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Post-market quality assessment of antibiotics: findings from a cross-sectional study using standardised patients in Tabalong and Bekasi districts, Indonesia

Yusuf Ari Mashuri ,[1,2] Miratul Hasanah,[2,3] Ihsanti Dwi Rahayu,[2,4] Marco Liverani,[5,6,7] Ari Probandari ,[1,2] Neha Batura ,[8] Gill Schierhout,[9] Astri Ferdiana,[2,10] Luh Putu Lila Wulandari,[11] Berlian Kusuma Dewi,[2,12] Stephen Jan,[9] Shunmay Yeung ,[5,13] Virginia Wiseman,[5,11] Richard Day ,[14] Tri Wibawa [2,15]

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RD and TW contributed equally.

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For numbered affiliations see end of article.

Correspondence to
Professor Tri Wibawa;
twibawa@ugm.ac.id

ABSTRACT

Objectives In Indonesia, antibiotics are often purchased without a prescription at community pharmacies, contrary to current regulations. This practice may increase the risk of out-of-specification (OOS) medicines being dispensed, potentially contributing to treatment failure and antibiotic resistance. To address this concern, we assessed the quality of antibiotics purchased without a prescription at private drug retail outlets (PDROs) in Indonesia.

Design and setting We conducted a cross-sectional study in Tabalong and Bekasi, Indonesia, using standardised patients (SPs) who purchased antibiotics without a prescription for three clinical scenarios: upper respiratory tract infection (URTI), tuberculosis (TB) and child diarrhoea. The pharmacies and drug stores were randomly selected from each subdistrict based on the probability proportional method. We measured the active pharmaceutical ingredient (API) content of the antibiotic samples using high-performance liquid chromatography (HPLC).

Samples and analysis The quality of 183 antibiotics including amoxicillin tablets (148/183, 80.9%, 95% CI 74.7% to 86.1%), amoxicillin dry syrup (12/183, 6.6%, 95% CI 3.6% to 10.8%), ampicillin tablets (5/183, 2.7%, 95% CI 1.1% to 5.9%) and ciprofloxacin tablets (18/183, 9.8%, 95% CI 6.2% to 14.8%) obtained from 117/166 (70.5%, 95% CI 62.8 to 77.2) PDROs were tested. Descriptive statistics were used to describe the characteristics of the purchased antibiotics, and the API content of each antibiotic was compared against the United States Pharmacopeia 43-National Formulary 38 (USP 43-NF 38) standards in absolute values and percentages.

Results Almost all samples produced in Indonesia (182/183, 99.5%, 95% CI 97.5% to 99.9%) were unbranded (123/183, 67.2%, 95% CI 60.2% to 73.7%) or branded generic (60/183, 32.8%, 95% CI 26.3% to 39.8%) and packaged in strips (165/183, 90.2%, 95% CI 85.2% to 93.8%). Around 12/183 (6.6%, 95% CI 3.6% to 10.8%) antibiotics were found to be OOS; these were mostly amoxicillin 125 mg dry syrup (6/12, 50%, 95% CI 24.3% to 75.7%) and ciprofloxacin 500 mg tablet (5/18, 27.8%, 95% CI 11.5% to 50.6%). Around 33% (4/12, 95% CI 12.5% to 61.2%) of amoxicillin 125 mg dry syrup samples had an API content above the label claim, the highest being 187%, whereas 16.7% (2/12, 95% CI 3.6% to 43.6%) were below the label claim, the lowest being 64%. About 27.8% (5/18, 95% CI 11.5% to 50.6%) of ciprofloxacin samples tested had an API content above the label claim; the highest was 120%.

