirements. • Arrangements should ensure that its management and personnel have no conflicts of interest that may adversely affect the quality of work; policies and procedures should be in place to ensure confidentiality. • Have charts that demonstrate organization and management structure of the laboratory. • Specify and precisely allocate responsibilities which ensure adequate information flow between staff at all levels. • Maintain an up-to-date collection of all specifications and all related documents for appropriate safety procedures. • Maintain a registry with function of receiving, distributing, and supervising the consignment of the samples to the specific units keeping records on all incoming samples and accompanying documents.

Note: Data adapted from WHO.[107]

analyzed, compared, and reported to all participating laboratories. In rechecking-retesting, samples that have been previously analyzed are being retested, allowing for inter-laboratory comparison whilst an on-site evaluation is used when it is difficult to conduct traditional proficiency testing or to use the rechecking-retesting method.[30–32]

A White Paper on PT for analytical laboratories on organization and statistical data assessment revealed that in general, for conducting proficiency tests, an organizing body is responsible for providing the protocol, operating the scheme, taking appropriate action, reviewing effectiveness of the scheme regularly, and, where necessary, amending the protocol.[33,34]

Implementation and operation of such an administrative body should consist of:

(i) A manager responsible for running the proficiency test, evaluating, documenting, and distributing the results, and conducting any follow-up action that might be required;

(ii) A statistical expert;

(iii) Representatives of government bodies, commercial companies, or accreditation agencies with a legitimate interest in conducting the tests;

(iv) A technical panel being formed of representatives of professional bodies with competence in the methodology of proficiency testing and a suitable qualification;

(v) Only a minority of members should have a commercial interest in the outcome of the scheme;

(vi) Identifying participating laboratories and assign a blinded code;

(vii) Specifying and recording the exact sample composition and distribution to the participants;

(viii) Setting time frames for the technical panel to be able to review individual results.

The study also revealed that the following steps must be followed during a proficiency testing scheme as described in ISO/IEC guideline 43-1:[35,36]

(i) All stages of a PT must be clearly identified;

(ii) A protocol has to be set;

(iii) All materials have to be organized and validated accordingly which includes choosing, preparing, and quality testing thereof;

(iv) Sample distribution must follow a distinct plan;

(v) Results must be collected from participating laboratories and data analysis has to be carried out as described by Thompson et al.[37]

(vi) Feedback to participants is important.

The accreditation of pharmaceutical quality control test laboratories in Sub-Saharan Africa according to the "ISO/IEC 17025 laboratory accreditation" had a huge impact on the validity of results obtained from such laboratories: analysis reports were more reliable and the overall quality control system was improved.[38] The US pharmacopoeia also tries to enhance the quality of medicines and dietary supplements by corresponding international programs.[30]

Materials and Methods

A systematic search was performed using PubMed, Google Scholar, and the website of the World Health Organization focusing on research papers, reviews, and White Papers using the terms "antibiotic", "resistance", "substandard", "quality", "Africa", and "Latin America".

Information on quality control systems and regulatory background was available because the authors are involved with regulatory authorities or are a part of it. Hence, they can describe, compare, and discuss many aspects within this topic.

Information related to particular countries is – in part – derived from personal communication and experience which could be directly contributed by some of the authors.

Results

Sampling, Proficiency Testing, and Monitoring the Quality of Medicines: The African Perspective

Case reports of substandard drugs mainly originate from LMICs such as those in Sub-Saharan Africa and South America. The WHO is reporting and warning on such incidences on a regular basis. Most of the incidents and treatment failures are probably due to low-quality medicines not containing any or not enough of the declared API. For example, Schiavetti et al.[39] reported on the quality of amoxicillin and the fixed-dose combination of artemether-lumefantrine, which were collected from wholesalers in the Democratic Republic of Congo: out of more than 400 collected products, 27% were of poor quality and approximately 60% of the antimalarials represented underdosed products. Many cases of tablets or capsules not being able to release the API have been found which is another crucial quality and efficacy attribute of FPs.[40]

Of note, poor-quality products are not only observed in the group of antibiotics and antiviral APIs. Studies report low quality and/or counterfeit products for other APIs such as oxytocin, ergometrine, misoprostol, or propofol in countries including Ethiopia, Rwanda, Zambia, and Ghana.[41–44] Further examples of quality assessment studies from Africa are outlined in the following paragraphs and displayed in Table 3.

