**Mycoplasma genitalium** and Antimicrobial Resistance Among a Cohort of West African Men Who Have Sex With Men Using Preexposure Prophylaxis (Coh MSM-PrEP ANRS 12369-Expertise France Study)

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### Background.
Antimicrobial resistance to macrolides and fluoroquinolones in Mycoplasma genitalium (MG) among men who have sex with men (MSM) is worryingly high in high-resource countries. Data in Africa are lacking. We aimed to assess the burden of MG including the presence of resistance-associated mutations (RAMs) in MG among MSM using human immunodeficiency virus preexposure prophylaxis in Burkina Faso, Côte d’Ivoire, Mali, and Togo.

### Methods.
MSM were included in a prospective cohort study (2017–2021). Molecular detection of MG in urine, anorectal, and pharyngeal samples was performed at baseline and after 6 and 12 months. Detection of RAMs to macrolides and fluoroquinolones was performed by sequencing the 23S ribosomal RNA, parC, and gyrA genes. A sample was found to be possibly resistant to fluoroquinolones if alterations were found in ParC position 83/87.

### Results.
Of 598 participants, 173 (28.9%) were positive at least once for MG and global point-prevalence was 19.4%. Interestingly, 238 of 250 (95.2%) infections were asymptomatic and 72 of 138 MG infections with follow-up data (52.2%) cleared during the study. Only 1 macrolide RAM was found (0.6%). Prevalence of fluoroquinolones RAMs was 11.3% overall, ranging from 2.4% in Burkina Faso to 17.5% in Mali.

### Conclusions.
Although MG was highly prevalent in these MSM, macrolide resistance was almost nonexistent. Nevertheless, >10% of the samples were possibly resistant to fluoroquinolones. Heterogeneity in the prevalence of fluoroquinolone RAMs between countries may be explained by different antimicrobial consumption in humans and animals.

### Keywords.
Africa; antimicrobial resistance; men who have sex with men; *Mycoplasma genitalium*; sexually transmitted infections.

Sexually transmitted *Mycoplasma genitalium* (MG) is a recognized cause of nongonococcal nonchlamydial urethritis and cervicitis in men and women, respectively [1]. Overall, the prevalence of MG is estimated to be 1.3% in high-income countries to 3.9% in low- and middle-income countries [2] but is higher in key populations behaviorally vulnerable to human immunodeficiency virus (HIV) or other sexually transmitted infections (STIs), such as men who have sex with men (MSM) (3.2%–6.0%) [2, 3]. Recent studies among HIV-negative MSM initiating HIV preexposure prophylaxis (PrEP) found prevalences of MG ranging between 10.5% and 19.4% [4–8]. In fact, MG was the most frequently detected STI in many PrEP cohorts [5, 7, 8].

A major limitation is that all of these studies were performed in high-resource settings. Data on the occurrence of MG among MSM, and in particular, among MSM using PrEP in African countries, are scarce. One study among MSM in Togo showed that MG was the most frequently detected anorectal STI (15%) [9]. Another study among MSM in Nigeria reported a prevalence of anorectal MG as high as 36% and 12% of urogenital MG, indicating that MG might also be thriving in African countries [10].
A major concern of MG is the rapid rise in the number of resistance-associated mutations (RAMs) that confer resistance to the first-line (azithromycin—a macrolide) and second-line (moxifloxacin—a fluoroquinolone) treatments [1]. A systematic review describing the global antimicrobial resistance (AMR) of MG to macrolides and fluoroquinolones showed that prevalence of macrolide resistance increased from 10% before 2010 to 51% in 2016–2017 [11]. However, differences between world regions were noted. For example, the increase was the highest in the Americas (from 0 to 67%) and the Western Pacific Region (from 9% to 68%). Moreover, macrolide resistance is estimated to be higher among MSM compared to heterosexual men [11]. Emerging data now show that macrolide resistance among MSM using PrEP in Europe is worryingly high, probably fueled by previous macrolide consumption for STIs [4, 6, 12]. Indeed, a study in Belgium found resistance to macrolides up to 95% in MSM with recurrent STIs, and RAMs to both macrolides and fluoroquinolones were found in 3 cases (33%) [13].

