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E. COLI, K. PNEUMONIAE AND *K. OXYTOCA* COMMUNITY-ACQUIRED INFECTIONS

Susceptibility to Cephalosporins and Other Antimicrobials in Lebanon

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ABSTRACT • OBJECTIVES : Cephalosporin resistance in *Enterobacteriaceae* has become an international concern. This article studies the distribution and trends of resistance of *E. coli* and *Klebsiella* species isolated from clinical specimens representing community-acquired infections.

METHODS : *E. coli*, *K. pneumoniae* and *K. oxytoca* specimen strains were collected from patients presenting to three acute care hospitals in Lebanon. The study period extended from January 2010 to January 2011 and included patients presenting with community-acquired infections only. Automated microbiological system (VITEK 2) was used for identification and antimicrobial susceptibilities.

RESULTS : Data from consecutive non-duplicate 589 *E. coli*, 54 *K. pneumoniae* and 40 *K. oxytoca* strains were collected of which 69.5%, 74.0% and 67.5% were susceptible to 3rd generation cephalosporins (3GC), respectively. Out of the 3GC-resistant *E. coli* strains, around 90% were susceptible to nitrofurantoin, 46% were susceptible to trimethoprim/sulfamethoxazole (TMP/SMX) and 53% to ciprofloxacin. The patterns of antimicrobial susceptibility in the two *Klebsiella* species did not parallel those in the *E. coli* strains. Yet, the number of *Klebsiella* strains was much lower than that of *E. coli*. Of note is that the 3GC-resistant strains of both *Klebsiella* species were less susceptible to nitrofurantoin compared to the overall groups reaching a maximum of 30%. However, susceptibility to TMP/SMX was much higher reaching 79% and that of ciprofloxacin reaching 86%.

CONCLUSION: Clinical specimens of *E. coli*, *Klebsiella pneumoniae* and *Klebsiella oxytoca,* causing community-acquired infections in Lebanon showed that these organisms are significantly resistant to many antibiotics. These patterns of resistance were mainly to internationally recommended drugs for empiric treatment of community-acquired infections like community-acquired urinary tract infections (UTIs) and intra-abdominal infections. Therefore, continuous antimicrobial susceptibility surveillance is advisable to track emerging resistance in *Enterobacteriaceae* and national guidelines would be tailored accordingly.

Keywords : *E. coli, Klebsiella*, 3rd generation cephalosporins, extended-spectrum-ß-lactamases, breakpoints, susceptibility, community-acquired infections, Lebanon

Moghnieh RA, Musharafieh UM, Husni RN, Abboud E, Haidar M, Abboud E, Abou Shakra D. Infections communautaires par *E. coli, K. pneumoniae* and *K. oxytoca* : Résistance aux céphalosporines et autres antimicrobiens au Liban. J Med Liban 2014 ; 62 (2) : 107-112.

RÉSUMÉ • OBJECTIFS : La résistance des enterobacteriaceae aux céphalosporines constitue une préoccupation internationale. Cet article étudie la répartition et les tendances de la résistance des espèces *E. coli* et *Klebsiella* isolées à partir d'échantillons cliniques représentatifs d'infections communautaires.

MÉTHODES : Des souches d'*E. coli*, *K. pneumoniae* et *K. oxytoca* ont été recueillies de janvier 2010 à janvier 2011 auprès des patients de trois hôpitaux de soins de courte durée au Liban. Cette étude a inclus des patients présentant uniquement des infections acquises dans la communauté. Le système automatisé de détection microbiologique (VITEK 2) a été utilisé pour l'identification et la sensibilité aux antimicrobiens.

RÉSULTATS : Les données relatives aux souches de 589 *E. coli*, 54 *K. pneumoniae* et 40 *K. oxytoca* ont été collectées dont 69,5%, 74,0% et 67,5% respectivement étaient sensibles aux céphalosporines de 3e génération (C3G). Parmi les souches d'*E. coli* résistantes aux C3G, environ 90% étaient sensibles à la nitrofurantoïne, 46% à la triméthoprime/sulfaméthoxazole (TMP/SMX) et 53% à la ciprofloxacine. Les profils de sensibilité aux antimicrobiens chez les deux espèces de *Klebsiella* n'étaient pas similaires à ceux des souches d'*E. coli*. Pourtant, le nombre de souches de *Klebsiella* était sensiblement inférieur à celui d'*E. coli*. Il est à noter que les souches résistantes aux C3G des deux espèces *Klebsiella* étaient moins sensibles à la nitrofurantoïne que l'ensemble des groupes atteignant un maximum de 30%. Cependant, leur sensibilité à la TMP/SMX et à la ciprofloxacine était beaucoup plus élevée atteignant respectivement 79% et 86%.

