

A study of the quality of cardiovascular and diabetes medicines in Malang District, Indonesia, using exposure-based sampling

Aksari Dewi ,¹ Anushka Patel,¹ Anna Palagy,¹ Devarsetty Praveen,² Bachtiar Rifai Pratita Ihsan,³ Ayuk Lawuningtyas Hariadini,³ Diana Lyrawati,³ Sujarwoto Sujarwoto ,⁴ Asri Maharani,⁵ Gindo Tampubolon,⁶ Stephen Jan,¹ Elizabeth Pisani ,¹

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For numbered affiliations see end of article.

Correspondence to

Aksari Dewi;
aksari.iraska@gmail.com

ABSTRACT

Background The WHO has warned that substandard and falsified medicines threaten health, especially in low and middle-income countries (LMICs). However, the magnitude of that threat for many medicines in different regions is not well described, and high-quality studies remain rare. Recent reviews of studies of cardiovascular and diabetes medicine quality recorded that 15.4% of cardiovascular and 6.8% of diabetes samples failed at least one quality test. Review authors warn that study quality was mixed. Because they did not record medicine volume, no study reflected the risk posed to patients.

Methods and findings We investigated the quality of five medicines for cardiovascular disease and diabetes in Malang district, East Java, Indonesia. Our sample frame, based on dispensing volumes by outlet and price category, included sampling from public and private providers and pharmacies and reflected the potential risk posed to patients. The content of active ingredient was determined by high-performance liquid chromatography and compared with the labelled content. Dissolution testing was also performed.

We collected a total of 204 samples: amlodipine (88); captopril (22); furosemide (21); glibenclamide (21) and simvastatin (52), comprising 83 different brands/products. All were manufactured in Indonesia, and all samples met specifications for both assay and dissolution. None was suspected of being falsified.

Conclusions While we cannot conclude that the prevalence of poor-quality medicines in Malang district is zero, our sampling method, which reflects likely exposure to specific brands and outlets, suggests that the risk to patients is very low; certainly nothing like the rates found in recent reviews of surveys in LMICs. Our study demonstrates the feasibility of sampling medicines based on likely exposure to specific products and underlines the dangers of extrapolating results across countries.

INTRODUCTION

In 2017, the WHO warned that substandard and falsified medicines posed a significant

WHAT IS ALREADY KNOWN ON THIS TOPIC

- The WHO suggests that as many as one in 10 medicines in low-income and middle-income countries are of poor quality, but studies of the prevalence of substandard and falsified rarely take into account patient exposure.
- Medicines for non-communicable diseases and studies from large middle-income countries are under-represented in existing studies.

WHAT THIS STUDY ADDS

- We showed that it is feasible to sample medicines based on patient exposure. Our exposure-based study of cardiovascular and diabetes medicines in Indonesia, a lower-middle income country that is the world's fourth most populous, found that all met quality standards.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- Adopting exposure-based methods for sampling and/or calculating the prevalence of substandard and falsified medicines would improve our understanding of the potential public health impact of poor-quality products globally.

threat to health and to budgets, especially in low and middle-income countries (LMICs). The warning, based on data from its newly strengthened case reporting system and a review of 100 studies of medicine quality (some unpublished), was summarised in a press release headlined: '1 in 10 medical products in developing countries is substandard or falsified'.^{1–3}

The WHO noted nine major limitations in its own review, many centring around heterogeneity in definitions, sampling designs and testing. In 2009, scholars proposed Medicine Quality Assessment Reporting



Guidelines (MEDQUARG), along with sampling and survey methods.⁴ A 2013 review, which rated medicine quality studies, published between 1948 and 2013 against the MEDQUARG guidelines found that only 15 of 44 meet what the paper's authors define as minimum standards for research design and reporting (scoring 6 or more on the MEDQUARG checklist).⁵ Standards have improved since the guidelines were published, according to McManus and colleagues, who identified a further 34 studies published between 2013 and 2018; just one of these scored less than 6.⁶ They note, however, that the studies use a variety of sampling methods and quality definitions, complicating the interpretation of results.

MEDQUARG became the basis for methodological guidelines for field surveys of medicine quality published by the WHO in 2016.⁷ The guidelines cover various sampling designs (convenience, simple or stratified random sampling, lot quality assurance and sentinel site monitoring), expressing a preference for random sampling where feasible. More recently, researchers have proposed surveillance methods focused on capturing medicines at highest risk of being substandard.⁸

Broadly speaking, these sample designs aim to estimate the prevalence of substandard medicines (which are made by registered pharmaceutical companies in regulated factories but do not meet the quality standards set out in their market authorisation paperwork, either because they were poorly made or because they have degraded since manufacture) or of falsified medicines. The latter are made, repackaged or sold by criminals who seek deliberately to misrepresent the identity, composition or source of the product.⁹ Prevalence of poor-quality medicines is usually expressed as the number of samples failing testing, divided by the number tested, though some designs calculate the proportion of outlets dispensing poor-quality medicines.⁴

MEDQUARG guidelines suggest reporting information on volumes of sales (potentially allowing the risk of exposure to be calculated), and at least one study has weighted prevalence by sales volume.¹⁰ However, none of the WHO-proposed sampling designs adequately captures the risk posed to patients. For a given level of physical harm caused by a poor-quality medicine, the risk of exposure is determined not only by the prevalence of poor-quality medicines but also by the likelihood that a patient will consume the type and particular brand of medicine at fault. A small number of brands or outlets may account for a large fraction of patient consumption. In addition, consumption varies by type of medicine and health condition; for example, medicines for chronic conditions are likely to be taken indefinitely, while patients generally only take antimicrobials when experiencing an infection.

Cardiovascular and diabetes medicines

Medicines for chronic conditions are under-represented among medicine quality studies; just 6.2% of the 48 218 tested medicines included in the WHO review were for

non-communicable diseases.² A 2019 review identified just five field-based quality surveys including medicines for diabetes, covering 31 countries and totalling 527 samples, of which 6.8% were substandard or falsified.¹¹ Two of the five surveys used random sampling designs. The medicine most commonly tested in the reviewed studies was metformin; 5.4% of 258 metformin samples collected across four surveys failed at least one quality test, glibenclamide featured in two surveys; 9.2% of 239 samples failed at least one test. A 2021 review of CVD medicine quality studies identified 27 prevalence surveys published between 1996 and 2020. The studies covered 23 active ingredients, in medicines collected in 28 low or middle-income countries.¹² Overall, 525 out of 3414 samples (15.4%) failed at least one quality test to which they were subjected. However, the authors are careful to note: 'we do not state that 15.4% of cardiovascular medicines globally are SF (substandard or falsified)'. Some 63% of all CVD medicine samples were collected in Africa, many in a study that used stricter criteria for tolerated deviations than permitted by the commonly-used United States Pharmacopeia (USP) standards.¹³ Failure rates in Africa were higher than in other regions.

Of close to 4000 samples included in the two reviews, just 212 were collected in Southeast Asia, and only four in Indonesia, the world's fourth most populous country, where prevalence of hypertension and diabetes among adults aged 45 or more are 52.8% and 13.5% respectively.¹⁴ The four samples, collected between 2009 and 2012, were labelled as a Japanese brand of candesartan; all were judged falsified.¹⁵

Cardiovascular disease prevention in Indonesia

In an attempt to reduce the burden of cardiovascular disease (CVD) in Indonesia, the Ministry of Health has since 2012 supported a prevention and early detection programme, including the prescription of medication to prevent cardiovascular events.¹⁶ Members of Indonesia's nationwide health insurance system *Jaminan Kesehatan Nasional* or JKN (which at the start of 2022 covered 235.7 million people, around 80% of the population) are entitled to free medication. However, to access it, they must follow cumbersome bureaucratic procedures, and medicines are not always available.^{17 18}

Some Indonesians are, thus, obliged to buy these medicines, and medicines for other conditions such as diabetes, from pharmacies or elsewhere; others choose to do so for convenience or because they prefer branded medicines which are not provided free. Some vendors do not comply with good pharmaceutical practice, for example, in terms of temperature control, or are not regulated by health authorities.¹⁹

Since an auction-based, single-winner procurement platform for JKN medicines known as e-catalogue was introduced in 2014, the volume of medicines procured by the state has risen, and the price paid by Indonesia's public sector for many essential medicines has fallen dramatically, to levels that producers complain

are unsustainably low.^{20 21} This, together with a number of medicine falsification scandals in the private sector, raised concerns (expressed in the news media and by professional medical associations) about the quality of the medicines taken by Indonesian patients.²² Public concern about medicine quality appears at odds with regulatory data. Indonesia's medicine regulator Badan Pengawasan Obat dan Makanan (BPOM) has been certified by WHO as maturity level 3, the second highest level.²³ BPOM is relatively well resourced, with a 2020 budget of US\$107 million (72% spent on oversight of medicines and food); over 5000 staff; and laboratories in every province. Annual postmarket surveillance was suspended during the COVID-19 epidemic, but in 2019, BPOM reported 340 of 17123 sampled medicines were out of specification (1.98%), far below the '1 in 10' intimated by WHO for LMICs.²⁴

Substandard cardiovascular and diabetes medicines may fail to deliver the correct dosage of active pharmaceutical ingredient (API), thus increasing the risk of cardiovascular events or compromising glucose control, and endangering patients. At a population level, the extent of the threat depends on the number of patients exposed to specific brands of medicine that are poor quality. Because quality may also be affected by handling and storage, the outlet from which medicines are acquired may also influence exposure. However, sampling methods designed to reflect population exposure have not, to our knowledge, been tried in medicine quality surveys, and no studies of the quality of CVD or diabetes medicines in Indonesia exist.