Democratic Republic of the Congo (DRC)

In 2017, samples of artemether-lumefantrine fixed-dose combinations were collected from eight cities in the DRC for determining the quality of these medicines sold in the market. Sampling locations covered the most populated regions and cities which have a high prevalence of malaria and those bordering neighbor countries. Samples were drawn from easily accessible public pharmaceutical outlets. All samples were transported to Germany for quality control analysis.[45]

Visual inspection revealed that three samples had a long shelf-life, which was quite suspicious; upon thin-layer chromatography (TLC) analysis, the suspicious ones had no API and one sample contained lumefantrine only. Generally, 2.7% of samples failed the tests.[45]

A prospective survey was done for the quality of medicines used for children; the study site was Kinshasa because it is the largest urban zone within the DRC. Sampling was guided by The Medicine Quality Assessment Reporting Guideline (MEDQUARG),[46] samples were selected based on criteria relevant for public health, and formulations were

Table 3 Findings of Sampled Anti-Infective Drugs from Various African Countries

Country	Investigated Medicine and Findings	Refer
Benin	*Imidazole antiparasitic medicines*: A study showed that 38.3% of drugs from the informal market did not conform with pharmaceutical and physicochemical tests, while only 3.4% from the formal market did not conform with these tests.	[98]
Burkina Faso	*Antimalarial drugs*: 12% of the samples had a substandard concentration of the API, 5% showed a very poor disintegration rate, and one sample did not contain any API.	[99]
Ethiopia	*Anthelmintic medicine*: The results on visual inspection did not show any sign of counterfeit, all samples conform with all the tests conducted which include disintegration test, mass uniformity tests, and the test on amount of active ingredient.	[100]
Gabon	*Antimalarial drugs*: The results showed that 2 out of 432 samples failed the Minilab semi-quantitative tests, in which one was falsified, and one was substandard.	[101]
Malawi	*Antimalarial drugs*: The samples passed the visual inspection test but a detailed analysis with HPLC showed that 88.4% of the samples failed the quality test either by the presence of excessive or insufficient API.	[102]
Nigeria	*Artemisinin-based antimalarial drugs*: Content analysis of the samples showed that 90.8% were of acceptable quality, 6.8% substandard, 1.3% degraded, and 1.2% were falsified.	[103]
South Africa	*Amoxicillin (single or in combination with clavulanic acid), analgesics (paracetamol alone or in combination with other drugs)*: The results of the study showed that 55.4% of the sample were able to fulfill all pharmacopeial requirements for quality, most of the failing sample failed a visual inspection test, 5.4% failed the dissolution test, and 4.8% failed the content uniformity test.	[104]
Togo	*Antibiotics and medicine for non-communicable diseases*: The sampled medicine was kept as suggested by the manufacturer and then shipped to the University of Tuebingen, Germany, for analysis using HPLC and pharmacopeia analysis. Seven (8%) samples did not comply with pharmacopeial specifications and none of the sample was falsified.	[105]
Sudan	*Antimalarial drugs*: The results showed that most samples from the public sector failed compared with the private sector, whereby 84% did not pass the visual inspection tests, 9% did not comply with assay testing, and 7% failed the dissolution test.	[106]

chosen after interviewing the key informants. Trained staff collected samples from registered wholesale pharmacies which were stored according to the manufacturers' recommendations and eventually shipped to two Belgian accredited laboratories for analysis. The results showed that upon visual inspection, most of the artemether-lumefantrine samples had irregularities (75) and 75.5% of these samples failed subsequent chemical analyses. Chemical analysis revealed that 27.2% had at least one nonconformity, the most frequent being incorrect content of the active ingredient.[47]

Kenya

In 2018, a post-marketing surveillance study was conducted in Kenya to check the quality of antimalarial medicines. It was conducted in the city of Embu, covering all levels of health facilities representing the private and public sector. Sampling included all APIs recommended by the WHO for malaria treatment, whereby many other products being "indicated" for malaria treatment were encountered.[48] Subsequent quality control tests were done at the Drug Analysis and Research Unit (DARU) at the University of Nairobi.[49] The results on visual inspection showed no sign of substandard dosage, and analytical tests proved that all samples complied with assay and dissolution tests as per pharmacopeia.

