A global survey of antibiotic leftovers in the outpatient setting

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Abstract

We performed a global survey of outpatients who had taken self-administered antibiotics within the last 12 months in order to identify factors that lead to possession of leftover antibiotics in the community. The study included 4514 subjects aged 18–99 years. Of 4192 respondents not currently taking antibiotics, 53.7% admitted having leftover antibiotics, of whom 77.0% saved them, 4.6% gave them away and 18.4% threw them away. Living in a country where antibiotics are dispensed in fixed packs rather than exact numbers of pills as well as believing that leftover antibiotics can be saved and used again were the strongest predictors for possession of leftovers. There was also a marked detrimental effect of lack of information from the doctor and/or pharmacist. This investigation suggests that dispensing of antibiotics in exact numbers of doses should be recommended in addition to the development of relevant information campaigns addressing patients' false beliefs about leftovers and the provision of basic information about the importance of completing antibiotic treatment.
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1. Introduction

In the most of antibiotics are dispensed according to strict regulations and are not available over the counter. However, for a number of reasons outpatients may retain leftover antibiotics following a course of treatment. These leftovers encourage self-treatment either with an insufficiently short regimen or for inappropriate indications. Using leftovers for a later infection in the same patient carries a double risk: the subsequent pathogen may not share the susceptibility of the original; and the medication may have lost potency due to improper or prolonged storage, thus creating an environment of subtherapeutic dosing. Similar risks are associated with sharing antibiotics with other individuals, with the additional risk of unforeseen allergic reactions. Finally, even when discarded, leftover antibiotics add to the problem of environmental pollution. Therefore, unlike most other drugs that, used incorrectly, may simply pose a risk to the particular patient, misused antibiotics add to the global risk of increased spread of resistance.

It is only in the last few years that antibiotic leftovers have attracted public attention [1]. However, this topic is of great public importance if one considers that as many as 25% of Americans may be keeping antibiotic leftovers in their homes [2]. Therefore, the aim of this cross-cultural international survey was to identify: factors associated with the retention of leftover antibiotics in the community; attitudes and behaviours towards the use of antibiotic leftovers; and those factors that characterise patients at risk of saving leftover antibiotics. This study was part of the larger COMPLy (COmpliance, Modalities by Population, Lifestyle and Geography) survey [3].

2. Method

Data were collected using a standardised, structured, interviewer-administered questionnaire in 11 countries: Brazil, China, Italy, Japan, Mexico, The Netherlands, The Philippines, Russia, South Africa, Turkey and the USA.

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2.1. Subjects

The fieldwork for the study was carried out in Autumn 2005. Adults ≥18 years of age who claimed to have taken a self-administered oral antibiotic as an outpatient within the past 12 months were included (self-administered antibiotics being those obtained with or without prescription, or leftovers, with no restriction on the antibiotic formulation). Interviewees were selected by random digit dial (RDD) telephone where national country coverage and penetration permitted (Italy, Japan, Mexico, The Netherlands and the USA); in Brazil, China and Turkey, RDD was used in urban centres. Face-to-face interviewing was used in The Philippines (door-to-door interviews conducted nationwide), South Africa (street intercept at random locations in major metropolitan areas) and Russia (door-to-door interviews in 12 large cities).

2.2. Questionnaire

The questionnaire was translated into local languages and then validated by physicians in the region to ensure consistent, standardised responses across countries. Respondents were asked about their demographics, health status, latest antibiotic regimen and any underlying disease, how the antibiotic was obtained, the source of information on antibiotic use, whether they had any leftover antibiotics and what they did with them, and their attitudes to antibiotics.

According to the local dispensing system, countries covered by the survey were divided into 'pack' and 'non-pack' countries. 'Pack' countries were defined as those that do not break up blister packs for dispensing antibiotics and as a result may overdispense for a particular course, and include Brazil, China, Italy, Mexico, Russia and Turkey.

A health status index was calculated from responses to the EQ-5D Health State Profile, using the UK tariff system [4], for each respondent to represent health status (utility) at the time of the infection [5].

Descriptive statistics were used to describe the prevalence of retention of antibiotic leftovers and saving/giving these leftovers to someone else. Univariate analyses were used to study the effects of individual characteristics and the country on possession of antibiotic leftovers as well as on saving/giving these leftovers to others. Factors associated with the likelihood of having leftovers and the likelihood of saving or giving away leftovers were tested using stepwise logistic regression [6,7].