Although MG resistance is frequently investigated in high-resource settings, data from the African region are scarce and mostly focus on women [14]. Studies from South Africa showed that the presence of RAMs to macrolides is rare to nonexistent, but RAMs to fluoroquinolones were more frequently detected [15–18]. A limited study in 2018 among 9 MG female samples of Mali detected a RAM to fluoroquinolones in ParC (S83I) in 5 of 9 cases [19]. In 1 study analyzing 266 samples of patients with HIV from 2007 to 2014, mutations in the gyrA and parC genes were detected in 3.4% and 20.3% of the cases, but only 1 mutation led to an alteration in ParC at position 87 (D87Y) [15].

To our knowledge, AMR data of MG among MSM living in the African region are unavailable. As such, there is a clear necessity to characterize the prevalence of MG among West African MSM, including the presence and emergence of antimicrobial RAMs to fluoroquinolones and macrolides in MG.

The objective of this study was to assess the prevalence and symptomatology of MG infections and the presence of RAMs of MG among MSM using PrEP in 4 West African countries (Togo, Burkina Faso, Mali, and Côte d’Ivoire).

METHODS

Study Setting

The CohMSM-PrEP prospective cohort study took place from November 2017 to June 2021 in 4 West African cities and community-based clinics: Lomé, Togo (Espoir Vie Togo); Ouagadougou, Burkina Faso (Association African Solidarité); Abidjan, Côte d’Ivoire (Espace Confiance); and Bamako, Mali (ARCAD-SIDA). Only MSM aged ≥18 years behaviorally vulnerable to HIV who were interested in using PrEP daily or event-driven were included in the study. An important inclusion criterion was having had at least 1 anorectal sexual episode with another man in the last 6 months. They were followed up quarterly and study-specific procedures were previously published [20]. Samples for STI testing were collected at the start of PrEP (baseline) and after 6 and 12 months. These included blood samples, first-void urine, and 2 physician-collected ESwabs (Copan Diagnostics, Brescia, Italy) of the anorectum and oropharynx. Syphilis serology and Chlamydia trachomatis/Neisseria gonorrhoeae (CT/NG) molecular detection (CT/NG Xpert assay, Cepheid) were performed locally. Samples to test for MG were immediately stored at −20°C until shipment to the Institute of Tropical Medicine, Antwerp, Belgium, serving as the central laboratory of this study where they were tested at the end of the study. Therefore, MG infections were not specifically treated and in case of symptoms, the syndromic approach was used.

Patient Consent Statement

The study was approved by ethics committees in Burkina Faso (Comité d’éthique pour la recherche en santé), Côte d’Ivoire (Comité national d’éthique de la recherche), Mali (Comité d’éthique de la Faculté de Médecine, de Pharmacie et d’Odonto-Stomatologie), Togo (Comité de Bioéthique pour la Recherche en santé), and Belgium (Institutional Review Board of the Institute of Tropical Medicine and the Ethics Committee of the University of Antwerp) and performed according to the ethical standards of the responsible committees and the Helsinki Declaration of the World Medical Association. All participants provided written informed consent.

Laboratory Procedures

Mycoplasma genitalium Detection

Detection of MG was performed in batches at the central laboratory using the S-Dia-MGTV multiplex molecular assay (Diagenode Diagnostics, Seraing, Belgium) on the m2000rt platform (Abbott Molecular Des Plaines, Illinois). Positive samples were further sequenced using Sanger sequencing (ABI 36730xl, Applied Biosystems) as described previously [21, 22]. Sequences were checked for the presence of RAMs in the 23S ribosomal RNA (rRNA), parC, and gyrA genes using BioEdit Sequence Alignment Editor (Nucleics.com). MG was defined potentially resistant to macrolides if RAMs in the 23S rRNA region V were detected. MG possessing alterations in ParC at position 83 and 87 was defined to be possibly resistant to fluoroquinolones.

Statistical Analysis

A descriptive analysis was performed to assess the MG prevalence per visit in each country. We also scrutinized the occurrence of MG per anatomical site of infection and per symptomatology. In case an individual was positive for MG at >1 anatomical site, the infection was only accounted as 1. STI symptoms were categorized as having urogenital, anorectal, or oropharyngeal complaints. Statistical associations of
sociodemographic and behavioral characteristics with detection of MG at least once were assessed using logistic regression models. Characteristics associated with outcome with a P value < .2 in univariate analyses were entered in the complete multivariate model. A manual backward selection was used to determine the final multivariate model. To calculate the prevalence of antibiotic resistance, we used samples of the first and of a new MG episode (negative in between visits). All analyses were performed using Stata version 15.0 software (StataCorp, College Station, Texas).