Conclusion While the proportion of OOS antibiotics identified was relatively small, at a population level,

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study aimed to provide an updated assessment of the quality of antibiotic products in Indonesia, including variations in active pharmaceutical ingredient (API) content, product presentation and accompanying information.
⇒ Antibiotics were obtained from private drug retail outlets (PDROs) in two districts, Tabalong and Bekasi, Indonesia, using standardised patients (SPs); the SP approach aimed to capture patterns in social interactions and behaviours while minimising response biases.
⇒ Only a limited range of antibiotics was analysed for the API content due to research budget constraints.
⇒ Dissolution and disintegration tests were not performed.
⇒ Information on antibiotic storage conditions across distribution channels could not be obtained. This is a potentially important factor influencing antibiotic quality.
⇒ As the study was conducted in two districts, the findings are not representative of all of Indonesia.

it represents a significant proportion of sub-optimally treated infections.

INTRODUCTION

Antibiotics are essential medicines that play a critical role in treating bacterial infections and preventing complications during procedures such as surgery.[1] However, they are frequently dispensed inappropriately, whether through unnecessary prescriptions, incorrect dosages or use for non-bacterial infections. This misuse contributes to the growing threat of antimicrobial resistance (AMR), making infections harder and more expensive to treat and complicating patient management.[2–5] In addition to inappropriate use, the circulation of poor-quality antibiotics, those with substandard or falsified active pharmaceutical ingredients, further undermines treatment outcomes. Such products may fail to eliminate infections fully, prolong illness and accelerate the development of resistant bacteria, posing a serious public health risk. According to the World Health Organization (WHO), authorised medical products, including antibiotics, that do not meet either laboratory quality standards or content specifications, or both, are defined as substandard, for example, antibiotics that have a higher or lower active pharmaceutical ingredient (API) content than the label claims.[2 6–8] Falsified medicines are medical products that deliberately or fraudulently misrepresent their identity, efficacy, safety or source. Available studies have shown that inadequate amounts of API, dissolution failure, excessive API, unidentified substances or impurities, fake packaging and substandard mass uniformity contribute to substandard antibiotics and other essential medicines.[9–15]

Substandard drugs can be found worldwide but are more prevalent in low- and middle-income countries, predominately in Africa and Asia,[9 16] where inadequate regulatory control over production processes and distribution is a key driver of poor-quality medicines.[17–20] Indonesia, with a population of more than 280 million,[21] has a large national network of private drug retail outlets (PDROs),[22] including 40 000 licensed and 95 000 unlicensed PDROs.[22 23] A standardised patient (SP) survey recently conducted by Protecting Indonesia from the Threat of Antibiotic Resistance (PINTAR) found that antibiotics were dispensed without a prescription by around 70% of PDROs in rural Tabalong and the city of Bekasi.[24] Licensed PDROs in Indonesia include both pharmacies and drug stores. Regulated by the national government, licensed pharmacies must always have a pharmacist present to oversee the dispensing of prescribed drugs, including antibiotics,[25 26] whereas licensed drug stores can only sell over-the-counter (OTC) drugs.[25]

Evidence about the quality of antibiotics at PDROs in Indonesia, to our knowledge, is limited to one published study, conducted in the city of Surabaya in 2006, which revealed a high prevalence (18%) of substandard antibiotics.[10] Given the lack of more recent evidence and Indonesia ranking high among countries with the most rapid rise in antibiotic consumption,[27] new studies of antibiotic quality are necessary to inform regulatory action and support the national strategy on AMR.[28 29] In this context, we assessed the post-market quality of antibiotics at PDROs in urban and rural areas in Indonesia based on API content requirements of the United States Pharmacopoeia (USP) 43 and National Formulary (NF) 38.