Another post-marketing surveillance study involving anti-retroviral drugs was done for which the country was stratified into eight regions corresponding to eight country provinces. Samples were collected from all health facilities and community pharmacies which provided antiretrovirals (ARVs), and any dosage forms containing an ARV were collected. Samples were kept according to conditions recommended by the manufacturer, taken to the National Quality Control Laboratory, and analysis was done using a pharmacopeial procedure. Almost all (99.63%) of the samples complied and only one failed uniformity testing.[50]

Tanzania

Within recent years, several studies were performed in Tanzania, e.g., a post-marketing surveillance investigation of antimalarial medicines to monitor the quality of registered drugs circulating in the market. Here, samples were collected from 21 out of 26 Tanzanian regions, the selection criteria were based upon malaria prevalence and whether the region is bordering other countries. Sampling sites were chosen by covering different aspects such as port of entry, domestic manufacturers, and a high malaria prevalence. All registered antimalarial drugs were collected from all formal levels of medicine distribution in the public and private sector. Samples were subjected to product information review and quality screening using the GPHF-Minilab kits; failing samples were subjected to further analysis at the WHO prequalified quality control laboratory at the Tanzania Medicines & Medical Devices Authority (TMDA) for a confirmatory test using pharmacopeial monographs.[24,51]

Another post-marketing surveillance study was conducted in markets of Tanzania mainland for determining the quality of selected anti-retroviral (ARV) medicines. For this study, 20 regions of Tanzania were selected based on pre-defined criteria including high population, high prevalence of HIV infection, bordering other countries, and whether it was known that quality problems occurred in this region before. Samples were collected from two distribution levels: level I, involving ports of entry and medical stores, and level II, involving private and public hospitals plus other medical outlets. Only ARV medicines being commonly prescribed for HIV infections as recommended per national guidelines were chosen.[52] All samples were subjected to screening using the GPHF Minilab, and samples failing the screening were transferred to a TMDA prequalified quality control laboratory for further analysis.[53,54]

Multi-Country Analysis

A post-marketing surveillance study was done for the quality of antimalarials in six parts of Africa which are affected the most by the disease; the study sites were in central, west, and east African regions. All available formulations of the APIs – except chloroquine – were bought from randomly selected private pharmacies in major cities. The collected drugs were kept in conditions as recommended by the manufacturer, then a risk-based testing was done using the GPHF Minilab kit. 35% of all tested samples either failed identity or identity and assay testing, and thus were substandard.[55]

The quality and composition of albendazole, mebendazole, and praziquantel was studied in Burkina Faso, Côte d'Ivoire, Ghana, and Tanzania. Samples from different batches were collected from randomly selected facilities and screening was done using the GPHF Minilab kits. A confirmatory test was conducted using HPLC and pharmacopeial methods which was carried out in Germany. The results showed that 22.7% of the samples passed all tests and contained the correct amount of the API.[42] Most of the samples presenting a low quality did not meet the disintegration requirements.

A survey study for the quality of antimalaria medicines circulating in Madagascar, Senegal, and Uganda revealed that 28.5% of samples failed to comply with the specifications.[56] Each country was divided into geographic zones based on the prevalence of malaria and the national malaria control strategy, all available antimalaria medicines were collected from all levels of drug distribution and were stored under ambient conditions. Minilab testing was performed at the National Medicine Control Laboratory in Madagascar and Uganda, and at the University of Dakar in Senegal, and samples selected for full-scale testing were transferred to the USP headquarters in the United States.