Aiming to fill this gap, we designed a exposure-based study that sampled the five medicines most commonly used by patients at high risk for CVD in eight villages in Malang district, East Java, testing them to ascertain whether they met the quality specifications listed in United States Pharmacopeia and Farmakope Indonesia VI for per cent of active ingredients (assay) and for dissolution—a proxy for availability of active ingredients in the body after consumption. Four of these medicines target CVD while one was a diabetes medicine, reflecting frequent comorbidity with the two diseases.

METHODS

We report according to MEDQUARG guidelines. The annotated checklist is available at <https://doi.org/10.7910/DVN/EBQYUB>.

Study setting and background

The study was based around eight villages in Malang district, a district of 2.5 million people in Indonesia's second most populous province, East Java. The eight villages, which include urban, semiurban and rural areas, hosted previous research about CVD risk management.^{25 26} Researchers screened 99.24% of all adults aged ≥40 in the eight villages in 2018; among the 22 093 people screened, 6579 adults were identified as at high

risk for CVD. For the 2534 who reported taking any CVD medicine, information was also collected about which medicines they consumed, by API and dosage.

In the study area, patients at high risk for CVD and diabetes may acquire all study medicines for free from public primary health centres, including village-level outreach posts. Most of these medicines are procured through a single national government-run e-catalogue platform and distributed from the District Medicine Warehouse. With rare exceptions (mostly for patented medicines), all are unbranded generics identified by their international non-proprietary name (INN). If the warehouse is out of stock, primary health centres may buy their own INN medicines using capitation funds, a mechanism through which JKN pays public primary health centres and private clinics that accept publicly insured patients a fee per registered participant to deliver preventative services and healthcare, including medicines.²⁷ The public hospital provides INN medicines free to JKN-insured patients, paying out of a flat-rate diagnostic-related reimbursement package. Hospitals charge non-insured patients for both INN and branded medicines. They may procure medicines for JKN patients through e-catalogue, independently of the District Medicine Warehouse, or may buy other brands directly from distributors.

Some 50.2% of Malang district residents were JKN members in 2020, well below the national average of 79%. Of those reporting using outpatient services, just 32.7% said they used JKN insurance.^{28 29} Most of the remainder sought care from private healthcare providers—doctors, midwives or nurses. Many doctors provide prescriptions for medicines which patients then buy from pharmacies. A rapid survey of healthcare providers (see below) indicated that many doctors and midwives also sell prescription medicines directly to patients themselves, although they are not authorised to do so in the study area. A further unauthorised sources of medicines are the medicine shops which sell prescription medicines in violation of their over-the-counter-only licenses.

Sample definition and sample size

Following WHO norms,⁷ we defined a single 'sample' of medicine as:

- One product (API).
- Of one dosage (strength and form).
- Of one brand.
- From one manufacturer.
- One batch number.
- Collected at one location, at one time.

Sampling of medicines differs from sampling of individuals because if good manufacturing and distribution practices are followed, quality should not vary within a batch. Exceptions occur, for example, when a genuine batch number is used on a falsified product, or if handling and storage have varied significantly between samples, leading to differential degradation. Broadly speaking, however, a single sample of a medicine should represent

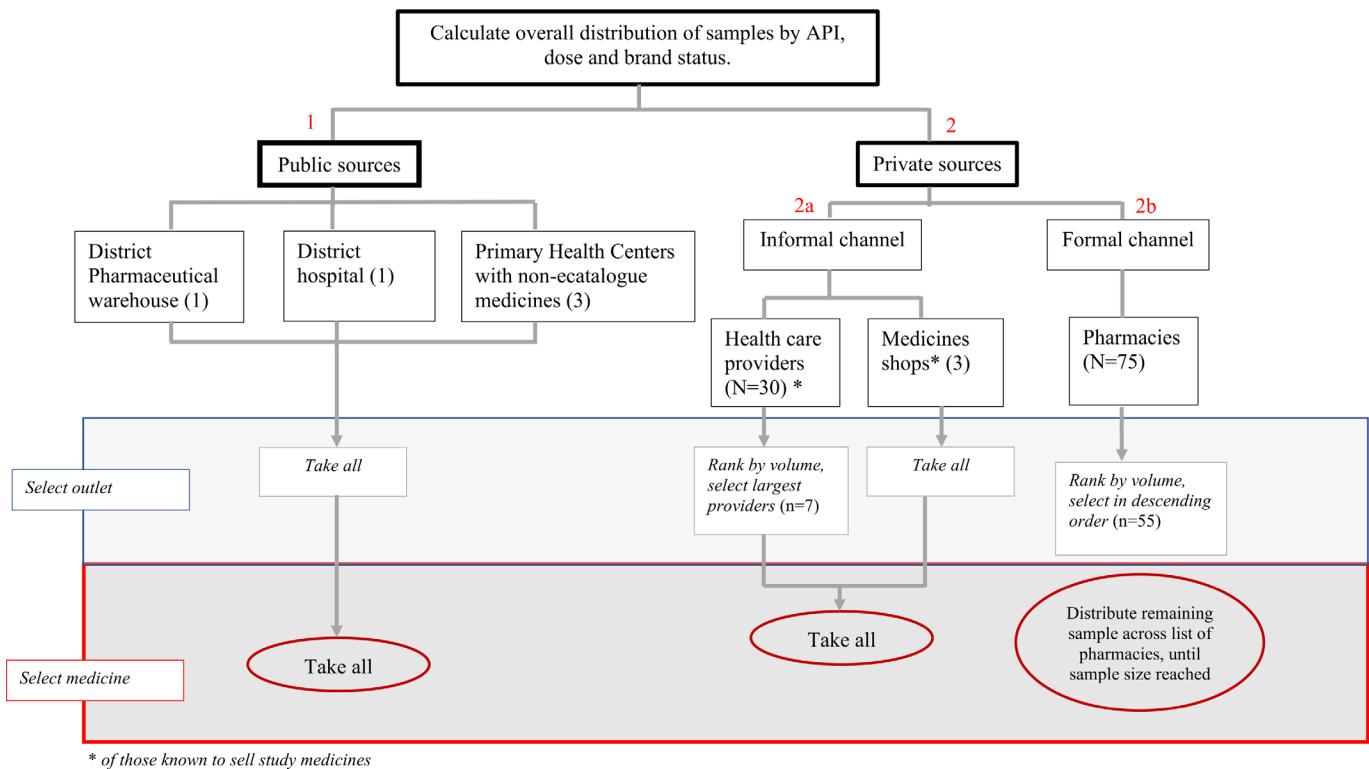


Figure 1 Steps undertaken in construction of sample frame. API, active pharmaceutical ingredient.

the quality of all products of the same API, dose form and brand, made by the same manufacturer, with the same batch number, sampled in the same location at the same time. A single sample can, thus, represent the risk of exposure to poor-quality medicines for a large proportion of patients.

Our maximum target sample size, determined by budgetary constraints, was of 200 samples, adequate to collect at least one sample from all major sources of medicine in the study area (see figure 1). The Malang District Department of Health gave written permission for the study (070/1102/35.07.103/2020). The study also received ethics approval from the Ethical Committee, Ministry of Research, Technology and Higher Education, Medical Faculty of Brawijaya University (No.83/EC/KEPK/04/2020) and the Human Research Ethic Committee of University of New South Wales, Sydney (HC200148). The reflexivity statement in online supplemental appendix provides further information about the relationship between institutions. Patients were not directly involved in the design, conduct or reporting of this study.

Construction of sample frame: data sources

To construct a sample frame reflecting the likelihood that a patient would take a particular medicine, we collected secondary data from a variety of sources and also conducted a rapid survey of listed outlets and healthcare providers. The data, summarised in table 1, were then triangulated to develop a sample frame reflecting the likely distribution of patients consuming different medicines, by INN status and source of acquisition.

