Supplementary appendix

Supplement to:

Over-the-counter antibiotic dispensing by pharmacies: a standardised patient study in Udupi district, India

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Supplementary methods

1. Rationale for the approval of a waiver of informed consent

A waiver of informed consent for the pharmacies visited was approved by the IRBs of both McGill University and Manipal Academy of Higher Education. We provide below the rationale for requesting and receiving such a waiver. Principally, we believe that if pharmacies were aware that they were part of our study, it would not have been possible to obtain scientifically valid estimates of antibiotic dispensing.

We cite a report by Rhodes et al. *(*2012) on the ethical aspects of standardised patient studies.[1] This report, commissioned by the US Department of Health and Human Services, concluded that "As long as adequate protections of confidentiality of research data are in place, minimally intrusive simulated patient research that gathers policy-relevant data on the health system without the consent of individuals working in that system can be ethically justified when the risks and burdens to research subjects are minimal and the research has the potential to generate socially valuable knowledge."

SPs have routinely been used in low- and middle- income countries for assessing pharmacist practice.[2] Members of our research team have validated the SP approach in India for assessing quality of care for tuberculosis (TB) patients,[3] and this was successfully extended to assess the management of TB in pharmacies.[4] The pilot study demonstrated that the methodology presents minimal to no risk for participants and providers, while being highly effective at measuring quality of care.

Regarding the objectives of the current study, it is difficult to estimate current practice in pharmacies. Prescription audits fail to measure off-prescription drug use, and the direct observation approach has several limitations. Notably, direct observation is limited by the Hawthorne effect, which suggests that individuals have a natural propensity to alter their behaviour when they are aware that they are being observed. If pharmacists are aware that they are in a study and the customer in front of them is an SP, they may be more or less likely to prescribe certain medications. In that case, the results in our study would not have reflected the actual practice in the pharmacies studied, and antibiotic prescribing rates would not have been accurately measured, compromising our study validity.

The lack of provider consent was unlikely to have an adverse effect on the pharmacists in our study. No financial losses were incurred, as SPs purchased any medications provided to them by the pharmacist as a regular customer would. Other customers were at most inconvenienced by the few minutes the SP interaction requires. Further, all information collected was kept strictly confidential by our team. The identities of the pharmacists and any identifying information on their store will not be released to the public or published in any format.

The study also poses minimal to no risk to individuals recruited to be SPs. No harm to SPs was documented in our previous pharmacy SP study in India, and the quality of care pilot study demonstrated that there is little to no risk of SPs being detected by health care providers. All SPs in our study presented with relatively common and non-severe symptoms, so there was no reason to expect extreme or unusual responses from pharmacy staff. Importantly, SPs were subject to any therapeutic or diagnostic interventions. They purchased medications prescribed by the pharmacist but were instructed not to take any of the medications. Pharmacists may provide referrals to a

physician or for further testing, but SPs did not visit any other health care providers or consent to any invasive or non-invasive medical procedures.

2. Choice of conditions represented by SPs

There is a lack of clear international guidelines on the management of URI, especially in pharmacies. URI is a common condition that is generally of viral aetiology, and for the symptoms of the common cold – runny nose, sore throat, cough, nasal congestion – only symptomatic treatment is recommended by the American Centers for Disease Control (CDC).[5] Symptomatic treatment includes the use antihistamines, decongestants, cough suppressants, and non-steroidal anti-inflammatory drugs (NSAIDs), so these drugs were considered 'acceptable' for adults in our study.[5] For children under age five with a cough and cold, the World Health Organization (WHO) primarily recommends oral rehydration therapy and paracetamol in the case of a fever, and discourages the use of combination drugs.[6] For this reason, combination cough syrups and antihistamines were considered 'unacceptable' for the paediatric case, though not 'harmful'. 'Harmful' drugs were antibiotics or other prescription-only medications that posed an unnecessary risk of side effects, such as bronchodilators.

Guidelines for the treatment of diarrhoea have been published by the WHO in the case of acute, uncomplicated diarrhoea, the recommended treatment is oral rehydration salts (ORS) and zinc supplementation in the case of children; the benefits of zinc in adults is yet unclear.[7] Anti-motility drugs such as loperamide may be effective in adults but are not recommended by the WHO for use in children as they appear to be less effective and are potentially associated with adverse effects in the paediatric population.[7] For this reason, we considered loperamide to be a harmful medication for children only. Prescription antiemetics and antacids such as H2 blockers or proton pump inhibitors were considered harmful for adult and paediatric SPs.