RESULTS

Sociodemographic Characteristics and Prevalence of Mycoplasma genitalium Infection

A total of 598 participants were tested for MG at least once and provided data of 1350 visits. Most of the participants were recruited in Mali (257), followed by Côte d’Ivoire (116), Burkina Faso (115), and Togo (110). Median age was 24.7 years (interquartile range, 21.9–28.0 years). Most of the participants identified themselves as bisexual (57.2%), and 49.5% were attracted to both men and women (Table 1). More than half of the participants provided samples of all 3 visits (312/598 [52.2%]), 21.4% (128/598) provided data of 2 visits, and 26.4% (158/598) were only tested at baseline. Figure 1 shows the point-prevalence data at the different visits for all sites and stratified per site. At baseline, global point-prevalence of MG was 19.4% (116/598). No statistically significant differences between the visits were detected except in Togo, where the prevalence decreased from 24.6% at baseline to 12.5% at month 12 (Supplementary Table 1).

Over the first year of the study, including baseline, 173 participants (28.9%) were positive at least once for MG, the highest percentage being in Burkina Faso (39.1% [45/115]), followed by Togo (30.0% [33/110]) and Mali (29.2% [75/257]), whereas it was the lowest in Côte d’Ivoire (17.2% [20/116]) (P = .004). Thirteen participants were positive for MG at the 3 visits.

Risk Factors Associated With Mycoplasma genitalium Infection

In univariate analyses, MG infection was significantly associated with self-defined sexual orientation but not with age, sexual attraction, having a wife or girlfriend, the number of male partners, or systematic condom use (Table 1). In multivariate analysis, MG infection remained associated with self-defined sexual orientation but was still not associated with age. Therefore, MG infection was only associated with self-defined sexual orientation, being more frequent in participants who self-defined as homosexual/gay compared to participants who self-defined as bisexual (odds ratio, 1.53 [95% confidence interval, 1.05–2.23]; P = .025).

Mycoplasma genitalium Infections

A total of 250 MG infections were detected (Table 2). Most of the infections were found in the anorectum (65.2%), followed by the urethra (40.0%) and 2 infections in the oropharynx (0.8%). Of those, 15 MG infections were found in 2 anatomical sites (all 15 in the anorectum, plus 14 in the urethra and 1 in the pharynx). More than half of the MG infections had a follow-up MG test result, and 52.2% of these (72/138) cleared by the next visit. Of those that cleared, 52 cleared spontaneously (72.2%), and 20 had received any treatment since the previous visit (azithromycin, doxycycline, or quinolones).

Table 1. Baseline Characteristics of Participants and Associations With Mycoplasma genitalium Infection

| Characteristic | All Individuals (N = 598) | At Least Once MG Positive (n = 173) | Remaining MG Negative (n = 425) | Association With MG Infection (Univariate Analysis) |
|----------------|--------------------------|----------------------------------|---------------------------------|-----------------------------------------------------|
| Age, y         | Median (IQR)             | Median (IQR)                     | Ref                             | OR (95% CI)                                          |
| Self-defined sexual orientation |                          |                                  |                                 |                                                     |
| Bisexual       | 24.7 (21.9–28.0)         | 24.4 (21.6–27.5)                 | 24.9 (22.2–28.1)                | 0.98 (.94–1.01)                                      |
| Heterosexual or gay | 214 (35.8)             | 72 (41.6)                        | 142 (33.4)                      | 1.53 (1.05–2.23)                                    |
| Transsexual or transgender | 7 (1.2)              | 2 (1.2)                          | 5 (1.2)                         | 1.21 (.75–3.38)                                     |
| Unknown        | 18 (3.0)                 | 7 (4.0)                          | 11 (2.6)                        | 1.92 (.69–5.04)                                     |
| Sexual attraction |                              |                                  |                                 |                                                     |
| To men         | 268 (44.8)               | 78 (45.1)                        | 190 (44.7)                      | Ref                                                 |
| To men and women | 296 (49.5)            | 84 (48.6)                        | 212 (49.9)                      | 0.97 (.67–1.39)                                     |
| To women       | 22 (3.7)                 | 8 (4.6)                          | 14 (3.3)                        | 1.39 (.54–3.38)                                     |
| No answer      | 12 (2.0)                 | 3 (1.7)                          | 9 (2.1)                         | 0.81 (.18–2.80)                                     |
| Wife or girlfriend | 279 (46.7)         | 82 (47.4)                        | 197 (46.4)                      | 1.04 (.73–1.49)                                     |
| No. of male partners in the last 3 mo | 1.0 (1.0–3.0) | 1.0 (1.0–3.0)                    | 2.0 (1.0–3.0)                   | 0.96 (.87–1.05)                                     |
| Systematic condom use in the last 3 mo | 249 (44.1) | 77 (47.2)                        | 172 (42.8)                      | 1.20 (.83–1.73)                                     |

