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BMJ Global Health

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 .xslx 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
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	% 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
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	Av. patients/month	6,212	6,500	-	2,804	5,039	3,705	9,331	7,756
F2	Malang (may sell in other districts)	%	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**

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

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

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

	A	B	C	Amlodipine		Captopril		Furosemide	Glibenclamide	Simvastatin	
				5mg	10mg	12.5mg	25mg	40mg	5mg	10mg	20mg
3	A1	Patient survey in 8 study villages	Patients	1289	564	170	358	352	247	760	49
4	A2	2018 data	%	34.0%	14.9%	4.5%	9.4%	9.3%	6.5%	20.1%	1.3%

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

This shows distribution to all public outlets in Malang district for March-October 2020.
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.
Row B2: Calculate **percent distribution of patients per medicine**, of all study medicines.

		Amlodipine		Captopril		Furosemide	Glibenclamide	Simvastatin	
		5mg	10mg	12.5mg	25mg	40mg	5mg	10mg	20mg
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%

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

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

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.

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

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	Glibenclamide	Simvastatin	
			5mg	10mg	12.5mg	25mg	40mg	5mg	10mg	20mg
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	% 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

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

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.

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	Av. patients/month	6,212	6,500	-	2,804	5,039	3,705	9,331	7,756
F2	Malang (may sell in other districts)	%	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%

68

69

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.

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 .xslx format at
92 https://doi.org/10.7910/DVN/EBQYUB, File 08), and broken down below.

93

| | | | Amlodipine | | Captopril | | Furosemide | Glibenclamide | Simvastatin | | |
		200	5mg	10mg	12.5mg	25mg	40mg	5mg	10mg	20mg	Total
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:

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

117
118
119 **Step 2: Distribute remaining sample by medicine, dose, and INN status**
120 We subtracted the 22 samples collected in the public sector from the total target sample of
121 200. This left 178 samples to be sampled from the private sector. These were distributed by
122 the proportionate distribution of patients served, based on in IQVIA retail data (these were
123 shown in Table S1 Row C2, and are shown below in blue row Data 1), to give the target
124 samples sizes shown in green Row Target 1. We chose to use the IQVIA retail data rather
125 than the 2018 survey data to inform distribution in the private sector because we feared that
126 shortages of simvastatin 20mg in the study area may have led to an overestimate of the
127 proportion of patients taking simvastatin in the 2018 data.

| | | | Amlodipine | | Captopril | | Furosemide | Glibenclamide | Simvastatin | | |
		200	5mg	10mg	12.5mg	25mg	40mg	5mg	10mg	20mg	Total
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**

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129
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.

| | | | Amlodipine | | Captopril | | Furosemide | Glibenclamide | Simvastatin | | |
		200	5mg	10mg	12.5mg	25mg	40mg	5mg	10mg	20mg	Total
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**

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135
136 **Step 3: Take-all sample from doctors, nurses and medicine shops.**
137 Malang district bureau of statistics reports that almost 60% of outpatients go first to private
138 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.

181

			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**

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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.