Antimalarial tablets found in the unofficial market in the DRC, Burundi, and Angola containing quinine, sulphadoxine/pyrimethamine, chloroquine, and mefloquine were purchased from small informal pharmacies in Goma (Congo), Bujumbura (Burundi), and Luanda (Angola). All samples were subsequently sent to the "Istituto Superiore di Sanità" in Italy. The assay of samples was done using validated liquid chromatographic methods including galenic properties such

as uniformity of mass determination, disintegration, and dissolution tests. The results of all analyzed samples indicated that one product had a low quality of the API, unraveled the substitution of the API in one case, and confirmed "out of specification" results for 13 samples.[57]

Overuse and Misuse Through Unauthorized Selling: The South American Perspective

In contrast to Africa, only very little data are available on the amount of falsified and/or poor-quality products circulating in the market in Latin America, and almost no information is accessible regarding the actual medicine quality. Most of the information is available from non-academic sources, e.g., in Argentina, where news about falsified drugs can be found in the media from time to time. However, the reported incidents represent single alerts without any reference to nationwide investigations (see Table 4).[58–60] In 2009, the Argentinian Minister of Health in Buenos Aires, Claudio Zin, reported an approximate percentage of 10% of falsified medicines.[61] The source of this number remains unknown – it can only be assumed that he was referring to data provided by the WHO because of scarce available local investigations. In 2016, Argentina's National Administration for Drugs, Food, and Medical Technology (ANMAT) initiated a training program for health professionals from Guyana, Jamaica, Suriname, and Trinidad and Tobago to trigger a "South-South and triangular cooperation as a potential tool for strengthening medicine quality control in official medicines control laboratories (OMCLs) of the Region of the Americas."[62] Unfortunately, this was a rather descriptive study and concrete data on medicine quality which could possibly be extracted from these projects is lacking. Other studies reported incidences in Guyana and Suriname, Mexico, and Colombia – but also here, the number of concluded studies and available data is very thin.

Informal selling and distribution of medicines and medicinal products (street vendors, kiosks, illegal "pharmacies") is very common in Latin America, constitutes a severe problem and is responsible for emerging resistance to antibiotic compounds as well as a rising failure rate of the affected therapies. Medicine is either sold "over-the-counter" upon client request or is offered for self-medication although it should be available on prescription only. Such conditions can mainly be found in poorer districts of big cities or in rural markets where all kinds of goods are offered without any control. As in many LMICs, distribution mechanisms are very blurry and cannot be traced, and a targeted quality control is not possible. Typical products which are distributed through such channels are APIs for the treatment of pain (acetylsalicylic acid, ibuprofen, acetaminophen), hypertension and anticonvulsive medicines (butylscopolamine, often in combination with acetaminophen, and/or propinox (pargeverine)), antacid medication (omeprazole), antibiotics such as amoxicillin, and a variety of other substances such as sildenafil, diazepam, and clonazepam.[63]

Governments in Latin America are aware of the situation and legal action has been taken to combat this problem; however, laws introduced e.g., in Argentina in 2009 are not followed by the population and valid data depicting the situation is not available. Although court decisions were made in the following years, e.g., in 2014 in Buenos Aires, informal selling remains an established way of distributing and receiving uncontrolled medicines up to an extent of approximately 20% as stipulated by the Argentinian pharmacist's association "COFA" as of 2009.[64–66] The numbers supposedly have not improved during the last 10 years, and there is no trusted information upon the quality of medicines sold through unofficial vendors. As far as any reliable information is available upon tracing the product origin at all, the sources of these products still remain unclear. Pharmaceutical manufacturers probably sell batches to unofficial distributors and wholesalers from where the products are given to street kiosks. Or, vice versa, the owners of these shops directly buy medicines from official pharmacies at a low price which indirectly undermines the system of officially licensed pharmacies. These are open doors for interrupting the quality control supply chain because nothing is known about the storage conditions or expiration date of the products. However, patients buying these products are not interested in the origin and are happy if they can buy one or two tablets only instead of paying for the whole package. This makes any tracing of origin, batch numbers, or shelf life impossible.

Argentina

Because one of the authors of this review is living and working as a pharmacist in Buenos Aires, Argentina, medicine samples have been collected in the capital city as well as in adjacent regions. They were subsequently sent to Germany to be analyzed by academia and pharmaceutical companies. Thus, more than 200 samples could be analyzed regarding identity and content of the API as well as uniformity of mass of the individual dosage forms since 2009 (unpublished