Abbreviations: CI, confidence interval; IQR, interquartile range; MG, Mycoplasma genitalium; OR, odds ratio; Ref, reference category.

*Data for univariate analysis are for at least 1 male partner versus none.
Almost all MG infections were asymptomatic (238/250 [95.2%]). Of the 12 symptomatic MG infections, 4 were coinfectected with CT and 1 participant had a triple infection with CT, NG, and MG.

### Presence of RAMs in *Mycoplasma genitalium*

Sequencing of the 23S rRNA gene was successful for 221 MG samples, quinolone resistance–determining region (QRDR) of *gyrA* for 201 MG samples, and QRDR of *parC* for 218 samples. Table 3 tabulates the mutations found in the 3 genes for all of the samples. Only 1 MG infection with a RAM to macrolides (*A2072G, MG numbering*) was found in a urine sample at the Burkina Faso site and did not harbor any other mutation in *parC* nor *gyrA* but was coinfectected with anorectal CT and NG.

Mutations in *gyrA* were also rare in our study (4/201 [2.0%], found in the same participant). No *gyrA* mutation coincided with *parC* or 23S rRNA gene mutations. Alterations in ParC were frequently documented (54/218 [24.8%]). P62S was the most common mutation and was regularly present in combination with other ParC mutations located at position 83/87 (Table 3). Alterations in ParC 83/87 were found in 10.6% of the cases (23/218: 4 S83I, 9 D87N, and 10 S83N).

Of the MG infections with follow-up results (n = 125), we noted that all MG infections with *gyrA* mutations (3/3) cleared the infection. For MG infections with ParC alterations, this was 44.4% (12/27) and for wild-type MG infections this was 54.1% (53/98). We could not detect any de novo RAMs as a result of previous antimicrobial treatment (Supplementary Table 2).

### Prevalence of Macrolide and Fluoroquinolone Resistance in *Mycoplasma genitalium*

Of all MG infections, 163 were coded as a new episode of MG. Only 1 was resistant to macrolides (1/163 [0.6%]). One hundred sixty could be further sequenced for *parC* mutation detection. Herein, 3 S83I, 6 D87N, and 9 S83N mutations were found.

As such, the overall prevalence of ParC 83/87 mutations was 11.3% (Figure 2). Most of the fluoroquinolone-resistant ParC 83/87 was found in the Malian site (17.5%); however, removing mutation S83N, the proportion was <5% (4.8%). Togo had a prevalence of 14.7% of fluoroquinolone-resistant ParC 83/87, and all except 1 were associated with clinical resistance (D87N). Burkina Faso was the country where the fewest mutations in ParC were found, and only 1 sample harbored a mutation S83I (1/43 [2.3%]).

### DISCUSSION

In our study in 4 West African countries, almost 30% of MSM using PrEP were positive for MG at least once during their 1-year follow-up. Interestingly, almost all MG infections were asymptomatic (95%). In addition, half of the infections cleared by the next visit and almost 75% of these infections cleared without receipt of treatment. This is in line with a PrEP study performed in Belgium among MSM in which almost half of the MG infections that did not receive treatment cleared spontaneously [23].