CONCLUSION : Les échantillons cliniques d'*E. coli*, *K. pneumoniae* et *K. oxytoca* provoquant des infections communautaires au Liban, ont montré que ces organismes sont hautement résistants à de nombreux antibiotiques recommandés au niveau international pour le traitement empirique d'infections acquises telles que celles des voies urinaires et les infections intra-abdominales. Par conséquent, la surveillance continue de la sensibilité aux antibiotiques est recommandée pour suivre les résistances émergentes aux enterobacteriaceae et adapter en conséquence les directives nationales.

Mots-clés : *E. coli, Klebsiella,* céphalosporines de 3e génération, ß-lactamases à spectre étendu, seuil, infections acquises communautaires, Liban

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INTRODUCTION

Infections with cephalosporin resistant *Enterobacteriaceae* are increasingly becoming serious impediments to successful empiric treatment of infections like urinary tract infections and intra-abdominal infections thus leading to increasing mortality [1]. Despite the fact that most studies on ß-lactam resistance have looked at extended-spectrum-ß-lactamases (ESBL)-producing *Enterobacteriaceae*, the 2010 European Committee on Antimicrobial Susceptibility Testing (EUCAST) emphasized that ESBL production reporting is not always clinically important.

It is enough to report susceptibility to 3rd and 4th generation cephalosporins (3GCs and 4GCs), according to updated breakpoints i.e. specifying only if the isolated organism is susceptible, intermediate or resistant. The recommended breakpoints for cefepime and ceftazidime are S ≤ 1 mg/L and R > 8 mg/L and thus the expert rules require no testing for ESBL in clinical specimens except for epidemiologic or infection control purposes [2].

In Lebanon, most studies have looked at ESBL-producing bacteria more than cephalosporin resistant bacteria. The current situation of ESBL in Lebanon can be summed up in an increase in the percentage of ESBL-producing strains in clinical specimens of *Escherichia coli* (*E. coli*) and *Klebsiella* species. In a study published by Araj *et al*. in 2008 [3], 250 clinically significant isolates of ESBL-producing *E. coli* (n = 150) and *K. pneumoniae* (n = 100) were recovered from different specimens submitted to the clinical microbiology laboratory of the American University of Beirut Medical Center. Results showed that 51% of the ESBL-producing *E. coli* (n = 150) were resistant to cefepime and 54% were resistant to ceftazidime. With respect to ESBL-producing *K. pneumoniae*, 53% of the isolates were resistant to cefepime and 82% were resistant to ceftazidime [3]. A study from Saint George University Hospital in Beirut showed that 2% of 4,299 *E. coli* isolates and 20% of 1,248 *K. pneumoniae* isolates collected between 1997 and 2001, produced ESBLs [4]. Recently, a study was conducted to look at ESBL-producing strains of *E. coli*, and *K. pneumoniae* isolated from both hospitalized and outpatients in a university hospital center in Beirut. This study, that extended over five years period from 2005 to 2009, revealed a significant increase in the percentage of ESBL-producing *E. coli* from 17.8% in 2005 to 30.4% in 2009. Similarly, the percentages of ESBL-producing *K. pneumoniae* increased significantly from 23.7% in 2005 to 31.8% in 2009 [5].

Beta-lactam antibiotics including 3GCs and 4GCs are frequently used to treat infections both in community and hospital settings in Lebanon. The European Antimicrobial Resistance Surveillance System described resistance of *E. coli* to 3GCs as the most dynamic expansion of multidrug-resistant pathogens in the entire region [6]. Although data in less than half of all European countries (14 of 33 countries) reported levels of resistance of *E. coli* and *Klebsiella* species to 3GC to be under 5% in 2008, the proportion of these resistant organisms to 3GC has increased in 19 European countries since 2004 [7-9].