3. Results

3.1. Respondent characteristics

A total of 4514 interviews were completed. Respondent characteristics are detailed in Table 1.

The most common conditions for which respondents had recently taken antibiotics were streptococcal throat/throat infection/sore throat (21.8%), influenza/cold (15.2%) and bladder/urinary tract infection (7.1%). Detailed characteristics of antibiotic regimens and information received by patients are given in Table 2. In Brazil, Italy, Mexico, The Philippines, Russia and South Africa, the majority of respondents were told how they should take their antibiotic by their doctor, whereas in China, Japan, The Netherlands, Turkey and the USA this was mostly done by the pharmacist.

Health status was assessed in 4387 respondents. The mean utility was 0.527 (standard deviation 0.394).

3.2. Attitudes to leftover antibiotics

There was a large diversity between countries in patient attitudes about saving leftover antibiotics. Respondents from 'pack' countries tended to believe more strongly that leftover antibiotics can be saved and used again compared with 'non-pack' countries (66.5% vs. 31.0%; $P < 0.0001$) and that when they feel better they may sometimes save the rest of their

Table 1
Demographic characteristics of surveyed population

Country	No. of respondents	No. (%) female	Mean (S.D.) age (years)	Marital status (%)[a]				Taking prescription medicines on regular basis (%)
				Married	Divorced	Widowed	Single	
Brazil	422	286 (67.8)	37.4 (14.1)	49.8	8.5	3.1	38.2	36.3
China	402	228 (56.7)	37.5 (15.5)	70.1	2.0	1.0	26.6	5.2
Italy	462	257 (55.6)	44.8 (16.2)	62.3	3.7	7.1	26.6	33.5
Japan	302	201 (66.6)	48.5 (15.6)	76.5	3.0	3.3	16.9	29.5
Mexico	415	206 (49.6)	36.3 (11.8)	61.9	2.9	1.4	33.0	27.0
Netherlands	400	271 (67.8)	46.7 (16.7)	69.3	6.3	7.3	16.5	46.5
Philippines	400	230 (57.5)	37.2 (12.1)	70.5	1.3	4.0	24.3	13.0
Russia	400	319 (79.8)	41.1 (13.9)	59.5	14.5	10.5	15.0	24.8
South Africa	402	247 (61.4)	36.6 (14.4)	42.5	8.2	4.7	44.3	32.8
Turkey	407	326 (80.1)	36.8 (12.1)	80.8	0.7	2.9	15.5	22.1
USA	502	327 (65.1)	50.4 (17.8)	65.7	9.0	8.8	15.7	63.9
Total	4514	2898 (64.2)	41.3 (15.6)	64.1	5.6	5.1	24.9	31.2

S.D., standard deviation.

[a] 'Refused' option not shown (percentages do not add up to 100%).

Table 2
Characteristics of antibiotic regimens and information received, as described by respondents

Country	No. of respondents	Antibiotic form (%)[a]		Antibiotic regimen[a]		Mean no. of days[b]	Source of antibiotic (%)[c]			Information provided (%)[e]	
		Pill	Liquid	Mean no. of daily doses			Filled doctor prescription	Medical professional	Non-medical professional[d]	Not told disease by doctor	Not told how to take antibiotic by either doctor or pharmacist
Brazil	422	86.7	7.1	2.2		8.0	78.0	8.5	11.4	12.6	0.3
China	402	88.3	6.0	2.6		3.6	58.2	23.6	16.9	62.6	16.4
Italy	462	82.0	8.2	1.8		5.9	79.4	16.5	3.5	17.4	4.7
Japan	302	97.0	2.0	2.4		5.1	82.5	10.9	6.6	25.5	5.0
Mexico	415	79.8	20.0	2.2		7.1	64.8	23.6	11.6	14.2	0.5
Netherlands	400	87.5	2.8	2.1		8.1	86.3	11.5	0.5	14.6	5.6
Philippines	400	93.3	0.3	2.2		6.2	42.5	14.0	43.5	0.9	0.9
Russia	400	84.0	7.5	2.6		6.4	65.8	6.5	27.3	5.5	0.7
South Africa	402	87.8	9.7	2.4		7.7	53.7	43.3	2.2	10.3	4.1
Turkey	407	92.1	5.7	2.0		6.6	81.1	9.6	9.1	28.5	0.5
USA	502	92.0	4.0	1.9		8.2	84.1	12.9	2.0	17.0	2.5
Total	4514	88.0	6.8	2.2		6.8	70.8	16.5	12.0	19.2	3.8