Besides the high prevalence of MG, we also report on the presence of RAMs to macrolides and fluoroquinolones in MG among African MSM, which was previously mostly documented in high-resource settings [11, 14]. The results found in our study population were different compared to MSM in high-resource settings. Almost no macrolide resistance was detected (0.6%), but the presence of RAMs to fluoroquinolones (ParC 83/87) was higher than previously reported in African settings (11%). Interestingly, we noted differences in possible fluoroquinolone resistance between the different countries. Although individuals in Burkina Faso had the highest detection rate of MG (39.1%), ParC 83/87 mutations were rare (2.3%). ParC 83/87 mutations were predominantly found in Mali (17.5%), followed by Togo (14.7%).
### Table 2. *Mycoplasma genitalium* Infections Detected During the CohMSM-PrEP Study (Including Baseline)

| Infections | MG Positive at a Visit With MG Test Result | Site of Infection | Dual-Site Infections |
|------------|--------------------------------------------|-------------------|---------------------|
|            | MG Positive at a Visit With MG Test Result | Site of Infection | Dual-Site Infections |
| Total MG infections | 250/1350 (18.5) | 163 (65.2) | 100 (40.0) | 2 (0.8) | 15 |
| Country | | | | | |
| Burkina Faso (n = 272 visits) | 71/273 (26.0) | 50* (70.4) | 28* (39.4) | 0 (0) | 7 |
| Côte d’Ivoire (n = 245 visits) | 24/242 (9.9) | 14* (58.3) | 10 (41.7) | 1* (4) | 1 |
| Mali (n = 559 visits) | 108/559 (19.3) | 72* (66.7) | 40* (37.0) | 0 (0) | 4 |
| Togo (n = 274 visits) | 47/276 (17.0) | 27* (57.5) | 22* (46.8) | 1 (2.1) | 3 |
| STI symptoms | | | | | |
| Asymptomatic | 238 (95.2) | 155 (95.1) | 96 (96.0) | 2 (100) | 0 |
| Anorectal symptoms | 3 (1.2) | 3 (1.8) | 0 (0) | 0 (0) | 0 |
| Urethral symptoms | 10 (4.0) | 7 (4.3) | 3 (3.0) | 0 (0) | 0 |
| Pharyngeal symptoms | 2 (0.8) | 0 (0) | 2 (2.0) | 0 (0) | 0 |
| Any STI symptom | 12 (4.8) | 8 (4.9) | 4 (4.0) | 0 (0) | 0 |
| CT/NG coinfection | 59 (23.6) | 36 (22.1) | 29 (29) | 1 (50) | 7 |
| Cleared MG infection (only of MG infections with follow-up data) | 72/138 (52.2) | 43/87 (49.4) | 33/59 (55.9) | 0 (0) | 4 |

**Abbreviations:** CT/NG, Chlamydia trachomatis/Neisseria gonorrhoeae; MG, *Mycoplasma genitalium*; STI, sexually transmitted infection.

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Intriguingly, ParC S83N and D87Y were the most frequently reported mutations in our study, whereas S83I and D87Y are most frequently detected in high-resource countries [12]. An explanation may be that high-resource settings more frequently use moxifloxacin, which is a fourth-generation fluoroquinolone, whereas ciprofloxacin is predominantly used in African countries. Currently, ParC S83N is not yet associated with clinical resistance in MG, although this mutation has been found in fluoroquinolone-resistant strains of other *Mycoplasma* and *Ureaplasma* species. Nevertheless, fluoroquinolone resistance would still be >5% for most of the countries.

Differences in prevalence of macrolide and fluoroquinolone RAMs in MG between world regions and individual countries may be explained by different patterns of antimicrobial consumption (AMC). For example, the geographical variations in the prevalence of macrolide and fluoroquinolone RAMs is very likely due to differences in macrolide/fluoroquinolone consumption and differences in national STI treatment guidelines. Indeed, in regions where single-dose azithromycin was used for the management of STIs, macrolide RAMs were found in at least 30%–45% of the MG samples among high-STI-incidence populations [24]. Moreover, prevalence of fluoroquinolone RAMs was found to be the highest in Japan (nearly 30%), which was using fluoroquinolones to treat nongonococcal urethritis and MG [11]. A limited ecological study investigating population macrolide consumption and macrolide resistance of MG also found positive correlates between both variables, showing that the presence of RAMs in MG may suggest the overuse of a certain antibiotic in a population [25]. Fortunately, macrolide resistance in MG is still almost nonexistent in African regions, which may indicate that macrolides could still be used to treat MG as well as other STIs in Africa. However, in our study and in other studies among MSM, we showed that individuals with MG are frequently coinfected with chlamydia or gonorrhea [12]. The development of de novo macrolide resistance in MG caused by the usage of 1 g azithromycin is estimated to be 12% [26]. As such, caution is warranted and national surveillance for MG and AMR should be established. Nevertheless, although more research is needed to confirm the correlation between the presence of fluoroquinolone RAMs in MG and fluoroquinolone consumption, surveillance of AMR determinants in MG may be helpful to tailor national STI treatment guidelines. For example, the high prevalence of macrolide resistance in MG in high-resource settings led to a change in many international guidelines to avoid the usage of single-dose azithromycin to treat STIs.