Table 4 Findings from Various Latin-American Countries

Country	Investigated Medicine and Findings	Ref.
Ecuador	*Legal framework to combat the falsification of medical products* Participation in the EU-based system of Medicrime (2021): members are obliged to criminalize manufacturing of counterfeit medical products, supplying and trafficking in counterfeit medical products, falsifying the respective documents and unauthorized manufacturing or supplying of medicinal products as well as medical devices.	[107]
Guatemala	*Uncontrolled selling of antibiotics* Common and uncontrolled selling of antimicrobial medicine led to a severe crisis which alarmed many health professionals and the Ministry of Health in 2019. New legal regulations were set up (e.g., keeping copies of each prescription, setting up a general quality assurance system for all pharmacies, regular inspection). Nevertheless, this informal market still exists, supplying many people with unauthorized drugs as only a few inspectors are available for approximately 6,700 pharmacies. Further problems involve a lack of trained personnel, poor information provided by the shop assistants, non-adherence to prescription rules, no communication about visiting a doctor in case of severe infections, strong interest in selling the products but no effort to provide any kind of assistance or pharmaceutical knowledge.	[108–112]
Guyana and Suriname	*Poor quality of antimalarials* Quality issues were observed in 45 out of 77 (58%) antimalarial samples in Guyana of which 30 failed visual and physical inspection and 18 failed quality control tests. The proportion of monotherapy and artemisinin-based combination therapy medicines failing quality control tests was 43% (13/30) and 11% (5/47), respectively. A higher proportion of medicines sampled from the private sector, 34% (11/32), failed quality control tests versus 16% (7/45) in the informal sector. In Suriname, 58 medicines were sampled, of which 50 (86%) were Artecom®, the fixed-dose combination of piperaquine-dihydroartemisinin-trimethoprim co-blistered with a primaquine phosphate tablet. All Artecom® samples were found to lack a label claim for primaquine, thus failing visual and physical inspection.	[113]
Mexico	*Sale of antibiotics without prescription and falsified batches of antivirals* Governmental estimations state that approximately 40% of antibiotics are sold without prescription. In 2021, during the COVID pandemic, falsified batches of remdesivir were discovered which were offered online and found in a hospital in the city of Tampico.	[114–117]
Perú	*Misuse of antibiotics* Almost no data are available from Perú, but similar to other countries, a serious problem is the continuous, misled application of antibiotics for the treatment of viral infections.	[118]
Paraguay	*Fight against the sale of antibiotics without prescription* Since 2018, selling antibiotics without prescription is prohibited by the Paraguay government. Paraguay started analyzing bacterial isolates for resistance to create a comprehensive picture of the problem.	[119–120]
San Salvador	*Misuse of antibiotics* A survey conducted in 2016 revealed that out of 50 people asked, 56% anticipated using amoxicillin for treating sore throat and 34% would prefer taking chloramphenicol when suffering from diarrhea.	[121]

data). In almost every case, the declared API was present and assay testing confirmed the correct content. However, the applied methods were not always fully validated for the respective determination (especially content) and all experiments were carried out by students and laboratory trainees. Nevertheless, these investigations suggest a surprisingly positive picture of the situation.

Besides the factor "quality", non-adherence to common therapy guidelines and inappropriate, unnecessary prescribing habits also exist in Argentina. All medicinal areas are affected, even pediatrics.[67] In 2017, a survey found that antibiotics represent the most demanded and sold medicine group within the country.[68] Argentina seems to have the highest consumption rate of antibiotics in Latin America.[69,70] Various national and international antibiotic stewardship programs

have been developed, but antibiotics are still sold in huge amounts without a prescription and resistance is growing, e.g., in the field of urogenital infections.[71,72]

Although many efforts were made, the problem of resistance persists. Many Argentinian people work in informal jobs and consequently do not have any health insurance. The poverty level is above 50%, thus consulting a doctor is not affordable. This results in experimenting with domestic remedies or, if this does not help, buying medicine in a pharmacy or corner shop. Due to a severe lack of trained personnel, consultancy is very low, and antibiotics are randomly sold according to the preferences of the clients. In Buenos Aires, almost any antibiotic API is freely available, even WHO reserve group medications such as aztreonam or colistin. During the Covid pandemic, antibiotic medicine was routinely prescribed and used, although distinct guidelines and recommendations for treating Covid patients exist.[73] Recently, warnings concerning the growing distribution of carbapenem-degrading enzymes were published which can be regarded as an outcome of this misapplication.[74]

Brazil

Brazil is the biggest country in Latin America by area and inhabitants, but only a very low number of incidents and reports on misapplication and antimicrobial resistance is described for this country. Nevertheless, bad prescription habits are also very present like in all other Latin American countries, and many hospitals suffer from multi-resistant bacteria which differ between two hospitals even closely within the same city.[75] A few of them established special units driven by microbiologists who monitor the situation and try to identify multi-resistance.