The WHO does not have published guidelines on fever specifically for pharmacies, and the initial symptoms of malaria are generally non-specific. However, in the guidelines for community health workers, children with fever in the last seven days living in a malaria endemic region should receive a malaria diagnostic test.[8] Further, the WHO guidelines on malaria recommend that in endemic areas, malaria should be suspected in any patient with a fever >37.5C.[27] Karnataka is a state with a relatively high burden of malaria,[9] with greatest incidence observed during the monsoon season when our study is carried out. We thus consider it reasonable to expect that pharmacists recognise the potential risk and refer the patient for malaria testing. Antibiotics (i.e. anti-malarials) or other prescription-only medications that posed an unnecessary risk of side effects were considered as 'harmful'.

3. Case development and SP training

Cases and ideal case management were defined prior to SP recruitment. After conceptualising the symptoms of the three cases, clinicians developed a list of potentially relevant questions that pharmacies may ask. Answers for each question were prepared with the intent of developing SP case scenarios that do not warrant the use of antibiotics.

SPs were recruited by advertising at the Manipal Academy of Higher Education and the local community. Ultimately, three individuals, all male, were hired as SPs. All were of a similar age (in their 20s) and from the local area, meaning they were familiar with the district geography

and spoke the local language of Kannada, as well as at least basic English. Each SP was responsible for one paediatric and one adult case as follows:

- SP1 – paediatric diarrhoea + adult URI
- SP2 – paediatric fever + adult diarrhoea
- SP3 – paediatric URI + adult fever

For each set of two cases, a script was developed. The SP was instructed to first present the paediatric case and upon the completion of that interaction, present the adult case. The adult case was presented regardless of the outcome of the paediatric case. The script included some basic information about the background of each SP, such as their living situation and some behaviours that would be relevant to their health (consumption of alcohol and/or tobacco). Scripts were developed in conjunction with the research team including local field staff, a local clinician, and the individuals recruited as SPs. We first prepared the scripts in English and then translated them into Kannada, again with SP participation. SP input was extremely helpful for this stage as they were able to provide examples of the vocabulary used in the community.

For SP training, the research team worked with a member of the Institute of Socio-Economic Research on Development and Democracy (ISERDD), an organisation based in Delhi, India, that has assisted our team with SP training in the past. Training began with a discussion regarding the relevance of the developed cases for the local community, followed by the development of the scripts as described above and a discussion regarding the relevance of the developed cases. Once the scripts were developed, SPs were trained to learn all aspects of the script. When supervisors felt that SPs had adequately learnt the script, we completed supervised dry runs at local pharmacies, where the supervisor would be present in the pharmacy under the pretense of purchasing something while the SP completed the interaction. This was followed by unsupervised practice visits. We aimed to ensure that 1) SPs correctly recalled all aspects of case presentation; 2) SPs correctly recalled all aspects of the interaction; 3) SPs successfully avoided detection.

SPs were trained to avoid detection by engaging in a discussion of potential questions pharmacy staff may ask, and role-playing exercises to help the SP internalise the details of their case and represent it more accurately. Mock interviews with both scripted and unscripted questions were used to aid with this as well as script recall. In addition, it was essential to train SPs to avoid any uncomfortable situations. SPs together with supervisors discussed potentially difficult situations that may arise, such as a pharmacist attempting to perform examination or insisting that the SP bring in the sick child for examination. Subsequently, SPs were trained on risk mitigation strategies in case such a situation arose. SPs were also instructed to immediately contact local field staff if they encountered any dangerous situations during field visits, though this did not ultimately occur.

4. Post-visit questionnaire

Upon completion of each visit, SPs were instructed to fill out a post-visit questionnaire using the Epicollect5 mobile application on their smartphones (iPhone/Android). The questionnaire allowed SPs to record: the approximate length of the interaction, the location of the pharmacy, the number of other clients present at the time of interaction (as a proxy for client volume), whether they were referred to another provider such as a hospital or medical practitioner, all questions asked by pharmacy staff, tests recommended, diagnoses mentioned, and total cost. The

length of the interaction was measured by checking a watch or smartphone upon entry and exit, and was reported as an interval, e.g. approximately 3-5 minutes.