We chose the study medicines based on a 2018 household survey data, in which over 6500 high-risk patients reported which (if any) medicines they took to control blood pressure or cholesterol.²⁵ We included all medicines and dosages taken by at least 10% of those reporting medicine use. Because of high levels of comorbidity, these included one medicine (glibenclamide) to control blood sugar. In order of frequency, the medicines were amlodipine, simvastatin, captopril, furosemide and glibenclamide, all in oral tablets. The first three are commonly prescribed in two dosages, the final two in just one, giving a total of eight products (APIs and doses) to be sampled.

With the consent of the management (and where relevant, district health authorities), staff at the District Medicine Warehouse (1/1) and a private medicines distributor (1/40) provided information on volumes of the study medicines distributed each month. Two primary health centres (2/5) and two pharmacies (2/75) provided data on volumes dispensed.

The public health division of health information science company IQVIA provided data on sales volumes of study medicines in Indonesia, disaggregated by INN/branded status. These data are collected on a quarterly basis from a nationally representative panel of >1000 pharmacies, 175 medicine shops and 250 hospitals in both the private and public sectors.

We obtained listings and contacts of pharmacies, medicine shops and healthcare providers from sources shown in table 1. All were contacted in person, and the purpose of the study was explained. From pharmacies, we asked

Table 1 Data used to inform sample frame

Data type	Source	Information provided	Time frame
Household survey data	Provided by authors of Reference 25.	% of patients consuming medicine, by API and dose	2018
Detailed distribution or dispensing data	Secondary data provided by facilities	Volumes distributed or dispensed by API, dose, brand and month: district warehouse; two primary health centres; one private distributor; two pharmacies	April–October 2020
National aggregate sales volume	IQVIA public health	Sales volume by API and dose, by INN status and outlet sector (hospital or retail).	April–October 2020
Listing of pharmacies	District health office, verified by research team	Location of pharmacies and medicine shops in eight study villages and four neighbouring market centres*; private healthcare providers in eight study villages	2019 data received March 2020, verified October 2020
Listing of healthcare providers and medicine shops	Internet search and public directories, verified by research team	Location of private healthcare providers and medicine shops in eight study villages	October–November 2020
Rapid survey of pharmacies and medicine shops	Primary data	Estimate of patients served per day with any study medicine	October–November 2020
Rapid survey of healthcare providers	Primary data	Estimate of patients served per day with any study medicine, medicines sold, source of medicines	November–December 2020

*These bordering locations are frequent shopping destinations for residents of the eight villages.

API, active pharmaceutical ingredient; INN, international non-proprietary name.

for consent to collect two pieces of information: the estimated number of customers served each day and the estimated number who were buying medicines for blood pressure, cholesterol or diabetes. Healthcare providers gave written consent for brief interviews around medicines provision and procurement. If they reported selling study medicines, we asked for details of dosages, brands, estimated monthly volume and source of medicines and requested permission to recontact them for possible sampling (see below). Medicine shops were visited to ascertain if they sold study medicines.

Most healthcare providers stated that they sourced their medicines from one of five pharmacies in the two cities nearest to the study area; we added these pharmacies to our sampling list.

Construction of the sample frame

We constructed a sample frame that reflects the risk that a patient will take any given medicine, by active

ingredient, source and brand. For all five study medicines (and eight dosage forms), we triangulated detailed distribution or dispensing data from different sources, dividing volumes by the average number of tablets taken by a patient each month to get an estimated distribution of patients taking each medicine and dose, by branded status. The maximum sample size of 200 was distributed across medicines and dosages to reflect the per cent of patients exposed to each medicine and dose.

The overall target was then distributed by sector and outlet type as shown in figure 1. A detailed explanation of how the sample frame was constructed to reflect estimated exposure is provided in online supplemental file 2, <https://doi.org/10.7910/DVN/EBQYUB>.

Sample collection

Samples were collected between 3 February and 6 May 2021. **Table 2** summarises sampling methods by facility. Prescriptions were provided by a doctor collaborating

Table 2 Sampling method by facility

Facility	Sampling method	Acquire by
District Medicine Warehouse	Overt, with letter from district health authorities	Replacement
Primary health centres	Overt, with letter from district health authorities	Replacement
District hospital	Overt, with letter from hospital director and formal request letter from university of Brawijaya	Purchase
Healthcare providers	Overt, with letter from district health authorities and formal request letter from university of Brawijaya	Purchase
Pharmacies and medicine shops	Mystery shopper, with prescription if requested	Purchase

with Brawijaya University and were only presented if requested by pharmacists.

For the mystery shopper approach, samples were collected by sample collectors trained using role-play and common vignettes, such as buying medicines for an elderly relative. At each outlet, they requested a single medicine, or a combination consistent with common clinical needs. In order to approximate likely exposure, mystery shoppers did not ask for a specific brand or manufacturer, but rather accepted pharmacists' suggestions. They did, however, target either branded or unbranded medicines using signalling phrases such as 'I'm looking for something affordable' (for INN generics) or mention specifically that they wanted to buy generic medicines. For the premium/branded, the mystery shoppers mentioned that they wanted a 'patent' product, the term commonly used in Indonesia to signify a premium product.

If the sample frame called for clinically incompatible combinations, or repetitions (eg, an INN and a branded version of the same product) from a single outlet, different mystery shoppers were used.

All the study medicines are normally packaged in strips/blisters of 10 tablets. We collected 40 tablets per sample; if 40 tablets were not available, we accepted a minimum of 30 tablets. All samples were in tablet form.

On exiting the outlet, sample collectors put each sample in a sealable plastic bag marked with a preprinted barcode. The barcode was scanned and field-related data were entered into a form preloaded onto the shoppers' mobile phones, using open-source KoboCollect software.³⁰ Further data entry, including product photographs and details of market authorisation holder, manufacturer, registration number and expiry date, took place at the end of the day, using a second form linked by the same barcode. Where the expiry date was expressed as month and year, we entered the last day of the month as the date of expiry. The ODK-format data collection forms are available at <https://doi.org/10.7910/DVN/EBQYUB>; online supplemental 3 and 4.

Research team members inspected packaging visually. No reference packaging was available for comparison, so visual inspection, using a magnifying glass as necessary, was limited to checking for anomalies such as mis-spellings and discrepancies in formatting of batch numbers and expiry dates.

Sample handling and testing

Samples were stored in a temperature-controlled environment, for an average of 21 days, temperature and relative humidity (RH) were recorded two times a day at the same time point everyday: 8.30–09.00 and 16.30–17.00 using calibrated thermohygrometer, highest temperature was 28.5°C and lowest was 25.2°C while highest RH was 75% and 60% the lowest. The samples were then batched and sent (with a temperature logger) for testing to PT Equilab International, an ISO/IEC 17025-certified private laboratory in Jakarta. They were tested according to USP 42 NF 37 monograph and using USP reference standards.

Methods were validated for all APIs before testing. The full protocols for each molecule are available at <https://doi.org/10.7910/DVN/EBQYUB>, online supplemental files 9–14.

Briefly

Laboratory staff inspected the temperature logger for breaches of the temperature threshold of 30°C recommended by manufacturers as the maximum for all study medicines. They inspected tablets visually, noting shape, colour, lettering and other defining characteristics. Chemical analysis was performed for determination of identity, assay (% of labelled active ingredient) and dissolution (% of labelled active ingredient in the tablet dissolved over time). For all APIs, assay testing was by high-performance liquid chromatography (HPLC-UV; Waters, Aliance 2695 with UV Detector 2489 for amlodipine, glibenclamide, furosemide and simvastatin; Waters, Aliance 2695 with Photodiode Array Detector 2996 for captopril), while dissolution was by Spectrophotometer-UV/VIS (Shimadzu UV-1800) with the exception of glibenclamide, where dissolution was tested by HPLC (Waters, Aliance 2695 with UV Detector 2489).

No testing was performed for uniformity or impurities.

Staff conducting the tests differed from those handling the packaged product but could see any defining marks on tablets or capsules. Testing took place April–August 2021, an average of 95 days after sample collection.

The certificate of analysis reported date of testing, identification (positive or negative), assay (%) and dissolution (%). Dates, assay and dissolution percentages were entered into a database by study staff, using the sample barcode as identifier. Initial analyses were performed on these data. Raw data (first and second assay test results and individual tablet values for dissolution testing) were not provided until later. Inspection of the raw data revealed that some samples required further stages of dissolution testing. This was undertaken in March 2022.

Analysis

The KoboCollect field data form, product data form and the laboratory data were merged on barcode number using Stata V.17. Stata V.17 was also used for reproducible cleaning and coding and to generate simple descriptive statistics and graphs. The merge and analysis code in Stata format are provided at <https://doi.org/10.7910/DVN/EBQYUB>, online supplemental file 5 and 6.

Table 3 shows the definitions used for compliance with specifications, following USP 42 NF 37 limits, along with the average number of tablets taken by a patient in a month. If any one of six tablets included in stage 1 dissolution fell below the stage 1 threshold of Q+5, we continued to stage 2 testing using additional six tablets. The sample was considered out of specification if:

- The assay fell outside the stated limits OR.
- One or more tablets fell below the Q threshold –25 in dissolution testing OR.