Misure and overuse of antimicrobials are the main drivers of AMR. Dispensing of antibiotics in humans is accelerating worldwide, particularly in low-resource settings, as drugs are becoming more accessible and more affordable [27]. In addition, AMC in animal production is also increasing in African countries, driven by an increased demand for foods of animal origin [28]. Besides resistant microorganisms that may spread between animals, humans, or the environment, antibiotic residues may remain in food derivates, which are then consumed by humans and may promote AMR. Indeed, ecological studies showed that the prevalence of fluoroquinolone resistance in gram-negative bacteria was positively associated with quinolone use for human consumption and with quinolone consumption by food-producing animals [29–31]. Likewise, macrolide usage twice a year led to an increase in macrolide and other nonmacrolide resistance genes in children [32].
Data on AMC in humans and agriculture are, however, sparse in African countries due to the unavailability of monitoring programs to surveill AMC in humans and food agriculture. The last World Health Organization report on surveillance of antibiotic consumption in humans only comprised 4 countries of the African region, including Burkina Faso and Côte d’Ivoire. In these countries, quinolones were the third most used antimicrobial (1.01–1.95 defined daily doses per 1000 inhabitants per day [DDD]) in 2015. Macrolide usage was much less (0.38 to 1.10 DDD) [33]. Consumption data, however, do not reflect the appropriate use of the antibiotic. Nonprescribed dispensing of antibiotic is a common practice in Africa. A systematic review showed that almost 70% of AMC was over-the-counter usage in Africa [34]. This inappropriate use of antibiotics may lead to an acceleration of AMR in the region. Due to the scarcity of data on AMC in humans and animals in African countries, we cannot make any assumptions that the heterogeneity of fluoroquinolone RAMs between the countries may be due to differences in AMC in humans and animals.

Association of clinical resistance to fluoroquinolones is more complex compared to clinical resistance to macrolides. Although single-nucleotide polymorphisms in the 23S rRNA gene are an excellent marker for macrolide resistance of MG, the presence of macrolide RAMs does not always lead to full resistance [35–37]. In addition, alterations in ParC position 83/87 have a lower association with fluoroquinolone treatment failure [38]. In our study, half of the MG infections with ParC 83/87 alterations cleared the infection by the next visit. Natural clearance of MG infections with fluoroquinolone RAMs was previously described, and the authors suggested that this could be explained by fluoroquinolone RAMs conferring a fitness cost [23]. As such, clinical fluoroquinolone resistance may be underestimated in our study. Nevertheless, more research is required to investigate why some infections with fluoroquinolone RAMs clear spontaneously and others may persist for several months and confer clinical resistance.

An important limitation of our study is that we were unable to assess whether an infection was a reinfection or a persistent infection. As such, we only took the first or new infections of MG into account to calculate AMR in MG. Second, it is difficult to assess whether the infection cleared spontaneously or due to treatment provided for another infection. Third, we only took sexual behavior data of the baseline visit into account to assess whether there were risk factors for MG infection. Individuals could have changed their behavior over time.
In conclusion, MG is predominantly asymptomatic and prevalent among MSM in West African countries, which is in line with studies in high-resource countries. As such, indications for testing and treatment for MG among African MSM should follow the United States MG guidelines [39]. This entails that testing and treatment should only be performed in symptomatic patients and in their current partners. However, differences in AMR to macrolides and fluoroquinolones were noted with high-resource countries, which may be due to variance in AMC in humans and agriculture. This finding reinforces the need for surveillance of AMR in MG but also to strengthen surveillance programs of AMC in humans and agriculture.

Supplementary Data

Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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