With the background recommendations from the EUCAST, we tackled *E. coli*, *K. pneumoniae* and *K. oxytoca* isolated from patients coming from the community. The aim of this study was to look at their distribution in clinical specimens, trends of susceptibility and co-susceptibility to ß-lactam, specifically, 3GC and 4GC, and non-ß-lactam antibiotics in Lebanon. The current data obtained describes the antibiogram of the above stated organisms regarding ß-lactam and non-ß-lactam antibiotics that are recommended in international guidelines where these organisms are implicated in causing infections. Most similar studies in Lebanon looked at data either obtained from hospitalized patients or lumped up data including isolates from both the community and hospitals.

MATERIALS AND METHODS

Data on all cases of *E. coli* and *Klebsiella* species infection, including those with *K. pneumoniae* and *K. oxytoca,* were collected from laboratory VITEK 2 machine results in three acute care hospitals in Lebanon: Ain Wazein Hospital in the Shouf district, Mount Lebanon Hospital and Bahman Hospital in suburbs of Beirut.

Specimens from patients presenting to the clinic or the emergency department were only included and were labeled as outside case or emergency department case respectively. All specimens coming from the hospital wards were excluded.

The automated microbiologic systems (VITEK 2 BioMerieu, Inc., Durham, NC) for identification and antimicrobial minimum inhibitory concentration (MIC) determination was used for testing the clinical specimens in all the three hospitals.

Quality control strain *Escherichia coli* ATCC 11775 was used periodically as a quality control strain to ensure proper performance of the VITEK 2 machine. Data on the *Klebsiella* and *E. coli* strains were collected from January 1, 2010, to January 1, 2011. Duplicate samples were excluded. Specimens collected included isolates from the urine, blood, sputum or deep tracheal aspirate, and wounds. Of these community-acquired strains, those that were resistant to 3GC independent of ESBL production were labeled as 3GC-resistant. In addition, strains that were ESBL-producers were selected and identified but this group was not the focus of our study.

The European Committee on Antimicrobial Susceptibility Testing (EUCAST) 2011 Breakpoints for different antimicrobials against *E. coli, K. pneumoniae* and *K. oxytoca* were used for interpretation of results as sensitive, intermediate or resistant.

Accordingly, these organisms are considered susceptible to cefepime, ceftazidime and ceftriaxone when the MIC 90 is ≤ 1 mg/L and resistant when MIC 90 is > 4 mg/L (cefepime and ceftazidime) and > 2 mg/L (ceftriaxone). Susceptibility to trimethoprim/sulfamethoxazole (TMP/SMX) and tobramycin is considered when

MIC 90 is ≤ 2 mg/L. Susceptibility to nitrofurantoin, and ciprofloxacin are defined as MIC 90 is ≤ 64 mg/L and ≤ 0.5 mg/L respectively [10]. Susceptibility to imipenem was judged only by evaluating its MIC, and strains were considered susceptible if MIC was ≤ 2 mg /L.

The antibiotic cards used in the three hospitals did not include MIC to ertapenem or meropenem.

RESULTS

The total number of consecutive non-duplicate strains of *E. coli, K. pneumoniae* and *K. oxytoca* was 682. *E. coli* represented 86.2% of the total sample i.e. 589 strains; whereas *Klebsiella* species represented 13.8% of the total sample (53 *K. pneumoniae* and 40 *K. oxytoca* strains), (Table I). Patterns of susceptibilities of the above stated organisms are shown in Table II.

Of the *E. coli* strains, 180 (30.5%) were 3GC-resistant. Most of totally collected *E. coli* strains (96.1%) and 3GC-resistant *E. coli* strains, in particular, were obtained from urine specimens. Of the cephalosporin-resistant strains, two were obtained from skin specimens, and three from blood. All cephalosporin-resistant strains were susceptible to imipenem, and most of them (80%) were susceptible to piperacillin/tazobactam. Only one *E. coli* strain was resistant to imipenem; interestingly, it showed susceptibility to 3GC and 4GC.

Since the majority of the strains were of urinary origin (94.4%) (Table I), nitrofurantoin susceptibility was checked on most of them. The highest susceptibility rates were for nitrofurantoin in the total *E. coli* strains (90.3%) and the 3GC-resistant strains (91.6%). Amikacin also exhibited good activity against *E. coli* where 86.4% of strains were susceptible to it, as well as 52.8% of the 3GC-resistant *E. coli* strains.