METHODS

Study design

In January–February 2020, we analysed the quality of antibiotic samples that had been obtained between July and August 2019 as part of the PINTAR study. PINTAR was a mixed-method study designed to measure the extent and determinants of inappropriate dispensing of antibiotics among community pharmacies and drug stores in Indonesia and evaluate potential solutions to this problem.[24] PINTAR included a cross-sectional survey of community pharmacies and drug stores in two districts purposively selected to capture differences in medicine supply and access to healthcare providers.[24] The city of Bekasi, with an area of 210.5 km^2 and a population of more than 3 million as of 2019, was selected to represent urban areas.[30 31] Tabalong, a district in the province of South Kalimantan with an area of 3946 km^2 and a population of 254 322, was chosen to represent rural communities.[32 33] The SPs visited 166 PDROs (121 community pharmacies and 45 drug stores), selected using stratified random sampling.[24] The sample size was calculated using the exact binomial CI method, as in a previous survey of antibiotic dispensing in Indonesia.[24] Pharmacies and drug stores were randomly selected from each subdistrict in two districts, with the number determined using the probability proportional method.[24]

Three different clinical scenarios were simulated by seven male and 14 female SPs[24]: upper respiratory tract infection (URTI), tuberculosis (TB) and child diarrhoea. The SPs received 5 days of training from the research team on how to portray clinical symptoms for an adult with URTI, an adult with presumptive TB or the parent of a child at home with diarrhoea. If the PDRO staff provided only advice or a medicine that was not an antibiotic, the SPs explicitly requested one. If the request for an antibiotic was rejected, the SPs presented a note with the name amoxicillin and mentioned that the drug was recommended by a relative. Amoxicillin was selected because it is well-known and widely used in Indonesia.[34 35] Following these interactions, antibiotic samples, if provided, were collected for laboratory analysis. In addition, data on antibiotic dispensing practices and outlet/staff characteristics were collected systematically and reported elsewhere with a detailed description of the overall study design.[24] Each PDRO was visited by three different SPs who simulated the three different clinical scenarios with 1–3 days between each visit.

Data collection

All purchased antibiotics were photographed with smartphone cameras by the SPs, including the packaging and information leaflets that, according to guidelines, should be provided when antibiotics are dispensed.[36] Antibiotics were labelled with a specific ID, packaged in separate Ziploc/closed plastic bags, protected from direct sunlight, placed in a safe, temperature- and humidity-controlled and monitored storage box and then delivered to the Centre of Tropical Medicine, Universitas Gadjah Mada (UGM). After logging and sorting, samples were couriered to two laboratories in Indonesia. Given the limited resources in each laboratory, the analysis could not be carried out at a single location. Amoxicillin and ampicillin analyses were undertaken by the Centre for Biotechnology, Agency for the Assessment and Application of Technology (Badan Pengkajian dan Pengenalan Teknologi) in Banten, and the testing of ciprofloxacin was undertaken by the Advanced Pharmaceutical Sciences Laboratory of Faculty of Pharmacy, UGM in Yogyakarta. Both laboratories are accredited by the International Organization for Standardization/International Electrotechnical Commission 17025:2017, ensuring the quality of the testing. The assay methods of amoxicillin, ampicillin and ciprofloxacin used are based on the validated criteria for the USP 43-NF 38.

Sample size

Quality testing of antibiotics was not performed on all 342 antibiotic samples obtained from the PINTAR study due to resource constraints in the two laboratories. A non-random, but purposive, selection of 183 of the 342 antibiotic samples (in manufacturer's packs) was performed to ensure quality. This selection included all the amoxicillin, ampicillin and ciprofloxacin samples collected, which accounted for more than half of the 342 antibiotic samples collected (n=183, 53.5%). In Indonesia, amoxicillin and ciprofloxacin are the two most commonly consumed antibiotics in outpatient primary care, whereas ampicillin from the access group (AWaRe classification) is the most frequently consumed antibiotic in hospital inpatient settings.[27] The analysed samples not only comprised different antibiotics but also different formulations, amounts and packaging from across Bekasi and Tabalong districts. The antibiotics collected were packaged by manufacturers as strips or blisters or in bottles, except for one sample without the manufacturer's packaging. The details of the samples, including antibiotic name, composition, dosage form, expiry date, medicine classification, manufacturer, type of packaging, API average percentage, availability of secondary packaging and leaflet, are provided in online supplemental table 2. All antibiotics in one package were assumed to belong to the same batch and tested as one sample. Thus, 10 tablets from one strip/blister were powdered together, and the powder was dissolved to form the test solution that was analysed for API content by high-performance liquid chromatography (HPLC). The average API content per tablet was then calculated. For dry syrup, the antibiotic powder in the bottle was reconstituted according to the instructions on the packaging label. Dilutions of the reconstituted solution were made to prepare test solutions for API content analysis by HPLC. Given the limited resources, identification and quantification of API in our samples were preferred over formal dissolution and disintegration studies required to determine the quality of antibiotic formulations. A total of 183/342 (53.5%) antibiotic samples, including amoxicillin tablets (148/183, 80.9%), amoxicillin dry syrup (12/183, 6.6%), ampicillin tablets (5/183, 2.7%) and ciprofloxacin tablets (18/183; 9.8%) obtained from 117/166 (70.5%) PDROs were tested.