SPs practiced using the applicating during piloting to ensure that there would be no errors. The questionnaire was available even if the phone was not connected to a data network; multiple entries can be saved offline and uploaded when a network is available. SPs were instructed not to fill out the questionnaire directly in front of the pharmacy, but rather walk or drive a short distance away before completing it in order to avoid drawing attention to themselves at the pharmacy. Epicollect5 was chosen as a data collection method as all uploaded entries are automatically saved on the server. The data was only available to the investigators and local research assistant. With this method, data was immediately digitised, minimising the risk of transcription errors. We also believed that using a smartphone would be less conspicuous than stopping to fill out a physical form, additionally helping to protect SPs from being detected. Each completed questionnaire was verified for missing data at the end of the day by a trained research assistant.

5. Sample size calculation and selection of pharmacies

The following formula was used to calculate sample size per SP case:

$$\mathbf{n = [Np(1-p)]/ [(d^2/Z^2*(N-1)+p*(1-p)]}$$

Where:

n = Number of pharmacies required
N = Number of pharmacies in sampling frame
p = Hypothesised outcome proportion
d^2 = Absolute confidence limits (%)
Z^2 = Z-score for confidence level

This is appropriate for a binary outcome, and our primary outcome was antibiotic dispensing (coded as yes/no). Sample size was calculated for outcome proportions from 0.1 to 0.5. The computation is symmetric around 0.5, so the sample size calculated for a proportion of 0.3 is the same as that needed for an outcome proportion of 0.7.

Required sample size	**100**	**145**	**169**	**180**	**184**
Pharmacies in sampling frame	350	350	350	350	350
Hypothesised outcome proportion	0.1	0.2	0.3	0.4	0.5
Width of confidence interval	+/- 5%	+/- 5%	+/- 5%	+/- 5%	+/- 5%
Confidence level	95%	95%	95%	95%	95%

Table S1. Required sample size for differing outcome proportions. The sample size represents the number of pharmacies needed per SP case.

Of the 350 pharmacies in the district, 47 (13.43%) were associated with hospitals or clinics and were excluded as these pharmacies generally serve hospital or poly-clinic patients and are not reflective of the typical retail pharmacy that an individual might spontaneously approach for

medical advice. A further 10 pharmacies (2.85%) were either permanently closed or undergoing renovations, and 4 pharmacies (1.14%) could not be identified by field staff at the listed address. One listed pharmacy was for veterinarian purposes only. SPs then visited 10 pharmacies for training purposes. This left 279 available for inclusion in the study, and this number satisfies the sample size calculation for any rate of antibiotic dispensing. This sample size also ensured that the study is powered to detect a subgroup difference (e.g., urban vs. rural) in antibiotic use rate of 10% with a power >80%.

6. Statistical analysis

The outcome of interest in our analyses was antibiotic dispensing for a given SP-pharmacy interaction, which was coded as follows: 1 = antibiotic dispensed, 0 = no antibiotic dispensing. For a binary outcome, logit models best account for the error structure.

Model 1: pooled model

The purpose of the pooled model was to determine which factors of the SP-pharmacy interaction were associated with antibiotic dispensing in the study. The pharmacy variables of interest were:

Variable name	Variable type	Variable coding
Referred to another provider	Dichotomous	1 = yes 0 = no
Urban vs. rural pharmacy	Dichotomous	1 = urban 0 = rural
Length of visit	Categorical	<1 minute (reference) 1-3 minutes 3+ minutes
Number of customers present at the time of the interaction	Categorical	No customers (reference) 1-3 customers 3+ customers
Questions asked by pharmacy	Continuous	Minimum: 0 Maximum: 7

Table S2. Variables of interest in pooled model.

All covariates were checked for collinearity prior to inclusion in the model, and no issues were found. To obtain efficient and accurate estimates of these effects, our final model should also account for other factors that affect antibiotic dispensing. It is likely that not all SP case scenarios will result in the same proportion of antibiotic dispensing. This was ultimately observed in the data, with diarrhoea being the condition for which antibiotics were provided more frequently. Further, we assumed that our observations are not independent due to clustering by pharmacy.