Since a lot of animal breeding is done in Brazil, the overuse of antibiotics in the field of animal feeding also contributes to an emerging resistance development which is finally passed on to humans.[76]

Brazil's national medicine regulatory authority "Agência Nacional de Vigilância Sanitária" (ANVISA) is very active, reliable, and has a high reputation worldwide; however, not all manufacturing industries can be thoroughly audited on a regular basis and in a few cases, poor quality products can enter the market. Brazil is also not free from illegal activities pushing counterfeit medicine into the market either by illegal manufacturing or illegal import.[77]

Discussion

Emergence of Resistance and Poor Quality of Antibiotics

How does resistance emerge? Its evolution is a multifactorial process, depending on a variety of parameters.[78] Resistance genes in bacteria are backdated to millions of years; 5000 years old DNA has been found in permafrost and in biological material of prehistoric caves indicating that a kind of resistome had developed long before antibiotics entered the market.[79] This might be the case because most antibiotic groups, e.g., streptomycin, tetracyclines, erythromycin, and vancomycin, are produced in Actinomyces, which are of course resistant against those antimicrobials. However, resistance genes were very rarely found in the human microbiome before the clinical use of antibiotics. Since the approval of antibiotics in the 1930s and 1940s, antimicrobial resistant bacteria (ARBs) and antimicrobial resistance genes (ARGs) have been increasingly spreading throughout the world. Bacteria can modify the structure of the antibiotic target by point modifications, inactivate antibiotics by lactam or ester hydrolysis or enzymatic acetylation/phosphorylation/ribosylation, (over)expressing efflux pumps, and altering the membrane composition of lipopolysaccharides which changes the permeability, and modification of porines transporting the antibiotics into the cell. Resistance may arise from one or more of these mechanisms. In the case of intrinsic resistance, the genes are coded on chromosomes. Bacteria can acquire resistance genes from their neighbors by horizontal gene transfer which often results in a multidrug resistance. Those genes are mostly sitting on plasmids, transposons, integrins, and prophages providing them with a high mobility.[80]

The point-mutation supply rate represents the probability of a mutation within a bacteria or virus population. The mutation rate within the genome is between 10^{-4} to 10^{-8} depending on the virus, and some 10^{-10} nucleotides per genome replication in bacteria. In some infections the total pathogen population can easily exceed 10^{10} per gram tissue. Hence single, double, and even triple mutants are most probable. Another key parameter is the fitness of a resistant bacterium, which is due to the fact, that not every mutation is stable. The success of a mutant is dependent on its fitness and the fitness cost. The lower the fitness cost of a variant the easier it can spread.

The selective pressure, primarily represented by the drug concentration, plays an important role. In the case of high antibiotic concentration all susceptible bacteria will be killed, and only pre-existing resistant mutants may survive. Falsifications and distribution of low-quality products are a problem in the field of anti-infective medicine. In particular, the use of underdosed products from these classes enforces an emerging formation of resistant types, because the selective pressure is lowered, and more and more resistant types can survive.

Enrichment and spreading of the resistant pathogens depends on the number of mutants and their fitness. Furthermore, recent studies have unraveled the difference between strong and weak selective pressure. In the case of low anti-infective concentrations, the mutants are characterized by mutations of little effect. In the case of lethal selection, the mutant phenotype shows pre-existing mutations of a high effect. Hence, low drug concentrations promote mutants with low fitness costs. The smaller the difference in fitness between susceptible and resistant pathogens, the lower is the antimicrobial concentration necessary for enrichment of resistance and spreading. Moreover, the stepwise small-effect mutations give rise to the acquirement of resistance by means of mutations and of horizontal gene transfer. Taken together, low drug concentrations as found in poor-quality antimicrobials promote the development of resistance and, thus, need to be avoided.