Data analysis

Antibiotic sample analysis

The information leaflet, expiration date, medicine classification (eg, unbranded generic or branded generic), strength, photos of the packaging and dosage form (eg, tablet, capsule or oral suspension) of each antibiotic sample were recorded.[37] WHO defines generic drugs as interchangeable drugs, which are produced without a licence from the innovator company and marketed after the expiration of the patent or exclusive rights of the innovator drug.[38 39] Generic drugs are identical or bioequivalent to innovator drugs in terms of API, route of administration, dosage form, strength and therapeutic indications.[40–42]

The API content of amoxicillin, ampicillin and ciprofloxacin was assessed for each of the 183 samples by comparing assay results to the monograph specifications outlined in the USP 43-NF 38, which was the latest edition of this pharmacopoeia (published in 2020) at the time of the analyses.[43] The API content was assayed by HPLC analysis, which is the gold standard assay method in the USP 43-NF 38. Published and validated methods were followed for amoxicillin, ampicillin and ciprofloxacin, with each HPLC assay meeting quality control (QC) standards. The USP 43-NF 38 quality standards for acceptable API contents were was 90%–110% for ciprofloxacin and 90%–120% for amoxicillin and ampicillin.[43] The antibiotic standards used were pure substance API that complied with the Indonesian Pharmacopoeia Comparison Standards obtained from The Indonesian Food and Drug Authority of The Republic of Indonesia. The details of the HPLC system used for ciprofloxacin analysis were as follows: HPLC from Hitachi, D2000; detector, spectrophotometer UV; wavelength, 278 nm; flow rate, 1.5 mL/minute; injection volume, 20 µL; reversed-phase column, Cosmosil C18, 250×4.6 mm, 5 µm; mobile phase, a mixture of 0.025 M H_3PO_4 pH 3.0 and acetonitrile with a ratio of 87: 13 v/v. The HPLC system used for amoxicillin and ampicillin analysis was as follows: HPLC from Waters Alliance; detector, photo diode array (PDA); wavelength, 225 nm; flow rate, 1 mL/min; injection volume, 20 µL; reversed-phase column, Gemini C18, 5 µm, 250X4.6 mm (Phenomenex); mobile phase, acetonitrile: methanol: 10 mM KH_2PO_4 with a ratio of 9.5: 5.5: 85 v/v.

Statistical analysis

Descriptive statistics were used to summarise the characteristics of the purchased antibiotics. The API content of each antibiotic sample tested against the USP 43-NF 38 standards is presented in absolute values and percentages. All statistical analyses were performed with Stata 14 (College Station, TX).

Patient and public involvement

None.