Four logit models were fit to the full dataset comprised of 1,522 SP-pharmacy interactions, and the coefficient estimates from all for are shown in Figure S1 as the difference in log odds. Odds ratios can be obtained by exponentiating these coefficients. We began by fitting a generalised linear model (GLM) with a logit link, or a logistic regression model, with only the pharmacy variables as covariates (model 1). For model 2, we added one dummy variable for age (as this variable has two levels, adult and child), and two dummy variables for case (this variable has the levels URI, diarrhoea, and fever) to account for all six SP case scenarios. We can show that

model 2 provides a better fit for the data by using the likelihood ratio test to compare the log likelihoods of the two models. The log likelihood of model 1 is -226 while the log likelihood of model 2 is -216, and the Chi-square test results a significant result ($p<0.001$).

Model 2 accounts for SP case scenario but does not take into consideration potential clustering by pharmacy (n = 279). We considered two different models that can account for this clustering. First, we fit a generalised linear mixed model (GLMM) with a logit link, where we included random intercepts for all pharmacies in the dataset (model 3). The second method was to model the data using generalised estimating equations (GEE) with a logit link (model 4).

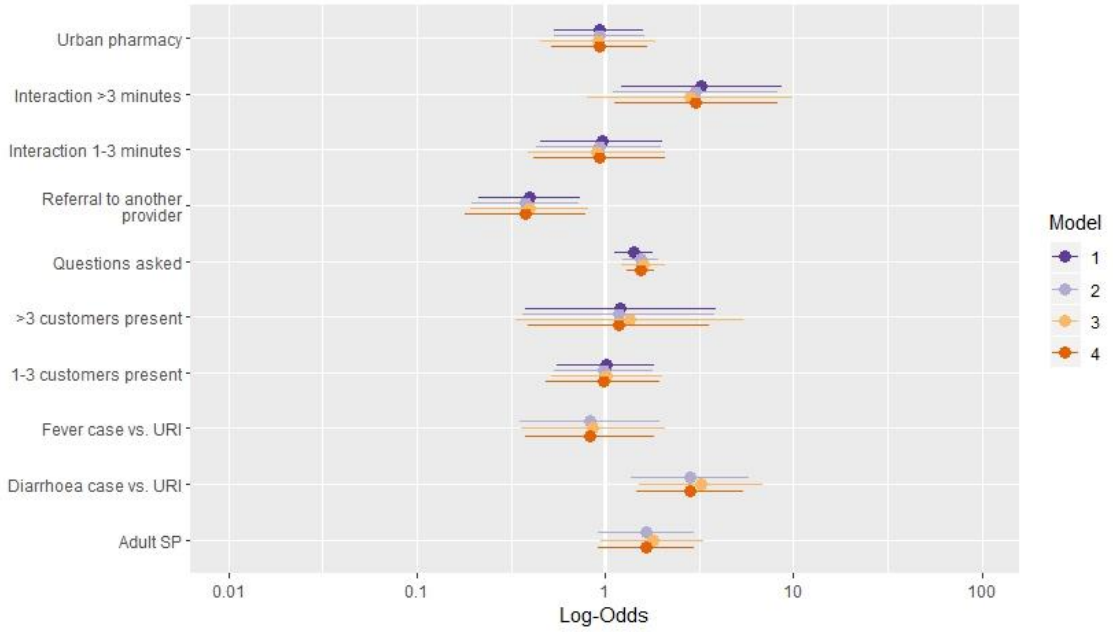

Figure S1. Comparison of logit models for pooled model (n = 1,522). Model 1 = logistic regression with no fixed or random effects; model 2 = logistic regression with case and age dummy variables; model 3 = GLMM with logit link with case and age dummy variables, and random intercepts by pharmacy; model 4 = GEE with logit link with case and age dummy variables, and clustering by pharmacy.

Both models 3 and 4 also include dummy variables for case and age; thus, both account for variation by SP case scenario and by pharmacy visited. However, the interpretation of the coefficients for the pharmacy variables (variables of interest) are different. GLMM estimates conditional effects, where a coefficient represents the effect of that variable, while holding the value of all other variables constant. Meanwhile, GEE estimates marginal effects, where the coefficient represents the population average effect of the variable.

