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Overview

Comparative Review of Antimicrobial Resistance in Humans and Nonhuman Primates

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Antimicrobial resistance (AMR) presents serious threats to human and animal health. Although AMR of pathogens is often evaluated independently between humans and animals, comparative analysis of AMR between humans and animals is necessary for zoonotic pathogens. Major surveillance systems monitor AMR of zoonotic pathogens in humans and food animals, but comprehensive AMR data in veterinary medicine is not diligently monitored for most animal species with which humans commonly contact, including NHP. The objective of this review is to provide a complete report of the prevalences of AMR among zoonotic bacteria that present the greatest threats to NHP, occupational, and public health. High prevalences of AMR exist among *Shigella*, *Campylobacter*, and *Yersinia*, including resistance to antimicrobials important to public health, such as macrolides. Despite improvements in regulations, standards, policies, practices, and zoonotic awareness, occupational exposures to and illnesses due to zoonotic pathogens continue to be reported and, given the documented prevalences of AMR, constitute an occupational and public health risk. However, published literature is sparse, thus indicating the need for veterinarians to proactively monitor AMR in dangerous zoonotic bacteria, to enable veterinarians to make more informed decisions to maximize antimicrobial therapy and minimize occupational risk.

Abbreviations: AMR, antimicrobial resistance; CDC, Centers for Disease Control; NARMS, National Antimicrobial Resistance Monitoring System

NHP play a critical role in biomedical research by serving as models for human diseases, helping researchers make vital discoveries and develop solutions for human health. Because of NHP research models, it is likely that we will soon be able to prevent HIV infection from mother-to-child,[37] we created an efficacious Ebola vaccine,[56] and we developed novel therapies for Parkinson disease.[26] During such investigations, zoonotic bacterial infections in NHP are not uncommon and can potentially affect study results.[72] Therefore, ensuring effective antimicrobial therapy is imperative to minimize possible depreciation of study results and to protect staff from zoonotic transmission.

Appropriate antimicrobial use is essential to maximize the efficiency and effectiveness of antimicrobial therapy. Antimicrobials chosen for therapy are often dependent on bacterial susceptibility testing or known prevalences of antimicrobial resistance (AMR). Ideally antimicrobial therapy is based on the results of susceptibility testing, but empirical treatment prior to culture and susceptibility is often necessary. In such cases, recent AMR prevalence data is imperative to maximize the likelihood of effective therapy. However, without comprehensive data on AMR prevalence, it is difficult to confidently prescribe antimicrobials empirically. AMR to fluoroquinolones, third-generation cephalosporins, and macrolides is especially concerning, because these antimicrobials have been identified by the World Health Organization as critically important to public health.[88] Physicians frequently rely on fluoroquinolones, third-generation cephalosporins, and macrolides for therapy, and if the prevalence of AMR increases, clinicians will have to use alternative antimicrobials that might be less effective against the given pathogen.

Such comparative data are important in biomedical research with NHP, because these species present occupational and public health risks due to circulating zoonotic enteric bacteria. The objective of this literature review is to present existing prevalence data on AMR of zoonotic pathogens that cause the greatest NHP health threats and the greatest occupational and public health risks. This overview excludes nonbacterial and nonenteric pathogens, because enteric bacteria are the greatest cause of morbidity and mortality among NHP.[24,29,31,33,74,83] Zoonotic bacterial diseases including colibacillosis, salmonellosis, and helicobacteriosis are diagnosed in NHP,[29] but we focus here on *Shigella*, *Campylobacter*, and *Yersinia* because these 3 pathogens are presumed to be of greatest concern among primate veterinarians. *Shigella*, *Campylobacter*, and *Yersinia* spp. commonly infect NHP and are the most frequently investigated NHP pathogens among published literature. Furthermore, members of these 3 bacterial genera can cause serious morbidity and mortality in both NHP and the personnel that work with them.[12,17,29,45,51,59] The Centers for Disease Control and Prevention identify *Shigella* and *Campylobacter*, in particular, as serious threats to human health.[17]

Shigella. *Shigella* spp. are among the most infectious zoonotic bacteria, with as few as 10 organisms leading to illness.[3,10] This pathogenicity leads to 500,000 infections annually in the United States, of which 27,000 are resistant to antimicrobials, leading to the definition of AMR *Shigella* as a serious threat to human health by the Centers for Disease Control and Prevention.[17] Worldwide,