In comparison, only 58.4% of all *E. coli* strains and 52.8% of 3GC-resistant strains showed susceptibility to ciprofloxacin. As to TMP/SMX, 47.3% of all total *E. coli* strains and 46.1% of 3GC-resistant strains were susceptible to it.

TABLE I
DISTRIBUTION of *E. COLI* and *KLEBSIELLA* SPECIES INFECTIONS in CLINICAL ISOLATES

Specimen Source	*Species*			Total
	E. coli	*K. pneumoniae*	*K. oxytoca*	
Urine	566	46	33	**645**
DTA*/Sputum	1	2	–	**3**
Wound	14	3	6	**23**
Blood	7	1	–	**8**
Miscellaneous	1	1	1	**3**
Total	**589**	**53**	**40**	**682**

DTA: deep tracheal aspirate

As for *Klebsiella* species, 74.1% *K. pneumoniae* strains (n = 40) and 67.5% *K. oxytoca* strains (n = 27) were susceptible to 3GC. The patterns of susceptibility for the cephalosporin resistant strains are shown in Table II. The patterns of antimicrobial susceptibility in these two species did not parallel those in the *E. coli* strains. Of note, is that the 3GC-resistant strains of both *Klebsiella* species were less susceptible to nitrofurantoin compared to the overall groups. The MIC of each strain was taken from the automated system results data. Authors independently based the interpretation of susceptibility or resistance on EUCAST Breakpoints as discussed before [10].

DISCUSSION

The rates and sites of community-acquired *E. coli, K. pneumoniae* and *K. oxytoca* infections at three Lebanese hospitals were studied. The specimens collected were mainly from the urine, skin and soft tissue and bloodstream infections with predominance of urinary specimens. This was not surprising, as UTIs are among the most prevalent infections in the general population [11], and specimens for urine culture are easier to collect than

TABLE II
DISTRIBUTION of *ESCHERICHIA COLI, KLEBSIELLA, PNEUMONIAE* and *KLEBSIELLA OXYTOCA* STRAINS ACCORDING to SUSCEPTIBILITY to the STUDY ANTIBIOTICS and CEPHALOSPORINS

Agent	No. (%)* of *E. coli* strains		No. (%)* of *K. pneumoniae* strains		No. (%)* of *K. oxytoca* strains	
	Total (n = 589)	3GC▼ Resistant 30.5% (n = 180)	Total (n = 53)	3GC Resistant 25.9% (n = 14)	Total (n = 40)	3GC Resistant 32.5% (n = 13)
Cefepime	429 (72.8)	120 (66.6)	39 (72.2)	12 (85.7)	29 (72.5)	10 (76.9)
Nitrofurantoin	532 (~90)	165 (91.6)	32 (59.3)	4 (28.6)	31 (77.5)	2 (15.4)
Imipenem	588 (~99.8)	180 (100)	52 (96.4)	13 (93.0)	26 (90.0)	11 (84.6)
TMP/SMX©	279 (47.3)	83 (46.1)	33 (61.1)	11 (78.6)	22 (55.0)	8 (61.5)
Tobramycin	379 (~64)	83 (46.1)	37 (68.5)	13 (93.0)	28 (70.0)	11 (84.6)
Ciprofloxacin	344 (58.4)	95 (52.8)	36 (67)	12 (85.7)	26 (65.0)	9 (69.2)
Amikacin	509 (86.4)	95 (52.8)	43 (79.7)	12 (85.7)	40 (100.0)	13 (100.0)
Piperacillin/Tazobactam	459 (~80)	130 (72.2)	34 (63)	11 (78.6)	23 (57.5)	–

* Percentages were rounded to the nearest ten. ▼**3GC**: third generation cephalosporins ♦ **TMP/SMX**: Trimethoprim/Sulfamethoxazole

sputum and blood cultures. Data was collected retrospectively from the VITEK 2 machine where no clinical chart reviews was done. This was a drawback in our study since we were not able to identify whether the blood isolates were secondary to primary infection or straight intravascular infection. In addition, the type of wound culture as well as that of skin infection were not classified for the reason stated above.