Table 3 Limits of compliance, US Pharmacopeia 42 (% of declared content), and average tablets per month used in sample frame calculations

API	Assay (%)	Dissolution (Q) (%)	Stage 1 dissolution (Q+5) (%)	Tablets per month
Amlodipine	90–110	75	80	30
Captopril	90–110	80	85	60
Furosemide	90–110	80	85	30
Glibenclamide	90–110	70	75	90
Simvastatin	90–110	75	80	30

- ▶ Three or more tablets fell below Q threshold –15 in dissolution testing OR.
- ▶ The average of 12 tablets fell below the Q threshold in stage 2 dissolution testing.

RESULTS

Details of sample frame construction following an exposure-based approach and more detailed information about target sample numbers by medicine, dose and branded status are reported at <https://doi.org/10.7910/DVN/EBQYUB>, online supplemental file 2.

Table 4 summarises the number of samples collected from different sources, by INN-branded status

In the private sector, we collected a total of 42 unique INN products and 32 different branded products. Including the public sector, we collected 83 different products (API, dose and either brand, or, for INN medicines, market-authorisation holder). All the medicines collected were manufactured in Indonesia, and all had valid national market authorisations. Thirty-five samples were packaged in blisters (of which four had secondary packaging), the remaining 186 (82.9%) in foil strips.

Mean time to expiry from the date of collection was 674 days in the public sector (IQR 273–1074, median 530), 712 days in pharmacies (IQR 538–914, median 610) and 773 days (IQR 538–1174, median 633) from unregulated sources (private healthcare providers and medicines shops, who are not technically permitted to

sell prescription medicines to patients in Indonesia). The minimum number of days to expiry was 162, 185 and 54, respectively. All samples were tested before expiry.

Retail prices varied by over 100-fold between brands for some medicines, and even the identical product saw up to 10-fold differences in price between retail outlets. Analysis of these data will be reported in detail elsewhere.

Observations from the field

We found fewer branded generics than expected on the basis of the national market data we used to construct the sample frame (details at <https://doi.org/10.7910/DVN/EBQYUB>, online supplemental file 2). Prescriptions are technically required for all study medicines, but sample collectors were instructed to present prescriptions only if requested. None of the 55 retail pharmacies we bought medicines from asked to see a prescription for any medicine.

Daytime temperatures in the study area at the time of data collection ranges between 28° and 30° centigrade, bordering on the unsafe range for storage of medicines. Packaging for all study medicines stipulated that the product should be stored below 30°C. Only 2 of 60 pharmacies (one wholesale and one other) were airconditioned at the time of our visits.

In basic visual inspection, we found two cases in which there were two or three tablets packed in a one-tablet pocket and one medicine with identical batch numbers

Table 4 Sources of samples collection, by INN or branded status

Source	Sector	Outlets	INN samples	Branded samples	Total samples
District warehouse	Public	1	6	0	6 (2.9%)
District hospital	Public	1	8	5	13 (6.4%)
Primary health centres	Public	2	3	0	3 (1.5%)
Doctor	Unregulated	4	7*	12	19 (9.3%)
Midwife	Unregulated	3	3	5	8 (3.9%)
OTC medicine shop	Unregulated	2	6	0	6 (2.9%)
Wholesale pharmacy	Private	5	18	8	26 (12.7%)
Retail pharmacy	Private	55	71	52	123 (60.3%)
Total		73	122 (59.8%)	82 (40.2%)	204 (100%)

*Six samples collected, but one sample contained one strip with different package printing, which was tested separately.
INN, international non-proprietary name; OTC, over-the-counter.

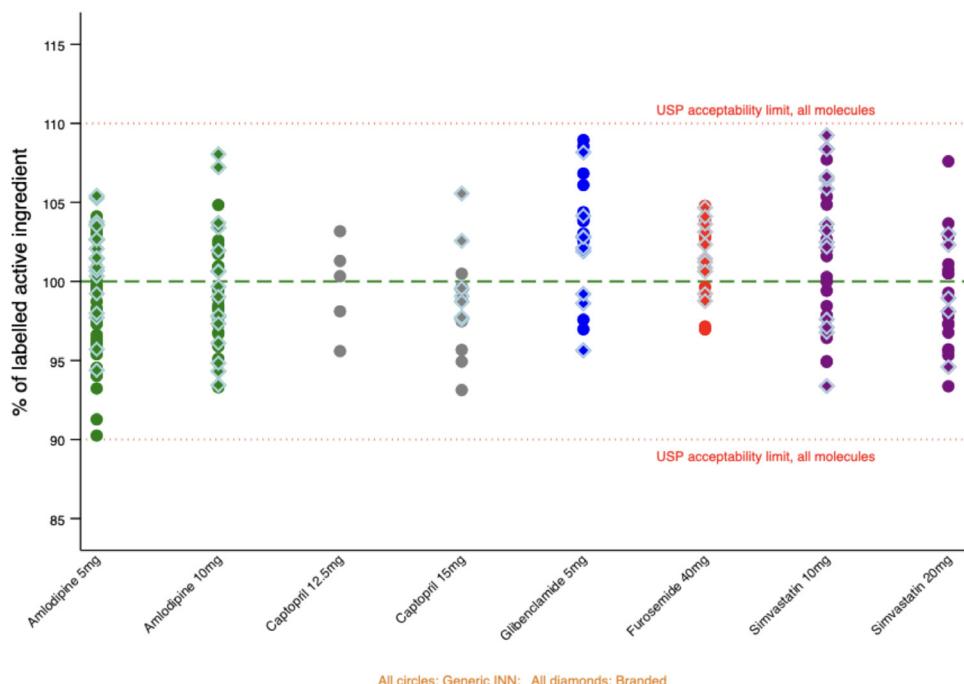


Figure 2 Results of assay testing, by API, dose and INN status. API, active pharmaceutical ingredient; INN, international non-proprietary name; USP, United State Pharmacopeia.

but with variations in printing pattern for batch number and other information. In addition, several manufacturers printed batch, price and expiry information in ink that easily rubbed off.

Pharmacopeial testing results

The entire data set including laboratory results, with brand names masked according to the terms of the ethics approval, is available in csv format at: <https://doi.org/10.7910/DVN/EBQYUB>, online supplemental file 7 (data set).³¹

The laboratory did not report any deviations from the expected temperature (consistently below 30°C) during storage or shipment. All samples contained the labelled active ingredient. Figure 2 shows the results of assay testing, by API and dosage. Generic INN products are represented by circles, and branded products by diamonds.

Assay values ranged from 90.3% to 109.3%, meaning that all samples fell within the USP 42 NF 37 (and Farmakoepo Indonesia VI) criteria for acceptability which is 90%–110%.

Dissolution testing was performed on 203/204 samples. Dissolution parameters differ for different study medicines, as shown in table 3. While the certificate of analysis showed that average dissolution of the first six tablets exceeded the required value for all samples, a later review of raw data showed that for 16 samples, not every individual tablet met the overall acceptability threshold plus 5%. Twelve of these samples passed at the second stage of dissolution testing, meaning that a total of 199 samples were considered acceptable by USP 42 NF 37 and Farmakoepo Indonesia VI standards. Limited remaining tablets meant we were not able to perform stage 2 dissolution for the remaining four samples. All were simvastatin for which the Q value is 75%. Thus, to pass stage 1, each individual tablet should show a dissolution value of at least 80%.

Table 5 shows the % of labelled API dissolved within the time specified in the USP 42 NF 37 for stage 1 dissolution testing, on average and by individual tablet, for those samples for which stage 2 testing was not possible. Sample 15 had a ‘twin’ sample of the same batch, which passed at

Table 5 Stage 1 dissolution values for samples where testing was incomplete

Dose	Brand	Batch	Stage 1 average	Tablet number (dissolution Stage 1)						
				1	2	3	4	5	6	
1	10 mg	013_inn	*	87.74	92.65	77.09	80.00	94.59	91.43	90.70
2	20mg	027_inn	18	77.08	75.65	79.99	76.89	78.13	78.13	73.67
3	20mg	027_inn	18	85.08	96.55	78.51	84.73	81.24	82.99	86.47
4	20mg	051_inn	15	82.70	81.36	79.76	79.03	84.54	89.06	82.46

*Only duplicated batches are labelled in masked data.