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80 to 165 million cases of shigellosis account for 600,000 deaths per year.[10] Unlike many zoonotic bacteria, *Shigella* is limited to humans and NHP, with humans as the primary reservoir.[10,29,35] Therefore, humans as the source of shigellosis among NHP should not be ignored. Although many *Shigella* spp. infect NHP, including *Shigella flexneri*, *S. sonnei*, *S. boydii*, *S. schmitz*, and *S. dysenteriae*,[3,5,10,17,18,24,29,31,33,34,47,67,83] *S. flexneri* is the most frequent etiologic organism of shigellosis, including serotypes 1a, 2a, 3, 4, 5, 6, and 15.[67]

AMR among *Shigella* in NHP. Among the zoonotic enteric bacteria that infect NHP and their associated prevalences of AMR, *Shigella* is one of the more commonly investigated pathogens. One of the most comprehensive studies reported the prevalence of AMR of *S. flexneri*, *S. sonnei*, and *S. dysenteriae* among NHP.[33] The study took place between 1964 and 1967 and included the following NHP species: *Aotus trivirgatus*, *Cercocebus atys*, *Cercopithecus aethiops*, *Macaca fascicularis*, *M. mulatta*, *M. nemestrina*, *M. radiata*, *M. speciosa*, *Presbytis cristatus*, and *P. entellus*.[33] Among the 6646 animals surveyed, 12% (816) were infected with *Shigella* spp., of which 10.5% (696 of 6646) were infected with *S. flexneri*.[33] In addition, 24% (104 of 431) of *S. flexneri* isolates from wild-caught NHP were resistant to chloramphenicol; 46% (199 of 431) and 13% (58 of 430) were resistant to the aminoglycosides dihydrostreptomycin and neomycin, respectively, and 36% (156 of 431) to tetracycline.[33] Among *S. flexneri* isolates from importer-conditioned NHP, 56% (81 of 144) were resistant to chloramphenicol, 92% (133 of 144) and 83% (118 of 143) to aminoglycosides (dihydrostreptomycin and neomycin, respectively), and 87% (125 of 144) to tetracycline.[33] Because the investigators used chloramphenicol to treat shigellosis, the antimicrobial selective pressure may explain the high observed prevalence of AMR to that antimicrobial.[33] However, the high prevalence of AMR to dihydrostreptomycin and tetracycline cannot be explained by their use[33] and may reflect coselective pressure due to chloramphenicol use. This publication is particularly useful because the authors differentiated between wild-caught and importer-conditioned NHP,[33] but their data may be less applicable to biomedical research institutions that no longer, or uncommonly, purchase wild-caught NHP.

In 1983, other investigators examined approximately 10,000 wild-caught cynomolgus macaques (*M. fascicularis*) over 4 y.[83] A total of 58 *S. flexneri* isolates were cultured, and among those, AMR was most frequently observed to penicillins (ampicillin, 67% [39 of 58]), tetracycline (64%, 37 of 58), and sulfonamides (sulphonamide–trimethoprim 57%, 33 of 58).[83] Resistance to chloramphenicol (24%, 14 of 58) and aminoglycosides (neomycin, 28% [16 or 58]) was observed also.[83]

In a third study, 32 of 35 (91.4%) *S. flexneri* isolates from 198 rhesus monkeys (*M. mulatta*) were tested for AMR to aminoglycosides (streptomycin, kanamycin), chloramphenicol, nitrofurans (furazolidone), tetracyclines (chlortetracycline), and penicillins (ampicillin).[5] AMR was observed among 15.6% (5 of 32) of isolates to chloramphenicol, and 3.1% (1 of 32) to streptomycin.[5] In addition, in a group of 14 gibbons (*Hylobates concolor*, *H. syndactylus*), all 112 (100%) *S. flexneri* isolates were resistant to penicillins (amoxicillin), aminoglycosides (gentamicin), tetracyclines (tetracycline), sulfonamides (trimethoprim–sulfamethaxazole), chloramphenicol, and first-generation cephalosporins (cephalothin), with 0% resistant to second-generation fluoroquinolones (enrofloxacin, ciprofloxacin).[7] The presence of AMR to first-generation cephalosporins is valuable information because of the drug's effectiveness against some gram-negative bacteria[64] as well as its contribution to resistance patterns that are used to identify important strains or the possibility of horizontally transferable genetic elements among bacterial populations.[64]