[a] 'Don't know/refused' option not included.
[b] 'Told to take until gone' and 'don't know/refused' options not included in calculation.
[c] 'Other' and 'don't know/refused' options not shown.
[d] Non-medical professional includes: bought from a pharmacy without prescription, filled/re-filled an old prescription, leftover antibiotic from previous illness or from other household member, and obtained from friend or relative, through mail order or the Internet.
[e] Base 3938: obtained antibiotic by filling prescription or directly from doctor/clinic/other medical professional.

antibiotic for the next time they get sick (50.8% vs. 27.7%; $P < 0.0001$).

3.3. Leftover antibiotics

Fig. 1 shows the prevalence by country of those reporting having had leftovers among those who obtained antibiotics by filling a new prescription or being given an antibiotic by a medical professional.

Fig. 2 shows the pattern of leftover use among respondents who reported having leftovers.

3.4. Univariate analysis

Univariate analysis revealed the impact of different factors on possession of antibiotic leftovers (Table 3). The highest proportion of leftover possession occurred in those who were not told how many days they should take their antibiotics (82.2% vs. 49.9% for total; $P < 0.0001$). The prevalence of leftover antibiotics was significantly higher among those on two or three daily doses compared with once-daily regimens ($P < 0.0001$). There was a negative correlation between possession of leftovers and obtaining antibiotics from a medical professional (Table 3), and leftovers were extremely prevalent among those who bought antibiotics without prescription (69.2%).

3.5. Multivariate analysis

Table 4 lists the factors significantly associated with having leftover antibiotics and saving/giving them away according to the logistic regression model.

4. Discussion

Despite several national appropriate-use campaigns, the results of this study confirm that leftovers are widely prevalent during current routine outpatient antibiotic treatment: they were identified in ca. 50% of respondents studied. Indeed, possession of leftover antibiotics and their use have been reported previously in a number of developed and developing countries [2,8–14]. A survey performed previously revealed the percentage of respondents who saved antibiotics and used them on future occasions ranged from 4% in the UK to 41% in Italy [15]. In a further publication assessing patient behaviour towards antibiotics in nine countries, representing Africa, Europe, Asia and South America, 24% of patients claimed to save antibiotic leftovers [16]. A recent survey found leftovers to be highly prevalent in all 18 European countries studied as well as in Israel [17]. A survey of 6983 UK households identified leftover or 'standby' antimicrobial drugs in 10% of cases [18]. Finally, a recent meta-analysis established the mean use of leftovers by 28.6% of subjects in the studies [1].
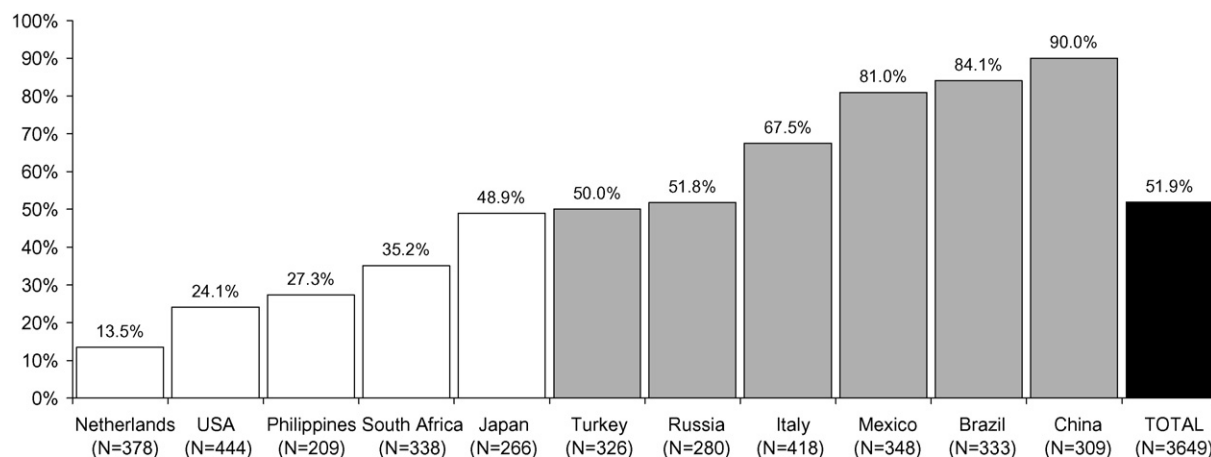
Fig. 1. Prevalence of possession of leftovers (%) in respondents who obtained antibiotics by filling a new prescription or being given antibiotic by a medical professional ($N = 3649$). Grey bars, 'pack' countries (countries where antibiotics are dispensed in fixed packs rather than exact numbers of doses); white bars, 'non-pack' countries.