RESULTS

Characteristics of the antibiotics purchased

The antibiotics were purchased from 124 PDROs (95 pharmacies and 29 drug stores). About one-fifth of PDROs (23/124, 18.4%) dispensed the same antibiotic to two SPs (online supplemental table 2). The majority of the antibiotics were purchased from pharmacies (135/183, 73.8%, 95% CI 67.1% to 79.7%). The packaging indicated that almost all antibiotics were produced in Indonesia (182/183, 99.5%, 95% CI 97.5% to 99.9%). Almost all antibiotics were sold in the manufacturer's original packaging, namely, strip packs (165/183, 90.2%, 95% CI 85.2% to 93.8%), bottles (12/183, 6.6%, 95% CI 3.6% to 10.8%) and blister packs (5/183, 2.7%, 95% CI 1.1% to 5.9%). Only one antibiotic sample had been re-packaged in a plastic pack by staff at a PDRO. Most antibiotics were unbranded generic (123/183, 67.2%, 95% CI 60.2% to 73.7%), whereas the others were branded generic (60/183, 32.8%, 95% CI 26.3% to 39.8%). Most antibiotics were provided without any information leaflets (169/183, 92.3%, 95% CI 87.8% to 95.5%). Almost all the antibiotics purchased had printed expiry dates that were after the date of purchase (181/183, 98.9%, 95% CI 96.5% to 99.8%). Two samples had no printed expiry date (table 1 and online supplemental table 2).

Test results for antibiotic quality

Amoxicillin tablets accounted for the majority of the samples tested for API content (148/183, 80.9%, 95% CI 74.7% to 86.1%). Around 12/183 (6.6%, 95% CI 3.6% to 10.8%) samples tested for API content were out of specification (OOS) (online supplemental table 1). Amoxicillin dry syrup was most often found as OOS; 33.3% (4/12, 95% CI 12.5% to 61.2%) had an API content above the label claim reaching 187%, and 16.7% (2/12, 95% CI 3.6% to 43.6%) were below the label claim, the lowest being 64%. About 27.8% (5/18, 95% CI 11.5% to 50.6%) of ciprofloxacin tested had API content above the label claim, the highest being 120%, and all of the API contents of ampicillin samples met the specification (online supplemental tables 1, 2). Half of the OOS antibiotics were branded generic medicines (6/12, 50%, 95% CI 24.3% to 75.7%) and more than half of these were obtained from pharmacies (4/6, 66.7%, 95% CI 28.6% to 92.3%) (online supplemental table 1). The OOS antibiotics came from seven (7/20, 35%, 95% CI 14.1% to 55.9%) different manufacturers. Three antibiotics (3/12, 25%, 95% CI 5.5% to 57.2%) came from "G" manufacturer (three amoxicillin 125 mg each for a different scenario), and two antibiotics (2/12, 16.7%, 95% CI 2.1% to 48.4%) each came from "L" (two ciprofloxacin 500 mg each for a different scenario), "R" (two amoxicillin 125 mg each for a different scenario) and "S" (one amoxicillin 125 mg and one ciprofloxacin 500 mg). Furthermore, one antibiotic (1/12, 8.3%, 95% CI 0.2% to 38.4%) each came from "D" (one amoxicillin 500 mg), "N" (one ciprofloxacin 500 mg) and "O" (one ciprofloxacin 500 mg) manufacturers (online supplemental table 2).

DISCUSSION

This study sought to assess the post-market quality of antibiotics purchased in accordance with API content requirements of the USP 43-NF 38 standard. We found that 6.5% of the sampled antibiotics did not meet the API content specification standards based on the USP in post-market quality testing. Our findings show that QC was lacking for the post-market quality in particular manufacturers (35%). This analysis indicates that some manufacturers' products and processes need closer monitoring, most notably those where more than one of their antibiotic products is OOS. Amoxicillin dry syrup samples were more frequently OOS than amoxicillin tablets (50% vs 1%; $p < 0.05$), consistent with findings from previous studies in Indonesia and Papua New Guinea.[3 44] Moreover, the API content of one amoxicillin dry syrup sample was almost double (186%) that of the USP 43-NF 38 standard. This finding is concerning and could be due to poor manufacturing practices or inadequate QC processes.[45] Conversely, several amoxicillin dry syrup samples returned API contents lower than the USP 43-NF 38 standard. The condition of the dry syrup form during production, distribution and storage can affect the quality of the antibiotic dispensed to consumers.[46] In addition, reduced API contents can occur when antibiotics are degraded by exposure to direct sunlight, high humidity and drug storage temperatures that do not comply with storage instructions.[47–49] This is also supported by research showing that the solid-state formulation of amoxicillin is sensitive to humid conditions, which encourages hydrolysis of the beta-lactam ring, thereby threatening the effectiveness and safety of the product.[3 48 50]