Figure S1 demonstrates that coefficient estimates were very similar between GLMM and GEE. The major difference is that the confidence interval estimated for the “Interaction >3 minutes” crosses the null in model 3, but not in model 4. However, the comparatively large standard errors

may be due to a loss of efficiency with GLMM with random effects when the number of clusters is large (n = 279 in this case), as a random intercept must be fit for each cluster.

We report results from the GEE analysis in the main paper for the reasons described above:

- Marginal effect estimates may be more conventionally interpretable.
- The number of clusters is large, potentially reducing the efficiency of GLMM.
- GEE does not require any distributional assumptions and the determination of standard errors is robust to misspecification of the correlation structure.

Theoretically, it is possible that SP characteristics such as sex, age, height, or weight, could affect pharmacists' behaviour. However, as each SP case scenario was only portrayed by one individual in this study, any potential variation here will be accounted for with the case fixed effect, and SP characteristics were never included as an additional covariate in the models.

Model 2: predicting paediatric antibiotic dispensing

To examine whether dispensing for adults and children was correlated, we chose to fit a second logit model where the outcome was antibiotic dispensing for the paediatric SP-pharmacy interactions (coded as 1 = yes and 0 = no). Due to the lower rates of antibiotic dispensing for the URI and fever conditions, this analysis was restricted to diarrhoea only. The variable of interest was antibiotic dispensing for the corresponding adult interaction, i.e., the adult SP with diarrhoea at the same pharmacy (again coded as 1 = yes and 0 = no). Thus, the model would hypothetically include 250 observations, the number of paediatric diarrhoea SP-pharmacy interactions. However, as not all visits were successfully completed and the number of interactions is not perfectly equal between adults and children, 17 paediatric diarrhoea interactions do not have a corresponding adult interaction, and these were excluded.

For this analysis, length of interaction and number of customers present were dichotomised and included as less than one minute vs. more than one minute, and no customers vs. customers present, respectively. This was done as there were very few observations in the categories "visit length more than three minutes" and "more than three customers present" when only a subset of all the visits were considered.

The coefficient estimates from the logit models fit to this data are displayed in Figure S2. As with the pooled model, we first fit a logistic regression model including only the pharmacy variables in addition to our new covariate of interest, antibiotic dispensing for the adult (model 1). Models 2 and 3 correspond to the GLMM and GEE models described above. Again, coefficient estimates are very similar between the two models, and we report the results from model 4 in the main paper for the reasons described above.