There are two sources of antibiotic leftovers, the better-known one of patient non-compliance and over-dispensing. Although outpatient antibiotic therapy is usually of short duration, and more severe symptoms appear to motivate patients better to follow their doctor's instructions, patient non-compliance in such circumstances remains a frequent phenomenon. A recent meta-analysis found that, on average, 37.8% of subjects were non-compliant [1]. In fact, non-compliance usually leads to two forms of inappropriate antibiotic use: incorrect amount of medication taken; and self-medication at a later date. Within the population in the current study, 22% of respondents admitted being non-compliant with their last antibiotic treatment [3].

A novel source of antibiotic leftovers, clearly identified in the current study, is associated with the method of dis-

pensing. In a number of countries antibiotics are dispensed in fixed packs and not in the exact number of doses per prescription, and therefore doctors are forced to overprescribe. Regardless of the geographic region, this factor was found to be the strongest predictor of possession of leftovers.

However, it is not the leftovers themselves but what patients do with them that is the crux of the problem. In this study, 77% of those who had leftover antibiotics said they saved them. Again, the antibiotic dispensing system was the strongest predictor of the risk of misuse: in 'pack' countries, patients were more prone to save leftovers or to give them to someone else. Both these behaviours create a natural reservoir for self-medication. Among other problems, this can lead to inadequately short treatment duration [19,20] and the potential for selection of resistant bacteria and the spread of
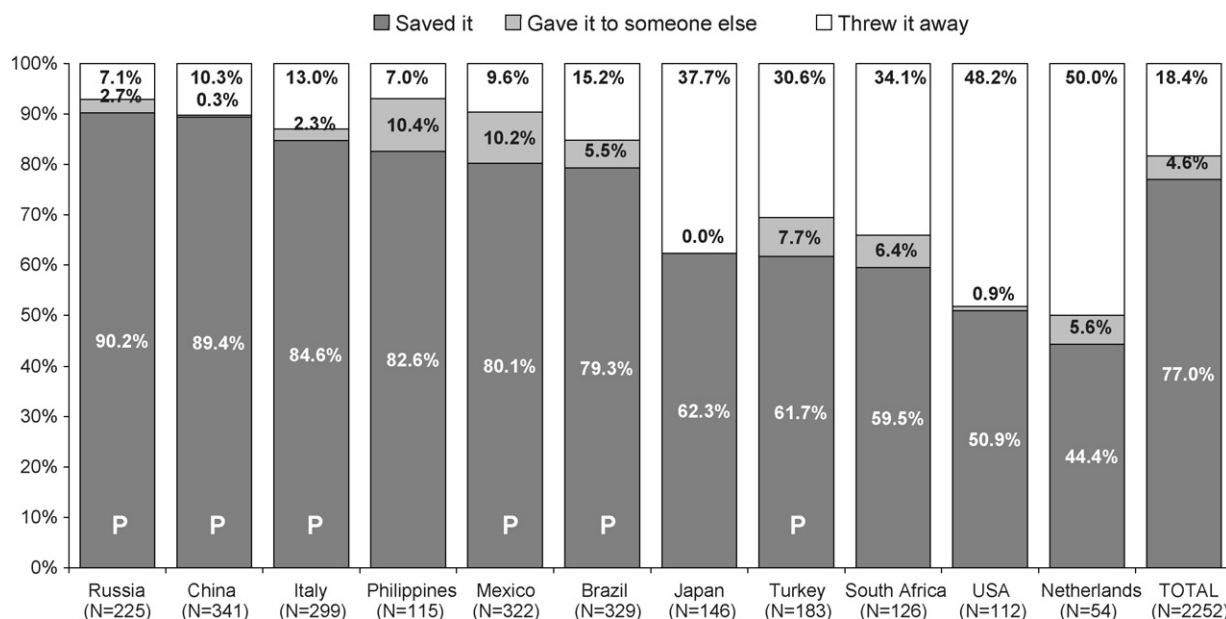