This study showed that the antibiotics are commonly dispensed in drug stores. This is in violation of Indonesian regulations, which require the dispensing of antibiotics only with a doctor's prescription and only in pharmacies under the supervision of a pharmacist.[51 52] Drug stores are only permitted to store and sell non-prescription drugs.[53 54] The continued practice of dispensing antibiotics without a prescription exposes the community to a high risk of unnecessary antibiotics.[8] In addition, the absence of regular supervisory controls in drug distribution channels creates opportunities for the illegal supply and sale of drugs, especially prescription drugs, as well as

Table 1 Characteristics of the analysed antibiotic samples

Variables	Amoxicillin 500 mg tablet n=148 (%); 95% CI	Amoxicillin 125 mg dry syrup n=12 (%); 95% CI	Ampicillin 500 mg tablet n=5 (%); 95% CI	Ciprofloxacin 500 mg tablet n=18 (%); 95% CI	Total n=183
District					
Bekasi	94 (79.7); 71.7 to 86.2	7 (5.9); 2.7 to 11.3	0 (0.0); -	17 (14.4); 9.0 to 21.6	118
Tabalong	54 (83,1); 72.6 to 90.7	5 (7.7); 3.0 to 16.0	5 (7.7); 3.0 to 16.0	1 (1.5); 0.2 to 7.0	65
PDRO					
Pharmacy	108 (80.0); 72.7 to 86.1	9 (6.7); 3.3 to 11.8	1 (0.7); 0.1 to 3.4	17 (12.6); 7.8 to 19.0	135
Drug store	40 (83.3); 71.0 to 91.8	3 (6.3); 1.8 to 15.7	4 (8.3); 2.9 to 18.6	1 (2.1); 0.2 to 9.3	48
Stated country of manufacture					
Indonesia	147 (80.8); 74.6 to 86.0	12 (6.6); 3.7 to 10.9	5 (2.7); 1.1 to 5.9	18 (9.9); 6.2 to 14.9	182
Unknown	1 (100.0); -	0 (0.0); -	0 (0.0); -	0 (0.0); -	1
Primary packaging					
Strip	147 (89.1); 83.7 to 93.2	0 (0.0); -	5 (3.0); 1.2 to 6.5	13 (7.9); 4.5 to 12.7	165
Bottle	0 (0.0); -	12 (100.0); -	0 (0.0); -	0 (0.0); -	12
Blister	0 (0.0); -	0 (0.0); -	0 (0.0); -	5 (100.0); -	5
No Package	1 (100.0); -	0 (0.0); -	0 (0.0); -	0 (0.0); -	1
Provided secondary packaging					
No	148 (85.1); 79.2 to 89.8	3 (1.7); 0.5 to 4.5	5 (2.9); 1.1 to 6.2	18 (10.3); 6.5 to 15.5	174
Yes	(0.0); -	9 (100.0); -	0 (0.0); -	0 (0.0); -	9
Leaflet available					
No	146 (86.4); 80.6 to 90.9	0 (0.0); -	5 (3.0); 1.1 to 6.4	18 (10.7); 6.7 to 16.0	169
Yes	2 (14.3); 3.1 to 38.5	12 (85.7); 61.5 to 96.9	0 (0.0); -	0 (0.0); -	14
Medicine classification					
Unbranded generic	108 (87.8); 81.2 to 92.7	2 (1.6); 0.3 to 5.1	5 (4.1); 1.6 to 8.7	8 (6.5); 3.1 to 11.9	123
Branded generic	40 (66.7); 54.2 to 77.6	10 (16.7); 8.9 to 27.6	0 (0.0); -	10 (16.7); 8.9 to 27.6	60
Expiry date					
After purchase	147 (81.2); 75.1 to 86.4	12 (6.6); 3.7 to 11.0	5 (2.8); 1.1 to 5.9	17 (9.4); 5.8 to 14.3	181
Unknown*	1 (50.0); 6.1 to 93.9	0 (0.0); -	0 (0.0); -	1 (50.0); 6.1 to 93.9	2
Before purchase	0 (0.0); -	0 (0.0); -	0 (0.0); -	0 (0.0); -	0