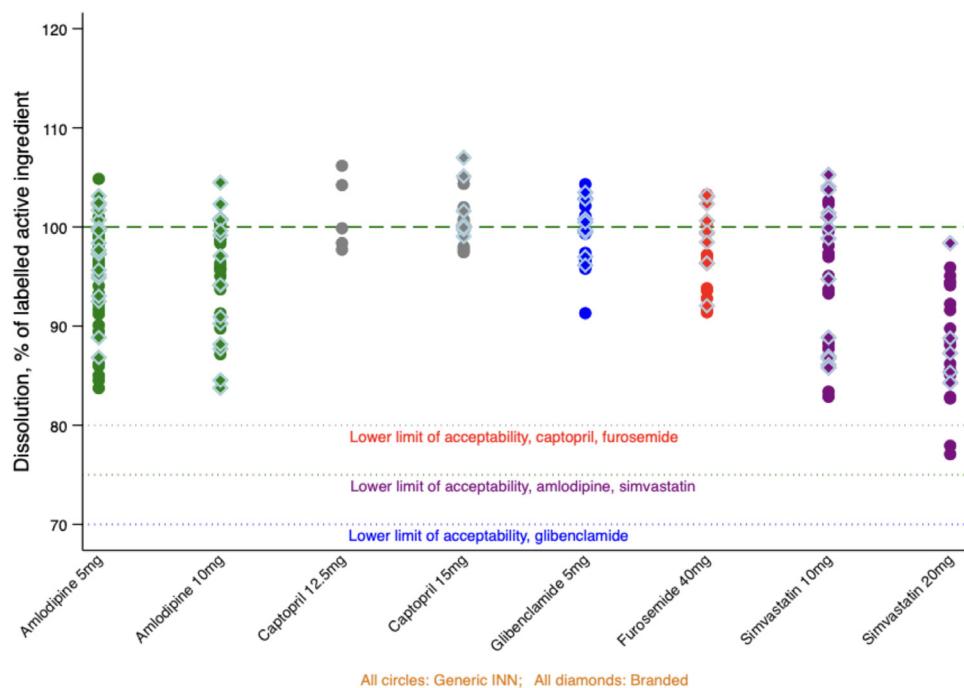


Figure 3 Results of dissolution testing, by API, dose and INN status. API, active pharmaceutical ingredient; INN, international non-proprietary name.

stage 1 dissolution, with an average of 95.07%. Samples 2 and 3 in table 5 were of a single batch; taken together, the 12 tablets tested at stage 1 dissolution averaged 81.1%, well above the acceptability limit of 75% required for 12 tablets at stage 2 dissolution testing.

Figure 3 shows the final dissolution results by API and dose. Data points represent the average of 6 tablets in Stage 1 dissolution testing, except where Stage 2 was performed, in which case they show the average value for 12 tablets.

Results were shared with the national and provincial offices of BPOM within a month of the completion of assay and stage 1 dissolution testing.

DISCUSSION

In our study of 204 samples of four common CVD medicines and one diabetes medicine sampled from public, private and informal sources, all were registered; within their expiry dates; all met USP 42 and Farmakope Indonesia VI specifications for assay; and 199 met specifications for dissolution. We were unable to complete dissolution testing for the remaining five samples, but there were no grounds to expect extreme deviations.

The use of mystery shoppers reduced the likelihood that retail sales staff would selectively provide better quality products, while our take-all approach for medicines provided free in public facilities prevented sampling bias there, despite overt sample collection. However, study limitations mean we cannot conclude that the risk of exposure to poor-quality CVD or diabetes medicines for patients in the study area is zero. We could not afford to test for impurities. Sample collection from doctors and midwives was overt, so although we bought a sample of

every variety of study medicine they offered, it is possible that they held back medicines they suspected were of poor quality. However, mystery shoppers also obtained samples of medicines from the pharmacies that doctors and midwives reported buying from, with similar results, suggesting that if bias did exist, it was not considerable.

We did not sample from the internet or from any of the five private general hospitals in the study area. We do not have data allowing us to estimate the volume of study medicines sold through these channels. However, the additional per-visit consultation fee would likely prevent many patients from choosing to buy medicines for a chronic condition from private hospitals.

Though we checked registration status, we did not have reference packaging or perform detailed packaging analysis. We are, thus, unable to rule out falsification, including extension of expiry dates or repackaging of quality INN products to imitate a more expensive brand.

However, there were no out-of-specification products on either assay or dissolution among 83 unique products sampled from 73 outlets, including the district warehouse (which supplies most of the public sector), any of the wholesale pharmacies mentioned as sources of medicine by healthcare workers who sell to patients, and 73% of retail pharmacies in the area, including all of the highest volume sellers. We can, thus, state with confidence that the risk of exposure to poor-quality versions of the study medicines is very low in this semirural setting in one of Indonesia's most populous provinces. The situation may differ in other areas of Indonesia. Overall, however, our findings support reports from BPOM's postmarket surveillance, which suggest that the overwhelming majority of medicines in the regulated supply chain in



Indonesia, including very low-cost unbranded generics in public facilities, meet quality standards.

Our findings differ from those of many previous field surveys in LMICs. The five diabetes prevalence surveys identified by Saraswati *et al* included 527 samples collected from 31 countries, 382 of them from LMICs. The failure rates in the latter group were 8.6%, compared with 2.1% in high-income countries. Within LMICs, failure ranged from 0 (in Chile, CIS, India Pakistan, Thailand and Turkey) to 37.5% in Argentina. However, sample sizes were mostly in single figures. While the failure rate reported for Indonesia was 25%, the 1993 study in question included just four samples from the country, all of glibenclamide. The 27 prevalence surveys for CVD medicines reviewed by Do *et al*¹² included 1889 samples collected in lower middle income countries, including Indonesia. In this subset, prevalence of failure was 16.5%. By country, it ranges from 100% failure in Indonesia (4/4 samples) to 0.6% of 521 samples in India (the only other country in the list with a maturity level 3 regulator and limited imports of generic medicines).^{15 32 33} In the lower middle-income group, 63.5% of samples were from Africa, with a failure rate of 24.4%. The remainder were from Asia, with a failure rate of 2.9%.

We, thus, find it difficult to agree with the conclusions of Redfern *et al* in their 2019 study of antihypertensive drugs in lower middle-income Nigeria, that 'a representative sample from three chosen Nigerian states is highly relevant and potentially generalisable across Africa and other developing countries'.³⁴

Indonesia has a large domestic pharmaceutical industry, and all authorised versions of the study medicines are manufactured locally.³⁵ Currently, the global market for medicines works on a 'buyer beware' system, and national regulatory authorities are not responsible for the quality of medicines made for export.³⁶ Unless countries that rely heavily on imported medicines can police their quality at import, they may, thus, be exposed to substandard medicines produced elsewhere without adequate regulatory oversight. We speculate that Indonesia's success in securing the quality of the medicines in our study may be in part related to the production-to-market supervision by a single, relatively well-resourced regulator. However, we also note that not all regulations or best practices are observed. Several manufacturers of low-cost medicines used very poor printing techniques or ink quality for important information such as expiry date and batch number, potentially facilitating extension of expiry dates by falsifiers. We were able to buy all samples without prescriptions, some from sources not permitted to sell these medicines, and most from pharmacies that were not temperature regulated.

Initial exploration of pricing data indicates that same company may sell a product at very different price points, often producing one or more brands as well as INN versions. This allows for cross-subsidisation across a company's portfolio, potentially protecting the quality of very low-cost products in the Indonesian market. We plan further investigation of this topic.

Obtaining requisite permissions to collect secondary data for the construction of the exposure-based sample frame, as executed, was time consuming but feasible. Because no substandard products were found, we were unable to proceed with more detailed estimates of exposure as originally planned. Schiavetti and colleagues, weighting the results of their study of medicines sampled from distributors in the Democratic Republic of Congo by market size, found that those with larger distributions were more likely to be of good quality.¹⁰ We suggest exposure-based sampling could be repeated in settings known to have more poor-quality products, in order to better estimate the true population exposure to substandard and falsified medicines.

Author affiliations

¹The George Institute for Global Health, University of New South Wales, Sydney, New South Wales, Australia

²The George Institute for Global Health, University of New South Wales, Hyderabad, India

³Department of Pharmacy, Brawijaya University, Malang, Indonesia

⁴Department of Public Administration, Brawijaya University, Malang, Indonesia

⁵Biology, Medicines and Health, University of Manchester, Manchester, UK

⁶Global Development Institute and Manchester Institute for Collaborative Research on Ageing, University of Manchester, Manchester, UK

Twitter Aksari Dewi @AksariDewi, Anna Palagy @annapalagy, Sujarwoto Sujarwoto @sujarwoto and Elizabeth Pisani @elizabethpisani

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Contributors The study was designed by EP and AD with input from all of the other authors. AD led the field data collection. EP and AD conducted the data analysis and drafted the first manuscript. All other authors provide comments for improvement to the manuscript. APatel is the guarantor of the study.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by The University of New South Wales and Brawijaya University. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. The sample level data are available at <https://doi.org/10.7910/DVN/EBQYUB>, File 07. In accordance with the terms of the ethics approval, names of individual manufacturers and batch numbers are masked, product registration numbers removed, and outlets grouped by type. Data are provided for reuse, with the expectation that users will cite the dataset and this paper.