Fig. 2. Pattern of leftover antibiotic use among those respondents who had leftovers (%) ($N = 2252$). P, 'pack' countries (countries where antibiotics are dispensed in fixed packs rather than exact numbers of doses).

Table 3
Univariate analysis: correlation of factors with possession of leftovers ($N = 4514$)

Factor	N	Possession of leftovers (%)	P-value[a]
Dispensing practice			<0.0001
'Pack'[b]	2508	67.7	
'Non-pack'	2006	27.6	
Age group (years)			<0.0001
18–29	1133	61.4	
30–39	1080	49.2	
40–59	1661	47.2	
≥60	610	37.4	
Marital status			<0.01
Single	1122	58.6	
Married	2895	48.0	
Divorced	251	41.0	
Widowed	228	40.8	
Gender			<0.01
Male	1616	52.5	
Female	2898	48.5	
Antibiotic form			<0.01
Liquid	306	58.8	
Pill	3973	49.0	
Length of treatment (days)			<0.0001
<5	896	59.3	
5–9	2186	48.3	
≥10	824	39.2	
Health status (EQ-5D)[c]			<0.0001
Poorest	1632	54.5	
Moderate	1278	50.2	
Best	1477	44.6	
Information about diagnosis			<0.0001
Not told by doctor	756	59.5	
Told by doctor	3123	45.3	
Source of antibiotic			<0.0001
Non-medical	565	61.9	
Medical	3938	48.1	
Believe 'leftover antibiotics can be saved and used again'			<0.0001
Yes	1838	66.8	
No	1689	29.0	
Agree 'if I'm feeling better, I sometimes save the rest of my antibiotic for the next time I get sick'			<0.0001
Yes	1450	69.9	
No	2218	33.9	

[a] χ^2 test reflecting differences between possession and non-possession of leftovers.

[b] 'Pack' country indicates a country where antibiotics are dispensed in fixed packs rather than exact numbers of doses.

[c] The terms 'poorest', 'moderate' and 'best' refer to the tertiles of the utility scores.

antimicrobial drug resistance [21]. In eastern European countries, the major source of self-medication with antimicrobials was found to be via the pharmacy without prescription (68%), followed by leftover medications (26%). By contrast, the use of leftover medications was the most prevalent source in southern (51%), northern (44%) and western (44%) European countries [17].

There is still an unanswered question as to what to do with antibiotic leftovers. In some countries, they are collected by charity organisations and re-used. In others, patients are encouraged to take their unused medications to their pharma-

cist for disposal. However, these practices are limited due to both organisational and legal constraints. In everyday practice, the best solution for patients with leftover antibiotics is to throw them away. Unfortunately, this option also has its disadvantages. Recently, the presence of antibiotics and antibiotic-resistant bacteria in wastewater oxidation ponds in the USA was attributed to the flushing of leftover medication down the toilet [22,23]. Therefore, avoiding leftover antibiotics appears to be the best solution to the problem. This may be achieved by addressing non-compliance, but a more practical solution might be to target dispensing systems.

Table 4
Predictors of having leftover antibiotics and saving or giving away leftover antibiotics