*No information because there was no packaging or the information on the pack was incomplete (antibiotic purchased in less than one strip).

opportunities for the distribution of 'OOS' and falsified drugs in the community.[55 56]

Most antibiotics tested were unbranded generic medicines, especially amoxicillin. Meanwhile, for ampicillin and ciprofloxacin, branded generics were more often collected by SP. These results will have been influenced by SPs' demands for amoxicillin. This reflects the fact that patient' requests have an important influence on the dispensing of antibiotics without a prescription. If there is no specific request from the patient regarding the name of the antibiotic, a branded generic antibiotic is often provided because healthcare providers believe that branded drugs are more effective than unbranded drugs.[57] However, this belief was contrary to the results of this study, which showed that half of the OOS antibiotics were branded generics.

In Indonesia, the government is responsible for regulating and auditing the production, distribution and consumption of medicines, including antibiotics.[51 58 59] Both unbranded generic and branded generic drugs registered for distribution and use in Indonesia must have evidence of bioequivalence to the originator drug.[42] Bioequivalence indicates that the generic drug is expected to be identical with respect to its efficacy, effectiveness and safety to the originator, registered medicine.[60 61] Generic drug use policies in many developing countries are enforced to increase access to affordable and quality medicines, improve health service outcomes and reduce high drug costs in treating diseases.[39 40]

Regular monitoring and testing of medicines that have received marketing permits are needed to meet the requirements for acceptable drug quality.[62] Several important factors are relevant for assessing antibiotic product quality, namely, dosage form disintegration and dissolution performance, degradation rates, sterility and presence of impurities, all of which can affect the

effectiveness and safety of treatment for many high burden diseases.[45 58] The key to the therapeutic effectiveness of drugs, including antibiotics, is their API content.[63] The API content can also be a useful indicator in monitoring the quality of medicinal products circulating across Indonesia. Knowledge that regular monitoring of products occurs is a stimulus to always strive to meet and maintain the established quality requirements, thereby assuring that products are effective and safe for consumption.[58] Insufficient API content can lead to a decrease in antibiotic therapeutic efficacy and have a wider effect on resistance,[63 64] whereas excessive API content increases the risk of adverse drug reactions.[65] Dissolution and disintegration tests were not carried out in the current study due to resource limitations.

There are strategies to maintain the quality of antibiotics so that they can meet the required standards, including consistent implementation of Good Medicine Manufacturing Practices (GMP), Good Distribution Practices (GDP) and Good Storage Practices (GSP) standards.[66 67] Other practices that can promote the quality of antibiotics dispensed to consumers, as well as give advice for safe and effective use, include providing product information leaflets and reflecting expiration dates and storage conditions on the packaging.[68–70] Our results showed that only one sample of antibiotics was not in the original packaging, and two samples did not display an expiration date. Almost all purchased antibiotics did not include product information leaflets. The absence of written information accompanying the drug poses a risk to patients who are unlikely to be aware of the need for temperature control for safe storage of some antibiotics, correct dosage information and what to do if an adverse event occurs.[10 71] Community pharmacists must help ensure the quality of drugs dispensed and provide quality information to accompany those medicines.