Although *S. flexneri* is the most frequent cause of shigellosis among NHP,[67] shigellosis outbreaks caused by other species have been reported.[24,31] In 1976, an epizootic of *S. sonnei* among 50 common marmosets (*Callithrix jacchus*) and black-mantled tamarins (*Saguinis nigricollis*) was reported.[24] Within 210 d since the epizootic's beginning, the investigators obtained 108 *S. sonnei* isolates and tested them for AMR against 17 antimicrobials.[24] All 108 (100%) of the isolates were resistant to macrolides (erythromycin, tylosin) and penicillins (penicillin, ampicillin).[24] High prevalences of AMR were also observed to aminoglycosides (streptomycin, 89.8% [97 of 108]) and tetracyclines including chlortetracycline (93.4%, 101 of 108), oxytetracycline (86.1%, 93 of 108), and tetracycline (85.2%, 92 of 108).[24]

Similarly, *S. schmitz* has been isolated from chimpanzees (*Pan troglodytes*), spider monkeys (*Ateles geoffroi*), and rhesus macaques.[31] The study illustrated an AMR report over 4.5 y, with colony sizes of approximately 45 chimpanzees, 15 to 50 spider monkeys, and 15 to 40 macaques. The authors reported that 73.3% (22 of 30) of *S. schmitz* isolates were resistant to sulfadiazine, the primary antimicrobial chosen for therapy.[31]

The emergence of pan-resistant strains of zoonotic enteric bacteria has enhanced public health officials' focus on AMR. For example, the emergence of *Salmonella* serotype Newport MDR-AmpC isolates prompted increased surveillance of AMR to ceftiofur.[89] Regarding *S. flexneri*, comprehensive data on the prevalence of AMR has been reported recently.[47] Those authors retrospectively investigated *S. flexneri* isolates and other zoonotic bacteria from NHP at 4 biomedical research institutions, accounting for approximately 23.3% (24,650 of 105,665) of all NHP in the United States.[47] Although no evidence of AMR in *S. flexneri* isolates was observed to second-generation fluoroquinolones (enrofloxacin), the primary antimicrobial used for therapy among participating veterinarians, high prevalences of AMR were observed to other antimicrobials, including macrolides (erythromycin, 87.5% [21 of 24]), penicillins (amoxicillin, 60.0% [12 of 15]), and tetracyclines including doxycycline (73.7%, 14 of 19) and tetracycline (38.3%, 157 of 410).[47] In contrast, other institutions yielded low levels of AMR to similar antimicrobials, including macrolides (erythromycin, 0% [0 of 410]) and penicillins (ampicillin, 0.2% [1 of 410]).[47]

Comparison of *Shigella* AMR between humans and NHP. In humans, ampicillin and trimethoprim–sulfamethoxazole were historically the primary antimicrobials to treat shigellosis.[17] However, current isolates of *S. flexneri* recovered from humans have a reported AMR prevalence of 73.5% (50 of 68) to ampicillin and 52.9% (36 of 68) to trimethoprim–sulfamethoxazole.[18] Consequently, physicians now rely on ciprofloxacin (second-generation fluoroquinolone) and azithromycin (macrolide).[17] According to the *National Antimicrobial Resistance Monitoring System for Enteric Bacteria (NARMS): Human Isolates Final Report 2014*, 5.9% (4 of 68) of *S. flexneri* isolates were resistant to ciprofloxacin, whereas 22.1% (15 of 68) were resistant to azithromycin.[18] The 2 studies that investigated *S. flexneri* AMR to fluoroquinolones among NHP observed no resistance to enrofloxacin (0 of 112 isolates,[7] 0 of 441 isolates[47]), which is metabolized to ciprofloxacin.[49,65] However, one of these studies[7] is compromised because the 112 isolates tested for susceptibility were cultured from only 14 NHP during 2 mo between 1988 and 1989.[7] The other study cited[47] provided more comprehensive data, and its lack of observed fluoroquinolone resistance may suggest clonal strains or strains with minimal genetic diversity.

However, the available information and the absence of genotyping data are nonetheless insufficient to conclusively support such claims.

Overall, macrolide resistance is important to evaluate because of the cross-resistance between azithromycin and erythromycin.[48] At one institution, 87.5% (21 of 24) of *S. flexneri* isolates were resistant to erythromycin,[47] and all 108 (100%) *S. sonnei* isolates in another study were resistant to erythromycin as well as to tylosin, another macrolide.[24] The observed AMR to macrolides among *S. flexneri* in NHP highlights its important public health risk. Several institutions have experienced high prevalences of AMR, and in the event of occupational exposure, treatment with azithromycin is not recommended, eliminating 1 of 2 key antimicrobials for therapy. Because no resistance to fluoroquiolones was observed, empirical treatment with ciprofloxacin may maximize the likelihood of antimicrobial effectiveness and minimize horizontal transmission. However, it is important to reiterate that only 2 studies investigated AMR of *S. flexneri* to fluoroquinolones, and the data are insufficient to confidently assess the public health risks associated with AMR of *S. flexneri* to ciprofloxacin and azithromycin in NHP.[7,47]