Variable	Having leftover antibiotics (N = 3448)[a]		Saving or giving away leftover antibiotics (N = 3159)[b]	
	OR	95% CI	OR	95% CI
Dispensing practice				
'Non-pack' (Ref.)	1.00	–	1.00	–
'Pack'[c]	4.42	3.71–5.26	5.15	4.18–6.35
Age	0.98	0.98–0.99		
Female	0.85	0.72–1.01		
Marital status				
Single (Ref.)			1.00	–
Married			0.64	0.52–0.79
Divorced			0.43	0.28–0.68
Widowed			0.38	0.23–0.63
Antibiotic form				
Liquid (Ref.)			1.00	–
Pill			1.66	1.18–2.32
Daily doses				
Once daily (Ref.)			1.00	–
Twice daily			1.17	0.91–1.15
Three times per day			1.45	1.11–1.90
Four times per day			1.16	0.66–2.06
Five times per day			0.50	0.12–2.06
Health status (EQ-5D)[d]				
Poorest (Ref.)	1.00	–	1.00	–
Moderate	1.13	0.93–1.38	1.23	0.98–1.54
Best	1.42	1.17–1.71	1.38	1.11–1.72
Details of information				
Doctor told condition	0.72	0.58–0.90	0.73	0.57–0.93
Doctor explained in person	0.74	0.60–0.92	0.91	0.71–1.19
Doctor gave written instruction	0.78	0.65–0.94	0.73	0.59–0.90
Pharmacist explained in person	0.86	0.73–1.01	0.79	0.65–0.96
'Leftover antibiotics can be saved and used again'[e]				
Disagree (Ref.)	1.00	–	1.00	–
Moderate	1.58	1.27–1.97	3.33	2.57–4.32
Agree	2.14	1.78–2.65	5.31	4.17–6.78
'If I'm feeling better, I sometimes save the rest of my antibiotic for the next time I get sick'[e]				
Disagree (Ref.)	1.00	–	1.00	–
Moderate	1.81	1.45–2.27	2.51	1.97–3.21
Agree	3.00	2.44–3.69	4.51	3.61–5.62

OR, odds ratio; CI, confidence interval; Ref., referent group.

[a] The pseudo R^2 value for this model was 0.22.

[b] The pseudo R^2 value for this model was 0.33.

[c] 'Pack' country indicates a country where antibiotics are dispensed in fixed packs rather than exact numbers of doses.

[d] The terms 'poorest', 'moderate' and 'best' refer to the tertiles of the utility scores.

[e] Responses rated on a Likert scale of 1–7: disagree (1, 2), moderate response (3, 4, 5), agree (6, 7).

The present study indicates that dispensing exact numbers of tablets might be an effective way to reduce the possession and re-use of antibiotic leftovers. However, this would need to be confirmed in prospective randomised trials. Finally, a single-dose antibiotic therapy, which became available recently for some indications, appears to overcome the problem of compliance by the simplest possible outpatient regimen [24].

The current study also revealed the important role of patient beliefs about saving and using leftover antibiotics. One-half of all respondents believed leftover antibiotics could be saved and used again. Similarly, it has been observed that consumers in the USA who obtain antibiotics over the counter believe that they should be available in this way [25,26], and respondents from countries where antibiotics are readily available over the counter were more likely to obtain them without a prescription [25,26]. Therefore, relevant appropriate-use campaigns should not only promote compliance, but should also advise why and how to avoid leftover antibiotics and what to do if they occur. Interestingly, respondents' incorrect beliefs appeared to be much more prevalent in 'pack' countries, where extra care should be taken to change them.

The risk of possession and re-use of leftovers was increased by respondents not being told the condition for which their antibiotic was prescribed and by the lack of information on how to take their antibiotic. Therefore, a simple approach of communicating this information to patients optimally both by doctors and pharmacists might be especially effective.

Finally, the limitations of the current study need to be taken into account. As with all self-reported data, results in this survey have the potential for recall bias. Nevertheless, as with most surveys where interviewees may be trying to please the researcher, it can be expected that respondents would under-report rather than over-report both possession of leftover antibiotics and their use. Moreover, as this was a cross-sectional survey, any associations between the factors and the findings may not be automatically interpreted as causalities. Participants were not asked directly about standby antibiotics, a practice that is commonplace in some countries. Different data collection techniques were used in different countries owing to the local telephone coverage, a factor that might be a source of bias. Finally, the results of this study can be generalised only to those who have taken self-administered antibiotics within the past 12 months, as this was the inclusion criterion in this study.

In conclusion, we have found that antibiotic leftovers were present in approximately one-half of the populations studied and that these were saved or given to other people in three-quarters of those who had saved them. The main predictors of these deviant behaviours were pack-based antibiotic dispensing systems and patients' beliefs. Therefore, to lower the risk associated with inappropriate re-use of antibiotic leftovers, dispensing of antibiotics in exact numbers of doses and the development of relevant information campaigns addressing patients' incorrect beliefs about leftover antibiotics are recommended.

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