Among the community-acquired strains of *E. coli, K. pneumoniae* and *K. oxytoca*, the 3GC susceptibility was 69.5%, 74.0% and 67.5% respectively. Previous studies from Lebanon showed equally high rates of ESBL production in *E. coli* [4,12]. Our study differs from other local reports in three ways. First, the data in the latter studies was gathered from nosocomial and community-acquired infections all summed together. Second, most of the studies conducted so far are based on ESBL detection whereas our data is based on the susceptibility to 3GC as per antibiogram, regardless of the presence or absence of ESBL enzymes. This might underestimate the presence of ESBL enzymes since some strains can still be susceptible to 3GC despite the existence of a low-level production of ESBL enzymes [13-14]. Last, the current results are based on EUCAST breakpoints while most of the previous reports were based on CLSI (Clinical and Laboratory Standards Institute) breakpoints. In spite of these differences, recent results from a 10-year compilation of data (2001-2011) in a tertiary care center in Lebanon, showed similar 3GC-resistance of *E. coli*, between 67 and 76% [15].

These results raise a concern, as the resistance to 3GC in *E. coli* is not related to the origin of the specimen whether community- or hospital-acquired.

The high rates (≥ 20%) of 3GC and fluoroquinolone resistance among *E. coli* and *Klebsiella* species in this study affect initial management decisions in treating these community-acquired infections. Extended-spectrum ß-lactams and fluoroquinolones are among the first therapeutic options recommended in international guidelines for treatment of infections caused by these organisms [16].

The current data showed that 90% of total *E. coli* isolates and 92% of 3GC-resistant *E. coli* strains were susceptible to nitrofurantoin, rates that were higher than those in *K. pneumoniae* (59%) and *K. oxytoca* (77%) strains. This is in agreement with reports from Singapore showing a high susceptibility of *E. coli* to nitrofurantoin (94.7%) but lower susceptibility of *Klebsiella* species (37.9%) [17]. Similar susceptibility patterns of *E. coli* to nitrofurantoin and fosfomycin (95%) have also been also reported in Lebanon [18].

Despite the fact that nitrofurantoin may be an effective therapeutic option for uncomplicated UTIs, it is less advocated when *Klebsiella* infection is suspected and when susceptibility is not available. This is due to *Klebsiella* species being less sensitive to nitrofurantoin when compared to *E. coli* (58% and 98%) [15]. Also, for patients with complicated UTIs, nitrofurantoin cannot be recommended because of its lower concentration in tissues and blood compared to urine [19].

Regarding TMP/SMX, the overall rate of susceptibility of *E. coli* to TMP/SMX was only 47.3%, with the 3GC-resistant *E. coli* strains reaching only 46.1% (Table I). These rates are comparable to the susceptbility rate in similar settings (40.8%) as reported by Guajardo-Lara *et al*. and Bean *et al*. [20-22]. Nine years after withdrawal of the sulfonamide antibiotics from human medicine in that country, the rate of resistance of *Enterobacteriaceae* to sulfonamides in United Kingdom remained steady at 45%.

When active against UTI causing organisms, TMP/SMX can be used to treat complicated and uncomplicated UTIs. The Infectious Diseases Society of America (IDSA) and EUCAST guidelines recommend TMP/SMX as (Level 1A*) option in empiric therapy in these two conditions. According to the current data, the low rate of susceptibility of organisms causing community infections to TMP/SMX reached 47% and is higher than some neighboring countries (37%) [23].

Thus, it is reasonable to advise using TMP/SMX as therapy only after susceptibility results are obtained [23-24].

Since the introduction of fluoroquinolones in Lebanon 30 years ago, their use as first-line options in the treatment of suspected Gram-negative nosocomial and community-acquired infections has been extensive. This was due to their excellent bioavailability in the first place, and augmented by the absence of governmental and institutional policies restricting their use with respect to their indications, duration, or dosing. Over the last 30 years, *E. coli* circulating in the Lebanese community has become resistant to fluoroquinolones and cephalosporins at large. Resistance to fluoroquinolones is closely linked to ESBL production since genes coding for these resistances can be carried and transmitted on the same plasmids [25]. The presence of these genes in the same plasmids or transposons contributes to the collateral damage caused by fluoroquinolones. Using fluoroquinolones predisposes patients to subsequent infection with an organism resistant to 3GCs, 4GCs or even ESBL-producing [26].