***Campylobacter*.** *Campylobacter* is among the most frequent causes of human gastroenteritis,[19] leading to diarrhea (often bloody), fever, abdominal cramps, and in serious cases, temporary paralysis.[17] *Campylobacter* causes approximately 1.3 million infections, 13,000 hospitalizations, and 120 deaths annually in the United States.[17] Similarly to *Shigella*, *Campylobacter*'s relatively low infectious dose of less than 500 organisms increases its occupational and public health risk.[32] Among the 1.3 million cases of campylobacteriosis, 310,000 are caused by AMR isolates.[17] Foodborne transmission commonly leads to a high number of cases.[17] In addition, *Campylobacter* is commonly enzootic in NHP colonies,[4,50,68,69,82,84] and consequently, zoonotic transmission through direct contact can also occur. *C. jejuni* and *C. coli* are the 2 species most frequently isolated from NHP.[4,22,25,50,69,74,82,83]

AMR among *Campylobacter* in NHP. Reports from longitudinal studies and national primate research centers demonstrate that the greatest proportions of resistance among *C. jejuni* and *C. coli* are to first-generation quinolones (nalidixic acid), first-generation cephalosporins (cephalothin), and tetracyclines (tetracycline).[4,25,69,82] In a colony of approximately 450 rhesus macaques, over 7 (nonconsecutive) years, and among 197 *C. coli* and 128 *C. jejuni* isolates, resistance to cephalothin was observed, but the frequencies of AMR were not reported.[4] In another study investigating AMR within 28 pigtailed (*M. nemestrina*) and rhesus macaques, 100% (16 of 16) of *C. jejuni* and *C. coli* isolates were resistant to cephalothin, and 31.3% (5 of 16) of *C. jejuni* and 6.3% (1 of 16) of *C. coli* isolates were resistant to nalidixic acid.[25] In addition, AMR was seen in a small infant nursery consisting of 18 pigtailed macaques, with 72.2% (13 of 18) of them infected with *Campylobacter* resistant to nalidixic acid.[69] And finally, in a colony of cynomolgus macaques, 63.2% (72 of 114) of the macaques were infected with *C. jejuni*, and of those, 34.7% (25 of 72) were resistant to tetracycline.[82] The presented data are insightful, but the reports are not comprehensive because only 1 to 3 antimicrobials were included in susceptibility testing.[4,25,69,82] Nonetheless, similar results were observed in Japan, along with complete susceptibility test results, where high prevalences of AMR among both *C. coli* and *C. jejuni* that infected cynomolgus macaques were observed to fluoroquinolones (ciprofloxacin), macrolides (erythromycin), aminoglycosides (amikacin), and tetracyclines (tetracycline).[50] Furthermore, in another study, the greatest prevalences of AMR in *C. jejuni* from NHP were observed in 99.5% of isolates to penicillins (methicillin, 569 of 572) and 98% to cephalosporins (cephalothin, 557 of 571).[47] Despite these broader data, the knowledge gap regarding the prevalence of AMR in *Campylobacter* from NHP remains large.

Comparison of *Campylobacter* AMR between humans and NHP. The prevalence of AMR among *Campylobacter* in NHP is similar to that of in humans. Among both *C. jejuni* and *C. coli* in humans, the highest prevalences of AMR were to nalidixic acid, ciprofloxacin, and tetracycline (Table 1).[18] The observed similarities in the prevalence of AMR between humans and NHP may be due to overlapping isolate populations and transmission between NHP and humans or to similar antimicrobial selective pressure between human medicine and medical primatology. Although the influence of overlapping populations is difficult to determine without thorough genotyping of isolates, similar antimicrobials are used in human medicine and medical primatology, such as macrolides (azithromycin, erythromycin).[17,19,29,47,87] Similar antimicrobial selective pressure from macrolides might have contributed to the similarities in observed prevalences of AMR between humans and NHP. However, although physicians also rely on ciprofloxacin to treat campylobacteriosis, frequent therapy of campylobacteriosis with fluoroquinolones among veterinarians is not evident within published literature. Even the authors who observed a high prevalence of AMR to ciprofloxacin did not use ciprofloxacin in their eradication regime (Table 1).[50] Although we are unable to demonstrate a causative relationship between antimicrobial use and resistance leading to the observed similarities of AMR between humans and NHP, discrepancies in antimicrobial use suggest that antimicrobial selective pressure is not the only contributor to the observed AMR prevalences. Because of the sparse data that are available on AMR of *Campylobacter* in NHP, definitive comparative conclusions cannot be made.