Underdosing and/or inappropriate release of the API is a crucial factor influencing the efficacy of any medicine application. Of note, this has a very high impact in the field of antimicrobial therapy: e.g., if an analgesic does not reach the necessary concentration at the locus of action, the patient will recognize ongoing pain and will probably solve the problem by taking one or more additional tablets. On the other hand, however, if an antibiotic drug does not reach a sufficient plasma level of the API – also referred to as the minimal inhibitory concentration (MIC) necessary for killing the bacteria at the locus of infection – this cannot be realized directly by the patient and he or she may only see after a few days that the treatment does not work. In this case, a small number of susceptible bacteria might be eradicated in the beginning of the therapy, but an insufficient amount of the antibiotic may trigger an unnoticed development of resistance instead of providing a cure. If the treatment failure becomes obvious, an antibiogram must be performed to unravel resistant and sensitive bacteria strains and to be able to choose an alternative appropriate antibiotic for further treatment. However, when not done properly for cost reasons, this can result in a nightmare of multiple consecutive treatments involving various antibiotics, eventually resulting in the development of multi-resistance and prolonged cure. This shows that misuse of antibiotic medicines is also triggered by poor knowledge, in particular when medicines are supplied by informal, uncontrolled sources.

The high impact of underdosed antimicrobials stresses the importance of quality control of the API and the FP. This holds true for production as well as post-marketing surveillance. Appropriate sensitive methods should be available.[81]

Regulatory Efforts for Curbing the Distribution of Low-Quality Products

Strong national authorities are undoubtedly required for assuring a safe distribution to licensed vendors, the availability of quality-checked medicines and medicinal products as well as working post-marketing surveillance mechanisms. However, only when connecting them accordingly, e.g., by establishing an international-multinational licensing authority and attaching a network of independent control laboratories, can vigorous action be taken against drug counterfeiting and substandard products. In the European Union, the European Medicine Agency (EMA) together with the European Directorate for the Quality of Medicine and HealthCare (EDQM) are a good example of how a licensing authority and a quality control institution can enhance the safety of the drug market. Such central organizations can have a network of well-connected laboratories which constantly monitor the quality of circulating medicines, and which are able to quickly disclose poor-quality or falsified drugs. The EU Official Medicine Control Laboratory (OMCL) at the EDQM in Strasbourg (France) is embedded in a widespread European OMCL Network (GEON). In addition, OMCLs have been established in each European country as well as in so-called "Observer States" which are not part of the EU but participate in the scientific work of the EDQM and can benefit from the expertise in quality control. South America provides two observers (Mexico and Argentina), whereas Africa has seven observer states, i.e., Algeria, Guinea, Madagascar, Morocco, Senegal, South Africa, and Tunisia. The concerted work is one of the main columns guaranteeing the broad enforcement of legal rules and represents a commonly accepted quality concept which is recorded within the

major pharmacopeias (Ph. Eur., USP, BP, JP). However, a higher number of observer states would enhance the efficacy of this system.

Nevertheless, close but autonomous collaboration with the pharmaceutical industry is a prerequisite for the work of any regulatory authority or quality control system. Of note, again citing the example of Europe, the OMCL network is fully independent from pharmaceutical manufacturers and thus free from any conflict of interest or financial disclosure. Reviewing, depicting, and documenting the development – and modification, if applicable – of the manufacturing process is vital during any authorization process, the development of the underlying quality control methods, as well as follow-up procedures in quality control. Although substantial amounts of this information must be provided during the authorization and approval process already, an ongoing collaboration between pharmaceutical companies and the respective regulatory authorities represents an important backbone of the quality control system in total. For example, manufacturers are obliged to report any modifications to the synthesis pathway of an API or an exchange of excipients by legal rule. History sadly shows, however, that adherence to these regulations was not always conducted: cases such as the occurrence of unknown new toxic impurities in tryptophan, the contamination of heparin with oversulfated compounds, or the recently discovered "sartan case" where carcinogenic/mutagenic nitrosamines were found in many original and generic FPs used for treating hypertension are only a few examples.[82] These – and many more – cases illustrate the relevance of close collaboration with manufacturers on the one hand, but also underline the necessity of routine independent investigation of drug samples on the other hand. Of course, observing unknown or unexpected side effects may also help in unraveling impurities or ineffective drugs – a concept also known as pharmacovigilance.