When compared to one study showing fluoroquinolone resistance in ESBL-producing *Enterobacteriaceae* [27], the current data revealed almost comparable resistance in 3GC-sensitive and resistant strains of *E. coli* (58.4% and 52.8% respectively). This might be attributed, in many strains, to presence of ESBL in small amounts that are insufficient to reveal the 3GC resistance. The high fluroquinolone resistance justifies avoiding their use as empiric therapy for life threatening community-acquired infections, such as intra-abdominal infections [28] and complicated UTI with sepsis [29], and conditions like febrile neutropenia [30]. The authors of this article advocate avoiding empirical treatment with fluoroquinolones for infections that are life threatening where the choice of first-line therapy is an independent predictor of mortality.

Aminoglycosides are therapeutic options for treating cephalosporin-resistant *Enterobacteriaceae*. We observed that amikacin was active against *E. coli*, *K. oxytoca* and *K. pneumonia*, with susceptibility rates of 86.4%, 100%, and 79.7%, respectively. These rates were higher than those in other previously reported studies. In a study done in India, community-acquired UTI sensitivity rates were as follows: amikacin (76.0%), ciprofloxacin (35.8%), TMP/SMX (30.0%), amoxicillin (17.7%) amoxicillin/clavulanate (41.6%), nitrofurantoin (65.7%), piperacillin/tazobactam (90.2%), and meropenem (100.0%) [31]. The combination of amikacin and ß-lactam is a reasonable option for combating serious infections [32].

When comparing the resistance of *E. coli* to 3GCs and 4GCs, the rates were 30.5% and 72.8% respectively. This difference could be due to differential sensitivity of 3GCs and 4GCs to different ESBL enzymes [33]. In our study, carbapenems, as represented by susceptibility to imipenem, were almost 100% active against our strains except only one single strain of each *E. coli*, *K. pneumoniae* and *K. oxytoca* strains being resistant to imipenem.

Although the majority of the 3GC-resistant *E. coli* and *Klebsiella* infections in this study were from the community, the specimens collected could have included patients who were recently hospitalized. This would result in misclassification of a number of hospital-acquired cephalosporin resistant-infections as community-onset cases. Despite this limitation, the study sheds the light on a serious problem arising in the community.

In this study, carbapenem susceptibility was reported only by testing imipenem MIC. Although the standard method for detecting carbapenem resistance by *K. pneumoniae* carbapenemase (KPC), carbapenemase production is based on ertapenem MIC (≥ 4 mg/L) [34]. In laboratories using VITEK 2 machine for antibiograms, the algorithm of imipenem/meropenem can be used when carbapenem resistance by dual mechanism (CTXM and Porin Loss) is suspected [35]. Resistance is defined as organisms that have imipenem MIC ≥ 2 mg/L and meropenem MIC ≥ 1 mg/L as proposed by Pasteran *et al*. [35]. Using imipenem susceptibility alone for detection of carbapenem resistance is a drawback in our study and may have contributed to underestimating occurrence of carbapenem resistance. Therefore, we recommend the use of either ertapenem MIC or imipenem/meropenem algorithm in order to detect carbapenem resistance in *Enterobacteriaceae,* especially for infection control purposes.

Carbapenems have been reported to remain the drugs of choice for infections caused by organisms secreting ESBL especially AmpC-beta-lactamase-producing *Enterobacteriaceae* [31]. On the other hand, the use of carbapenems as empirical therapy should be limited to life-threatening conditions like sepsis, and high-risk patients with febrile neutropenia in order to decrease antibiotic selection for carbapenem resistance knowing that carbapenemase-producing *Enterobacteriaceae* strains started to emerge in Lebanon [36-37].

CONCLUSION

This study looked at the resistance patterns to 3GC and other classes of antibiotics in patients with community-acquired infections. The prevalence of resistance to these antibiotics of choice is high and resistance determinants of organisms formerly seen only at hospitals are now prevalent in the community. We recommend continuous surveillance of antibiotic resistance in bacteria in community, as well as in hospital-acquired infections. Such knowledge would help scientific societies set national guidelines for optimal treatment of these infections. Only then, planning antibiotic policies that aim at decreasing antibiotic resistance and limiting its spread would be realistic.

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