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Author note The reflexivity statement for this paper is linked as an online supplemental file 1.

ORCID iDs

Aksari Dewi <http://orcid.org/0000-0002-2232-5215>

Sujarwoto Sujarwoto <http://orcid.org/0000-0003-4197-4592>

Elizabeth Pisani <http://orcid.org/0000-0002-3674-631X>

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Appendix S1 – Reflexivity Statement

1. How does this study address local research and policy priorities?

Since the National Health Insurance (JKN) system was implemented in 2014, Indonesia has suffered several scandals around substandard and falsified medicines. Articles in mainstream media regularly call into question the quality of medicines procured by providers of JKN services. The topic of medicines quality is regularly mentioned as a priority topic in a forum of Indonesian academics interested in medicine policy convened by the Special Adviser to the Minister of Health.

CVD medicines are of particular interest to the government of Malang district, because the elected district head (Bupati) has joined with health officials to prioritise investment in CVD control services. In the beginning of the study, prior to research protocol development, we discussed the research with relevant officials, including from the district department of health, the district medical stores, the provincial and national medicine regulators. The district health department provided written support for the study, with the specific proviso that the study results should be shared with department officials for follow up action. Meanwhile the national regulator has expressed an interest in understanding better exposure to the risk of poor-quality medicines, and the contribution market mechanisms and procurement practices might make to reducing that risk.

2. How were local researchers involved in study design?

The study was conceptualised by a foreign researcher who has worked with Indonesian health authorities for two decades. Researchers from Brawijaya University were consulted at length at the design stage, and gave material inputs to the protocol. The study was managed and implemented entirely by Indonesian nationals based in the study area; they also guided the re-design occasioned by the COVID pandemic.

3. How has funding been used to support the local research team?

With the exception of salary support for one foreign researcher and publication fees, the budget was spent entirely in Indonesia, on locally-based staff, data collection and testing.

4. How are research staff who conducted data collection acknowledged?

We have thanked two data collectors who are not in academic positions and not authors by name in the acknowledgements. Other data collectors are authors.

5. Do all members of the research partnership have access to study data?

Yes

6. How was data used to develop analytical skills within the partnership?

We held regular research meetings with all authors throughout the process. All team members provided input regarding the adaptations required by COVID, as well as suggesting relevant analyses as fieldwork progressed.

Preliminary analysis was performed by the first and last authors, and discussed in an extended research meeting within the partnership, some of whom suggested additional

analyses as well as enriching interpretation. We did not provide formal analytic skills training during this research.

7. How have research partners collaborated in interpreting study data?

In addition to the regular research meetings with academic colleagues from all involved institutions described above, we presented preliminary results to the medicine regulator before development of our final manuscript. Their interpretation and observations added texture and context to our own.

8. How were research partners supported to develop writing skills?

The first author AD (an early-career Indonesian national) was supported by senior academics in the group to develop and refine writing skills throughout the research process. Mentoring focused on developing policy presentations and policy briefs as well as academic paper writing skills.

9. How will research products be shared to address local needs?

We conducted a dissemination meeting with the local and national medicines authority soon after receiving the medicine samples laboratory testing result from the third party laboratory. Brawijaya University researchers plan further dissemination of results to the district health department in the context of other on-going research related to CVD care in which the Health Department is involved.

10. How is the leadership, contribution and ownership of this work by LMIC researchers recognised within the authorship?

Seven of the 12 authors are Indonesian nationals. This includes first author AD, an early career Research Fellow who managed the study, conducted much of the data collection and analysis, and co-drafted this manuscript. Other roles are recognised in the contribution of authors statement.

11. How have early career researchers across the partnership been included within the authorship team?

Three authors, including the first author, are early career researchers (AD, BI, AL). All are Indonesian nationals based in the study area, although the first author was affiliated as a Research Fellow at The George Institute for Global Health at the time of the study.

12. How has gender balance been addressed within the authorship?

Five authors are male (DP, BI, SS, GT, SJ) and seven authors -- including the first and last authors -- are female (AD, AP, AP, AL, DL, AM, EP).

13. How has the project contributed to training of LMIC researchers?

A weekly and bi-weekly online discussion has been held during the research period to allow knowledge transfer, discussion and analytical training from the senior researchers (EP, AP, DP, SJ) to the junior researchers based in LMIC (AD, AL, BI).

We note also that the participation of senior Indonesian researchers (JS, GT, AM, DL) contributed to building the skills of researchers based in HICs, including by helping them to better understand policy processes and research-policy interaction in the Indonesian

context, and by highlighting the importance of culture in considerations related to research ethics.

14. How has the project contributed to improvements in local infrastructure?

This project has not directly contributed to improvements in local infrastructure.

15. What safeguarding procedures were used to protect local study participants and researchers?

We sought ethical clearance from both local and international institutions, and were careful to observe all of the terms of those clearances as they relate to protecting researchers and medicine sellers from any potential harm associated with the study. In addition, we made major changes to our original research plan to reduce risk of exposure to COVID-19. We eliminated a household survey that would have required contact with thousands of often elderly individuals at high risk for CVD, conducted much of our preliminary or formative research by phone rather than in person, and followed strict COVID-prevention protocols when collecting and processing samples.

Dewi et al.: Constructing an exposure based sample frame

1 Steps taken to construct an exposure-based sample frame for CVD
 2 medicines, and details of sampling.

3
 4 This document accompanies the paper "A study of the quality of cardiovascular and diabetes
 5 medicines in Malang District, Indonesia, using exposure-based sampling", by Aksari Dewi
 6 and colleagues. It provides a detailed account of the steps taken to develop a sample frame
 7 based on the likelihood that a patient will consume a specific brand and dose of a medicine,
 8 dispensed by a specific health care provider (public hospital, primary health centre, doctor or
 9 midwife or retail outlet) in the study area.

10 We believe that failure rates derived from a study using this design can be applied to a
 11 denominator of the local patient population to estimate the number of patients exposed to
 12 poor quality medicines of the types studied.

13 **Data sources**

14 The sample frame is constructed using primary and secondary data as shown in Table 1 of the
 15 accompanying paper.

16 ***Construction of the sample frame***

17 **Triangulation of data to calculate overall distribution of samples by medicine
 18 and dose**

19 For all five study medicines (and eight dosage forms), we triangulated detailed distribution or
 20 dispensing data from different sources. Our intention was to estimate the number of patients
 21 exposed to poor quality medicines. Because the number of tablets taken per patient varies by
 22 medicine, and because one patient may take more than one medicine at a time, we chose to
 23 calculate distributions in terms of percent of patients exposed to each medicine, rather than in
 24 terms of raw volumes of medicines. We thus divided volumes by the average number of
 25 tablets taken by a patient each month (shown in main paper, Table 3) to get an estimated
 26 distribution of patients taking each molecule and dose.

27 Table S1 (provided in .xlsx format at <https://doi.org/10.7910/DVN/EBQYUB>, File 08) shows
 28 the data eventually used to construct the sample frame. In the sections below, we break the
 29 table down to explain how each row is derived.

		Amlodipine		Captopril		Furosemide		Glibenclamide		Simvastatin	
		5mg	10mg	12.5mg	25mg	40mg	5mg	10mg	20mg	5mg	10mg
A1	Patient survey in 8 study villages	Patients	1289	564	170	358	352	247	760	49	
A2	2018 data	%	34.0%	14.9%	4.5%	9.4%	9.3%	6.5%	20.1%	1.3%	
B1	District warehouse	Av. patients/month	2,100	745	10	434	173	278	690	-	
B2	(For all of Kabupaten Malang)	%	47.4%	16.8%	0.2%	9.8%	3.9%	6.3%	15.6%	0.0%	
C1	IQVIA retail sales	Av. patients/month	301,931	169,402	13,988	49,086	63,079	42,507	143,514	95,493	
C2	(National)	%	34.3%	19.3%	1.6%	5.6%	7.2%	4.8%	16.3%	10.9%	
C3	INN (national data)		35.6	37.8	48.6	51.1	60.6	47.2	44.0	52.0	
D1	Independent pharmacy,	Av. patients/month	26	35	8	14	7	19	17	10	
D2	Kepanjen (district capital)	%	19.1%	25.6%	5.7%	10.3%	4.9%	14.0%	12.7%	7.7%	
E1	Chain pharmacy	Av. patients/month	187	187	5	22	49	7	124	105	
E2	Kepanjen (district capital)	%	27.3%	27.3%	0.7%	3.2%	7.1%	1.0%	18.1%	15.3%	
F1	Local private distributor Malang (may sell in other districts)	Av. patients/month	6,212	6,500	-	2,804	5,039	3,705	9,331	7,756	
F2	%		15.0%	15.7%	0.0%	6.8%	12.2%	9.0%	22.6%	18.8%	
G1	Primary health centre 1	Av. patients/month	54	11	6	4	3	6	22	-	
G2	%		51.8%	10.2%	5.5%	3.4%	2.6%	5.6%	20.9%	0.0%	
H1	Primary health centre 2	Av. patients/month	173	17	27	14	3	23	26	-	
H2	%		61.1%	5.9%	9.5%	4.8%	1.2%	8.3%	9.2%	0.0%	
X	Unweighted average of Malang based sources, 2020 data		36.9%	16.9%	3.6%	6.4%	5.3%	7.4%	16.5%	7.0%	
Y	Target sample from private sector (N=178), distributed by IQVIA retail proportions (C3)		61	34	3	10	13	9	29	19	