In LMICs, limited resources are allocated to cater for post-marketing surveillance programs and therefore, only a small percentage of essential medicines is surveyed to ascertain their compliance to marketing authorization requirements.[51,58,83] The situation is amplified by the limited services of quality control laboratories as evidenced by a survey on the status of the regulatory system in Africa conducted in 2017 by Ndomondo-Sigonda et al. who reported that out of 39 countries assessed, 18 did not have any medicine quality control laboratory at all.[84] The WHO and other international institutions dealing with quality assurance of medicines advocate for the implementation of risk-based sampling and testing as a solution to ensure surveillance of a significant number of medicinal products which have been granted marketing authorization.[85,86] As mentioned earlier, the WHO prequalifies national and international quality control laboratories to allow them to support the National Medicines Regulatory Authorities during marketing authorization and post-marketing surveillance studies, respectively.[87,88] Nevertheless, to date only 10 out of 57 WHO prequalified laboratories are located in Africa, which is not a sufficient number for a thorough quality control system.[89–91]

Informal Distribution and Poor Education

Substandard quality is only one side of the story – resistance towards antimicrobial therapies can also massively emerge when non-qualified personnel deliver antibiotics, as has been described for many countries in South America and Africa. A quite high fraction of medicine distribution still happens through informal markets. As outlined above, this comprises unlicensed street vendors or unofficial "street pharmacies" selling huge amounts of cheap pharmaceutical products with unknown origin, composition, and quality, as well as unknown and insufficient information on efficacy and safety.

Of note, the focus of attention should be inquiring where corner shops and other vendors receive the respective products from: obviously, manufacturers and/or licensed pharmacies are responsible for the illegal distribution of medicine towards these channels which should be pushed back by the respective authorities. A huge amount of medicines is sold via informal distribution methods in Africa and South America as well as in many parts of Asia; here, lacking education of the "health" personnel and little knowledge on the part of the patients regarding treatment errors, resistance, or falsified medicine merge into a very serious and complex problem.[92] Moreover, many countries do not have educational schemes for pharmacists and/or pharmaceutical scientists, as e.g. in Europe, Australia, Northern America, and some parts of Asia.

Poverty and Missing Prescription Practice

In many LMICs, visiting a doctor is not affordable for most of the population. Waiting queues are very long and in many cases, a whole day of working time – and thus, money – must be sacrificed in order to see a specialist. Then, the decision

for buying a medicine from informal sources is quickly made. Money also determines which medicine is chosen and, of note, which amount is bought and taken – almost nobody is aware of antibiotic resistance at all and is satisfied with two or three tablets which they can afford. 80% of the population of Latin America lives in cities, where finding a "pharmacy" is very easy. Consequently, the problem is almost incontrollable. The situation described for Latin America does not differ from that in almost all African countries.[93–96]

Reports from these countries describe that prescribing habits are very inaccurate and inappropriate, even if a physician is consulted. Guidelines are neglected on purpose or are unknown at all. Public health-care systems are responsible for supporting and supplying a huge number of poor people or people with informal jobs. Trained personnel are missing in many cases, may be undermotivated due to low salaries, are very young and inexperienced when choosing a suitable medicine, or are not able to deny patient requests for certain APIs, e.g., antibiotics.

Conclusion

Despite the limited availability of reported data, the results of all considered studies indicate that many influences trigger the emergence of resistance. Poor medicine quality is an important factor, but not the only reason why more and more infections cannot be treated properly today. Of course, all types of medication are subject of falsification which has a serious impact on health of all people worldwide, not only in developing but also in industrialized countries.[97] Nevertheless, the broad distribution of substandard products is a very prominent factor in resistance formation, and the constant application of such products enhances the spread of resistant bacteria which eventually cannot be eradicated even when using reserve antibiotics. Constant quality control testing is inevitably necessary to depict the situation and unravel poor-quality medicines along with regulatory enforcements to withdraw them from the affected markets.

Furthermore, the prescription and distribution of all medication, especially of antibiotics and antivirals, need educated personnel to avoid their overuse. But sadly, even in Europe too many antibiotics are prescribed and sold over-the-counter, which is very hard to control.

Disclosure

The authors report no conflicts of interest in this work.

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