This study reinforces the need for ongoing, more geographically dispersed and comprehensive surveillance of antibiotic quality across drug stores and pharmacies in Indonesia. In addition to the verification of API identity and content, formulation performance through disintegration and dissolution testing, along with evaluation for excipients, contaminants and sterility, should also be monitored in line with USP requirements.

Study limitations include insufficient resources to examine the quality of the collected antibiotic samples comprehensively. Specifically, we were unable to undertake dissolution and disintegration tests, or screen for impurities, toxins and falsified products. Neither could we collect information on the storage conditions of antibiotics across the distribution pathways, an important factor that may affect the quality of antibiotics. This purposive sampling approach, necessitated by laboratory with resource constraints, achieved good geographical coverage for the commonly used antibiotics in Indonesia, although potentially limiting the generalisability of our results across all regions of Indonesia. Moreover, while our study tested the three most commonly purchased antibiotics, there is a limitation due to lack of information on API content of other antibiotic types that we could not test due to resource constraints.

CONCLUSIONS

We found that a small proportion of antibiotic samples collected from drug stores in Indonesia were OOS with API content compared with the USP 43-NF 38 limits. This suggests that QC systems for antibiotic production and distribution through to drug sales at the pharmacy level may need attention. It is a community and government expectation that all processes must be in accordance with GMP, GDP and GSP standards. Regular monitoring of the quality of antibiotic products circulating in the community is needed to ensure ongoing safety and effectiveness. Strict QC through regular testing of products dispensed in the community is justified as antibiotics are commonly accessed, making people vulnerable to OOS products as well as potentially exposing them to falsified medicines.[4] Improving community understanding regarding health conditions where antibiotics are or are not needed and how to store and use these products to maintain effectiveness are important and practicable. Finally, regulations regarding the production, distribution and use of antibiotics must always be enforced to ensure the public are accessing medicines proven to be safe, effective and of good quality.

Author affiliations
[1]Faculty of Medicine, Universitas Sebelas Maret, Surakarta, Indonesia
[2]Center for Tropical Medicine, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia
[3]Faculty of Medicine, Universitas Jember, Jember, Indonesia
[4]Department of Pharmacy, Faculty of Medicine, Universitas Lampung, Bandar Lampung, Indonesia
[5]Department of Global Health and Development, London School of Hygiene & Tropical Medicine, London, UK
[6]School of Tropical Medicine and Global Health, Nagasaki University, Nagasaki, Japan
[7]Faculty of Public Health, Mahidol University, Bangkok, Thailand
[8]Institute for Global Health, University College London, London, UK
[9]The George Institute for Global Health, Sydney, New South Wales, Australia
[10]Faculty of Medicine and Health Sciences, University of Mataram, Mataram, Indonesia
[11]The Kirby Institute, University of New South Wales, Sydney, New South Wales, Australia
[12]Politeknik Negeri Indramayu, Indramayu, Indonesia
[13]Department of Clinical Research, London School of Hygiene & Tropical Medicine, London, UK
[14]Department of Clinical Pharmacology & Toxicology, St Vincent's Clinical School - University of New South Wales, Sydney, New South Wales, Australia
[15]Department of Microbiology, Facuty of Medicine, Public Health and Nursing Universitas Gadjah Mada, Yogyakarta, Indonesia

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provided critical input, reviewed the draft and approved the final manuscript. TW acted as guarantor.

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ORCID iDs
Yusuf Ari Mashuri http://orcid.org/0000-0002-3494-9842
Ari Probandari http://orcid.org/0000-0003-3171-5271
Neha Batura http://orcid.org/0000-0002-8175-8125
Shunmay Yeung http://orcid.org/0000-0002-0997-0850
Richard Day http://orcid.org/0000-0002-6045-6937
Tri Wibawa http://orcid.org/0000-0003-0477-4575

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