31 **Table S1: Data used to inform a sample frame reflecting risk of exposure to poor
 32 quality medicines in Malang district, Indonesia**

Dewi et al.: Constructing an exposure based sample frame

33 **Source A: Household survey of patients in study area, 2018 [1,2]**

34 Row A1: The **number of patients** reporting taking different medicines in the 2018
 35 household survey (see main paper, reference Maharani et al, and Patel et al)

36 Row A2: Calculate **percent distribution of patients per medicine**, of all study medicines.

A	B	C	D	E	F	G	H	I	J	K
1			Amlodipine		Captopril		Furosemide	Glibendamide		Simvastatin
2			5mg	10mg	12.5mg	25mg	40mg	5mg	10mg	20mg
3	Patient survey in 8 study villages	Patients	1289	564	170	358	352	247	760	49
4	A1 2018 data	%	34.0%	14.9%	4.5%	9.4%	9.3%	6.5%	20.1%	1.3%

37 **Source B: Distribution data provided by Malang District Medicine Warehouse.**

38 This shows distribution to all public outlets in Malang district for March-October 2020.

39 Row B1: Divide average *monthly distribution* of each API and dosage by number of *tablets taken per patient per month* to get average **number of patients** served by the district warehouse each month.

40 Row B2: Calculate **percent distribution of patients per medicine**, of all study medicines.

		Amlodipine		Captopril		Furosemide		Glibendamid	
		5mg	10mg	12.5mg	25mg	40mg	5mg	10mg	20mg
B1	District warehouse	2,100	745	10	434	173	278	690	-
B2	(For all of Kabupaten Malang)	47.4%	16.8%	0.2%	9.8%	3.9%	6.3%	15.6%	0.0%

41 **Source C: Nationwide retail sales, from data analytics firm IQVIA**

42 IQVIA collects data quarterly, and provides data on national sales by brand for April to September 2020, in both hospital and retail channels. The volume data provided to us were aggregated by INN status and sales channel; additional information was provided on the % of all marketed products which are branded generics. Data come from a panel of over 1,000 pharmacies selected to be representative at the national level

43 Row C1: Divide average *monthly retail sales* of each API and dosage by number of *tablets taken per patient per month* to get average **number of patients** buying each medicine at pharmacies per month.

44 Row C2: Calculate percent distribution of patients per medicine, of all study medicines.

45 Row C3: Percent of unique products (single API, dose, brand or INN manufacturer) sold in retail outlets that are non-branded INN generics. These data were used to estimate the proportion of branded versus non-branded generics we should aim to sample in pharmacies.

		Amlodipine		Captopril		Furosemide		Glibendamide	
		5mg	10mg	12.5mg	25mg	40mg	5mg	10mg	20mg
C1	IQVIA retail sales	301,931	169,402	13,988	49,086	63,079	42,507	143,514	95,493
C2	(National)	34.3%	19.3%	1.6%	5.6%	7.2%	4.8%	16.3%	10.9%
C3	% brands in retail outlets that are INN (national data)	35.6	37.8	48.6	51.1	60.6	47.2	44.0	52.0

60 **Sources D - H: Detailed sales volume data provided by 2 retail pharmacies and one medicine wholesaler in Malang district**

61 Rows D1, E1, F1, G1 and H1: Divide average *monthly sales* (D-F) or *dispensed volumes* (G-H) of each API and dosage by number of *tablets taken per patient per month* to get average **number of patients** directly (D, E, G, H) or indirectly (F) served by the outlet each month.

62 Rows D2, E2, F2, G2 and H2: Calculate **percent distribution of patients per medicine**, of all study medicines.

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		Amlodipine		Captopril		Furosemide	Glibenclamide	Simvastatin	
		5mg	10mg	12.5mg	25mg	40mg	5mg	10mg	20mg
D1	Independent pharmacy, Av. patients/month	26	35	8	14	7	19	17	10
D2	Kepanjen (district capital) %	19.1%	25.6%	5.7%	10.3%	4.9%	14.0%	12.7%	7.7%
E1	Chain pharmacy Av. patients/month	187	187	5	22	49	7	124	105
E2	Kepanjen (district capital) %	27.3%	27.3%	0.7%	3.2%	7.1%	1.0%	18.1%	15.3%
F1	Local private distributor Malang (may sell in other districts) Av. patients/month %	6,212	6,500	-	2,804	5,039	3,705	9,331	7,756
F2	Primary health centre 1 Av. patients/month %	54	11	6	4	3	6	22	-
G1	Primary health centre 2 Av. patients/month %	173	17	27	14	3	23	26	-
H1	Primary health centre 2 %	61.1%	5.9%	9.5%	4.8%	1.2%	8.3%	9.2%	0.0%

68

69

70 **Triangulation and comparison between sources**

71 We proceeded to compare distributions across the various data sources, using the full table
 72 show as Table S1 above, comparing particularly the local data sources (averaged in Row X)
 73 and the 2018 survey.

74 Row X: Calculate the simple average of all data sources derived locally. These include all
 75 sources with the exception of IQVIA data, which represent national distributions.

		Amlodipine		Captopril		Furosemide	Glibenclamide	Simvastatin	
		5mg	10mg	12.5mg	25mg	40mg	5mg	10mg	20mg
A2	Patient survey, 2018 %	34.0%	14.9%	4.5%	9.4%	9.3%	6.5%	20.1%	1.3%
B2	District warehouse %	47.4%	16.8%	0.2%	9.8%	3.9%	6.3%	15.6%	0.0%
C2	IQVIA retail sales %	34.3%	19.3%	1.6%	5.6%	7.2%	4.8%	16.3%	10.9%
D2	Independent pharmacy, %	19.1%	25.6%	5.7%	10.3%	4.9%	14.0%	12.7%	7.7%
E2	Chain pharmacy %	27.3%	27.3%	0.7%	3.2%	7.1%	1.0%	18.1%	15.3%
F2	Local private distributor %	15.0%	15.7%	0.0%	6.8%	12.2%	9.0%	22.6%	18.8%
G2	Primary health centre 1 %	51.8%	10.2%	5.5%	3.4%	2.6%	5.6%	20.9%	0.0%
H2	Primary health centre 2 %	61.1%	5.9%	9.5%	4.8%	1.2%	8.3%	9.2%	0.0%
X	Unweighted average of Malang based sources, 2020 data	36.9%	16.9%	3.6%	6.4%	5.3%	7.4%	16.5%	7.0%

76

77 The proportionate distribution averaged across the 6 Malang-based sources (row X) was
 78 broadly consistent with the consumption data reported in the 2018 household survey (row
 79 A2), although the distribution of Simvastatin doses was significantly different. We note that
 80 two years after the 2018 survey, the district warehouse had no medicines of this dose in stock.
 81 This may suggest that a number of patients prescribed 20mg of Simvastatin were taking
 82 2x10mg because of a localised shortage of 20mg tablets at the time of the 2018 survey. In
 83 addition, we noted that the relative distribution of study medicines differed between public
 84 and private sectors, with the district warehouse and primary health centres (B2, G2, H2)
 85 reporting higher relative dispensing of amlodipine, and the private distributor, pharmacies
 86 and IQVIA's national pharmacy sales data (C2-F2) recording more patients supplied with
 87 simvastatin.

88

89

Distribution of total sample size across sectors, medicines, dosages and INN status

90 Having examined the data, we followed a number of steps in constructing a sample frame.
 91 These are summarised in Table S2 (provided in .xlsx format at
 92 <https://doi.org/10.7910/DVN/EBQYUB>, File 08), and broken down below.