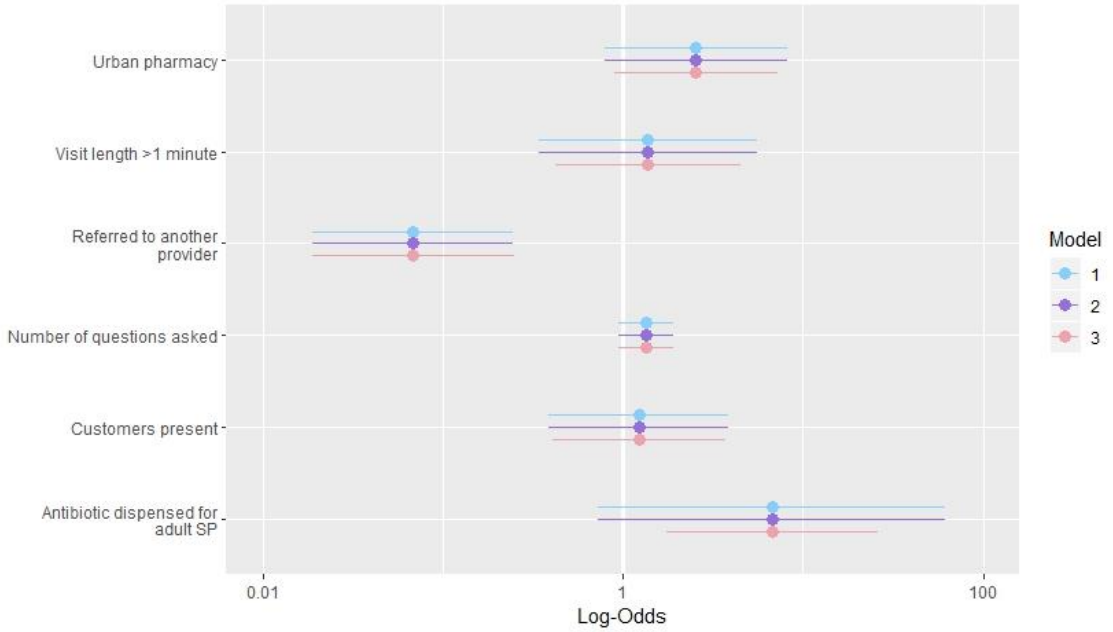

Figure S2. Comparison of logit models for paediatric diarrhoea antibiotic dispensing model with adult and child outcomes paired based on condition (n = 233). 'Antibiotic dispensed for adult SP' refers to whether the adult SP with diarrhoea received an antibiotic at the same pharmacy. Model 1 = logistic regression with no fixed or random effects; model 2 = GLMM with logit link with random intercepts by pharmacy; model 3 = GEE with logit link accounting for clustering by pharmacy.

We additionally fit a second model using antibiotic dispensing for paediatric diarrhoea as the outcome, but the corresponding adult interaction was defined as the adult SP case scenario presented in the same visit. With our experimental design, paediatric diarrhoea was presented alongside adult URI. Figure S3 presents the logit models fit using this definition. Antibiotic dispensing for the adult was also a significant predictor here. We present the results of the model comparing children and adults with diarrhoea in the main paper as that better takes into consideration the differing frequency of antibiotic dispensing according to condition.

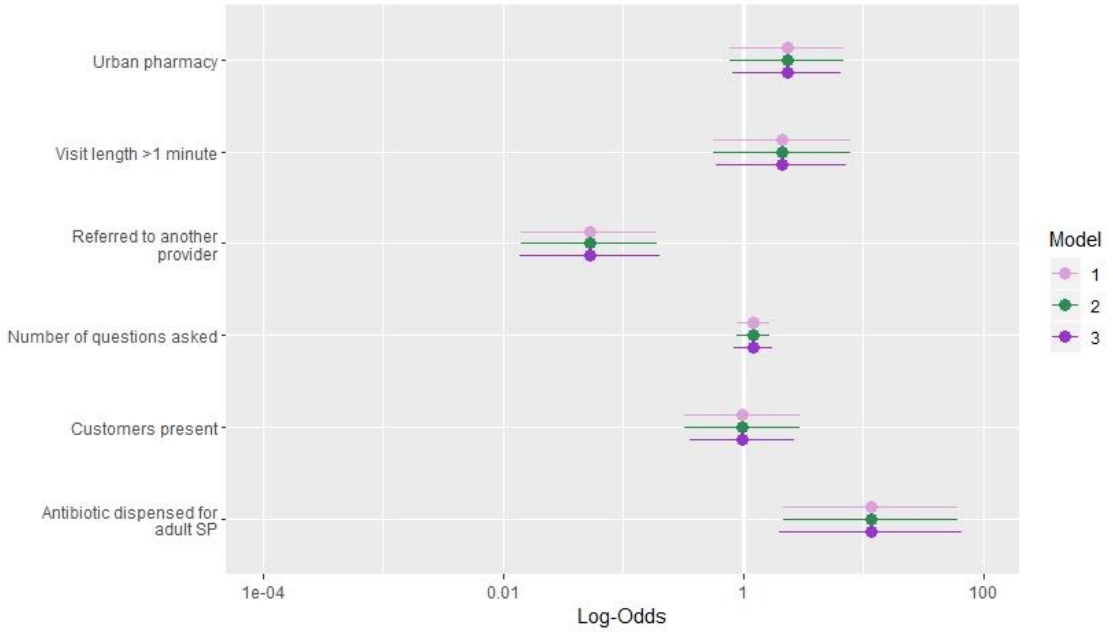

Figure S3. Comparison of logit models for paediatric diarrhoea antibiotic dispensing model with adult and child outcomes paired based on SP visit (n = 250). 'Antibiotic dispensed for adult SP' refers to whether the adult SP case presented during the same visit as the paediatric case received an antibiotic. Model 1 = logistic regression with no fixed or random effects; model 2 = GLMM with logit link with random intercepts by pharmacy; model 3 = GEE with logit link accounting for clustering by pharmacy.

Supplementary table

		Percentage of interactions (95% CI)	
		Adult	**Paediatric**
URI	Age (child only)	NA	98.4% (95.7%, 99.4%)
	Degree of fever	29.6% (24.2%, 35.7%)	16.3% (12.1%, 21.5%)
	Cough containing sputum	61.4% (54.9%, 67.2%)	1.2% (0.31%, 3.73%)
	Cough containing blood	0.79% (0.14%, 3.1%)	1.2% (0.31%, 3.73%)
	Presence of runny nose	31.2% (25.6%, 37.4%)	4.8% (2.6%, 8.4%)
	Difficulty breathing or wheezing	0 (0, 1.9%)	0 (0, 1.9%)
	Any pain (child only)	NA	0 (0, 1.9%)
	Throat or ear pain (adult only)	0.79% (0.14%, 3.1%)	NA

	Chest pain (adult only)	5.9% (3.5%, 9.9%)	NA
	Sick household members	0 (0, 1.9%)	0 (0, 1.9%)
	Any question (excluding age)	88.9% (84.2%, 92.4%)	28.2% (22.8%, 34.2%)
Diarrhoea	Age (child only)	NA	97.6% (94.7%, 99.0%)
	Duration of diarrhoea	29.7% (24.3%, 35.8%)	14.6% (10.6%, 19.7%)
	Number of stools per day	13.9% (10%, 18.9%)	12.% (8.6%, 17.1%)
	Blood or mucus in the stool	0.77% (0.13%, 3.1%)	0.79% (0.14%, 3.1%)
	Vomiting in the past 8 hours	0.39% (0.02%, 2.5%)	4.7% (2.6%, 8.3%)
	Presence of a fever	1.9% (0.71%, 4.7%)	3.6% (1.7%, 6.9%)
	Any problems urinating	0 (0, 1.8%)	0 (0, 1.9%)
	Feeding practices while sick	0 (0, 1.8%)	6.3% (3.8%, 10.3%)
	Medication taken while sick	0 (0, 1.8%)	3.6% (1.7%, 6.9%)
	Any question (excluding age)	35.9% (30.1%, 42.1%)	19.4% (14.8%, 24.9%)
Fever	Age (child only)	NA	97.7% (94.8%, 99.1%)
	Duration of symptoms	88.5% (83.7%, 92%)	7.3% (4.6%, 11.4%)
	Presence of cough	21.4% (16.6%, 27.1%)	16.6% (12.4%, 21.8%)
	Any pain (child only)	NA	0.39% (0.02%, 2.5%)
	Throat or ear pain (adult only)	0 (0, 1.9%)	NA
	Headache (adult only)	22.2% (17.3%, 28%)	NA
	Occurrence of fits or fainting	0 (0, 1.9%)	0 (0, 1.8%)
	Regular feeding and bowel movements	0 (0, 1.9%)	0 (0, 1.8%)
	Any question (excluding age)	100% (98.1%, 100%)	19.7% (15.1%, 25.2%)

Table S3. History taking by pharmacies, separated by SP case. Percentages refer to percentage of interactions where the pharmacist posed this question. Values do not sum to 100% as some pharmacies posed multiple questions.

		Antibiotic dispensed for paediatric SPs	
		No	**Yes**
Antibiotic dispensed for adult SPs	**No**	710	18
	Yes	29	4

Table S4. 2x2 table for overall antibiotic dispensing to adult and paediatric SPs.

Schedule H medications provided to children	**URI** Bromhexine (8) Cetirizine (11) Chlorpheniramine (45) Dextromethorphan (45) Levocetirizine (2) Levosalbutamol (2) Montelukast (1) Salbutamol (2) Terbutaline (1)
	Diarrhoea Loperamide (23)
	Fever Bromhexine (1) Cetirizine (1) Chlorpheniramine (7) Levocetirizine (1) Montelukast (1)
Schedule H medications provided to adults	**URI** Bromhexine (109) Cetirizine (8) Chlorpheniramine (115) Dextromethorphan (62) Levocetirizine (13) Montelukast (5) Salbutamol (1) Terbutaline (26)
	Diarrhoea Domperidone (2) Loperamide (227) Omeprazole (3) Ranitidine (2)
	Fever

	Bromhexine (9) Cetirizine (65) Chlorpheniramine (53) Dextromethorphan (4) Levocetirizine (3) Nimesulide (23)

Table S5. Non-antibiotic schedule H medications provided to SPs: name and number of interactions where the medication was provided.

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