93

		Amlodipine		Captopril		Furosemide	Glibenclamide	Simvastatin		Total
	200	5mg	10mg	12.5mg	25mg	40mg	5mg	10mg	20mg	
Realised 1	Actual sample public sector	3	4	1	4	4	2	2	2	22
Data 1	Retail sector distribution, IQVIA national	34.3%	19.3%	1.6%	5.6%	7.2%	4.8%	16.3%	10.9%	100%
Target 1	Target sample, private sector	61	34	3	10	13	9	29	19	178
Data 2	% of brands in private sector INN	35.6%	37.8%	48.6%	51.1%	60.6%	47.2%	44.0%	52.0%	
Target 2	Target INN samples, private sector	22	13	1	5	8	4	13	10	76
Target 3	Target branded samples, private sector	39	21	1	5	5	5	16	9	102
Realised 2	Actual INN samples, private sector	28	20	4	6	8	10	13	16	105
Realised 3	Actual branded samples, private sector	19	14	0	7	9	9	14	5	77
Realised 4	Actual sample private sector	47	34	4	13	17	19	27	21	182
Realised 5	Total final sample	50	38	5	17	21	21	29	23	204
	Number of different brands/producers sampled	20	20	2	5	8	6	13	9	83

94

95 **Table S2: Sample frame: targets and realised samples**

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96 **Step 1: Take-all sample from the public sector**

97 The public sector has a wider reach than any single retail outlet; the number of patients
 98 exposed to any public sector medicine is thus likely to be greater than those buying from a
 99 single pharmacy. For this reason, and to minimise any bias that might be introduced by our
 100 overt sampling approach, we employed a take-all strategy in the public sector, as follows:

- 101 • The district warehouse supplies all public primary health facilities in the district. We
 102 aimed to include one sample of every unique version (single API, dose, brand or INN
 103 manufacturer) of all study medicines supplied by the district warehouse.
- 104 • In case of shortages, primary health facilities may also procure using capitation funds.
 105 We planned to collect one sample of every additional unique version (single API,
 106 dose, brand or INN manufacturer) of a study medicine from all five health centres in
 107 the study area. (We did not re-sample medicines supplied by the district warehouse.)
- 108 • The public hospital procures independently, although some of its medicines may also
 109 be acquired through the e-catalogue platform, from the same manufacturers as supply
 110 the district warehouse. We aimed to collect one sample of every unique version
 111 (single API, dose, brand or INN manufacturer) of study medicines offered to public
 112 patients by the hospital, other than those that duplicated medicines supplied by the
 113 district warehouse. In addition, we planned to collect one sample of each unique
 114 branded product sold by the hospital to patients not using public insurance.

115
 116 The results of this sampling are shown below:

	200	Amlodipine	Captopril	Furosemide	Glibenclamide	Simvastatin	Total			
Realised 1	Actual sample public sector	5mg	10mg	12.5mg	25mg	40mg	5mg	10mg	20mg	Total
		3	4	1	4	4	2	2	2	22

117
 118 **Step 2: Distribute remaining sample by medicine, dose, and INN status**

119 We subtracted the 22 samples collected in the public sector from the total target sample of
 120 200. This left 178 samples to be sampled from the private sector. These were distributed by
 121 the proportionate distribution of patients served, based on in IQVIA retail data (these were
 122 shown in Table S1 Row C2, and are shown below in blue row Data 1), to give the target
 123 samples sizes shown in green Row Target 1. We chose to use the IQVIA retail data rather
 124 than the 2018 survey data to inform distribution in the private sector because we feared that
 125 shortages of simvastatin 20mg in the study area may have led to an overestimate of the
 126 proportion of patients taking simvastatin in the 2018 data.

	200	Amlodipine	Captopril	Furosemide	Glibenclamide	Simvastatin	Total			
Realised 1	Actual sample public sector	5mg	10mg	12.5mg	25mg	40mg	5mg	10mg	20mg	Total
Data 1	Retail sector distribution, IQVIA national	34.3%	19.3%	1.6%	5.6%	7.2%	4.8%	16.3%	10.9%	100%
Target 1	Target sample, private sector	61	34	3	10	13	9	29	19	178

130 We then considered the distribution of brands by branded or unbranded (INN) generic status
 131 in the private sector, using data shown in Table S1 Row C2, and reproduced below in blue
 132 row Data 2. We applied these to the overall target (Target 1), to give the target sample sizes
 133 by branded/unbranded status shown in green rows Target 2 and Target 3.

	200	Amlodipine	Captopril	Furosemide	Glibenclamide	Simvastatin	Total		
Target 1	Target sample, private sector	61	34	3	13	9	29	19	178
Data 2	% of brands in private sector INN	35.6%	37.8%	48.6%	51.1%	60.6%	47.2%	44.0%	52.0%
Target 2	Target INN samples, private sector	22	13	1	5	8	4	13	10
Target 3	Target branded samples, private sector	39	21	1	5	5	5	16	9
									102

134
 135 **Step 3: Take-all sample from doctors, nurses and medicine shops.**

136 Malang district bureau of statistics reports that almost 60% of outpatients go first to private
 137 providers, and formative research undertaken during our study planning indicated that many

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- 139 of these doctors and midwives sell medicine to their patients, although they usually stock
 140 only a limited variety of medicines and brands.
- 141 We used publicly-available information to map doctors and midwives in private practice in
 142 the study area, conducted a rapid survey of study medicine sales volumes among those
 143 consenting, and ranked them by volume. In order to minimise any bias that might be
 144 introduced by our overt sampling approach in this group, we aimed to collect one sample of
 145 every unique study medicine (single API, dose, brand or INN manufacturer) sold by all
 146 doctors or midwives who reported sales of 300 tablets a month or more.
- 147 We mapped and approached 56 health care providers in private practice; 17 did not provide
 148 study medicines to patients; 7 others refused interview. We interviewed a total of 32 health
 149 care providers (11 doctors, 16 midwives, 5 nurses). Thirty reported selling at least one study
 150 medicine; half said they always sold medicines to patients. They reported selling between 30
 151 and 2000 tablets of study medicines a month. We sampled all the study medicines sold by
 152 those reporting highest sales volumes (≥ 300 tablets per month), a total of 19 samples from 4
 153 doctors and 8 samples from 3 midwives.
- 154 In our rapid survey of the study villages, we identified three medicine shops not licensed to
 155 sell prescription medicines which did in fact sell study medicines. One over-the-counter
 156 medicine shop sold all study medicines (with a single product for each) and one other sold
 157 one captopril product; we took them all, collecting all 6 samples.
- 158 Step 4: Adjust remainder of sample, and distribute across pharmacies**
- 159 We subtracted the samples collected from doctors, midwives and medicine shops (n= 33)
 160 from the targets shown for INN or branded generics shown in Table S2 lines Target 2 and
 161 Target 3 as appropriate.
- 162 We ranked pharmacies by estimated patient numbers for hypertension/cholesterol/diabetes
 163 medicines collected in our rapid survey, and distributed the remaining sample size in
 164 proportion to that volume, to a maximum of one INN and one branded sample of any
 165 medicine/dose combination per outlet. These outlets included "wholesale" pharmacies most
 166 frequently reported as supplying health workers (all of them in nearby cities). Twenty-six
 167 samples were collected from these wholesale pharmacies, the remainder from retail
 168 pharmacies in the study area.
- 169 We verified the existence of 75 pharmacies in the study area, and ranked them in order of
 170 estimated volumes of CVD customers served per month they provided. To ensure geographic
 171 coverage, we first sampled from the highest-volume outlet in each village, drawing several
 172 samples of different products, INN and branded, from all but the smallest one. We assigned
 173 samples to the remainder of the outlets by patient volume regardless of location, until
 174 exhausting the sample size.
- 175 We collected 123 samples from 55 pharmacies (73% of those in the study area).
- 176 We made a number of adjustments to the targets as sampling progressed. Although national
 177 data suggested that branded medicines outnumbered INN products, mystery shoppers found
 178 early on that the variety of INN products on offer in the study area was greater than that of
 179 branded medicines, perhaps reflecting the semi-rural setting of the study area. Since our aim
 180 was to reflect what local residents were likely to use, we adjusted sampling accordingly.

	Amlodipine			Captopril		Furosemide	Glibenclamide	Simvastatin		
	200	5mg	10mg	12.5mg	25mg	40mg	5mg	10mg	20mg	Total
Target 2 Target INN samples, private sector	22	13	1	5	8	4	13	10	76	
Target 3 Target branded samples, private sector	39	21	1	5	5	5	16	9	102	
Realised 2 Actual INN samples, private sector	28	20	4	6	8	10	13	16	105	
Realised 3 Actual branded samples, private sector	19	14	0	7	9	9	14	5	77	

181

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- 182 In the case of Furosemide and Glibenclamide, the target number of samples was smaller than
183 the 20-sample minimum accepted for testing by the laboratory. We thus increased the total
184 target sample sizes for these two molecules to 20 each, compensating by reducing the sample
185 sizes for Amlodipine, which dominates public sector provision in the study area. We added
186 three additional samples to our expected maximum to accommodate additional Captopril
187 samples.
- 188 One four-strip glibenclamide sample contained one strip with the same batch number as the
189 other three but printed in different format. This was split out for separate testing, giving us a
190 total final sample size of 204.
- 191 The realised samples from private sources by INN status are shown in orange rows Realised
192 2 and Realised 3. Table S2 gives the total realised sample size per active ingredient. More
193 information about samples by molecules and source are provided in the main paper, Table 4.