***Yersinia*.** *Yersinia pestis*, *Y. pseudotuberculosis*, and *Y. enterocolitica* are the only 3 *Yersinia spp.* pathogenic to humans.[9] In particular, *Y. pestis*, which evolved from *Y. pseudotuberculosis* approximately 1500 to 20,000 y ago,[2] was the cause of one of the most famous and catastrophic public health pandemics, called the plague or Black Death.[16] However, yersiniosis today is more frequently caused by *Y. enterocolitica* and usually leads to self-limiting enteric disease in humans and many animal species.[39,58] Among zoonotic enteric bacteria affecting NHP, *Y. enterocolitica* and *Y. pseudotuberculosis* are especially virulent.[12,53,59,79] *Y. enterocolitica* is characterized by over 50 serotypes.[9,41,71,79] Serotypes O3, O5/27, and O9 have low pathogenicity in NHP, but serotype O8 is highly pathogenic.[41,42,59,79] In comparison, 15 serovars have been characterized for *Y. pseudotuberculosis*;[41] the most virulent strains—those with the *ypmA* gene—are currently limited to Korea, Japan, and Eastern Russia.[30]

AMR among *Yersinia* in NHP. Antimicrobials are critical for the treatment of yersiniosis in NHP and humans. Although *Y. enterocolitica* and *Y. pseudotuberculosis* have frequently been isolated from NHP in biomedical research,[6,11,12,21,38,41-44,53,55,57,59,62,63,66,74,77,79,81,85] the prevalence of *Yersinia* AMR has not been thoroughly investigated. Only 1 research team has published a study that specifically investigated the prevalence of *Yersinia* in a biomedical research NHP colony, but no *Yersinia* isolates were recovered.[85] However, because the authors investigated 3 closed NHP colonies only, ranging from 40 to 64 clinically healthy animals in total, the study's results likely are not representative of larger biomedical institutions. *Y. pseudotuberculosis* outbreaks in similarly small NHP colonies have been reported.[81] Isolates from 6 red-bellied tamarins (*Saguinus labiatus*) were resistant to sulfonamides and penicillin.[81] In a separate larger colony with 250 ill NHP, 9 of the animals (*M. fascicularis*, *M. nemestrina*, *M. radiata*,

Table 1. Reported prevalences of antimicrobial resistance (% [no. AMR/total no. isolates]) among *Campylobacter jejuni* and *C. coli* isolates from NHP and humans

		NHP					Human
Antimicrobial	*Campylobacter* spp.	Dassanayake et al.	Koga et al.	Russell et al.	Kim et al.	Tenover et al.	NARMS 2014
Nalidixic acid	*C. jejuni*	31.3% (5/16)	—	72.2% (13/18)[a]	—	—	26.5% (332/1251)
	C. coli	6.3% (1/16)	—	72.2% (13/18)[a]	—	—	35.6% (52/146)
Ciprofloxacin	*C. jejuni*	—	94.1% (16/17)	—	—	—	26.7% (334/1251)
	C. coli	—	95.1% (39/41)	—	—	—	35.6% (52/146)
Tetracycline	*C. jejuni*	—	58.8% (10/17)	—	0% (0/572)	34.7% (25/72)	48.6% (608/1251)
	C. coli	—	70.7% (29/41)	—	—	—	50.0% (73/146)

[a]*Campylobacter* species not specified

and *Cercocebus fulliginosus*) were infected with *Y. pseudotuberculosis* isolates resistant to nitrofurans (furazolidone, 4 of 9) and polypeptides (polymyxin B, 4 of 9) as well as chloramphenicol (1 of 9), aminoglycosides (dihydrostreptomycin, 1 of 9), and penicillin (1 of 9). In addition, a *Y. enterocolitica* isolate from a bush baby (*Otolemur crassicaudatus*) was resistant to penicillins (penicillin, cloxacillin), macrolides (erythromycin), and aminocoumarins (novobiocin).[55]

In 2012, 15 African Green monkeys (*Chlorocebus aethiops sabaeus*) of approximately 2000 died of *Y. enterocolitica* infections that were resistant to sulfonamides (sulfisoxazole), penicillins (amoxicillin–clavulanic acid, ampicillin, oxacillin, and amoxicillin), macrolides (erythromycin), glycopeptides (vancomycin), and lincosamides (clindamycin).[79] However, evaluating a prevalence of AMR is difficult, because frequencies were not described.

A study investigating the prevalence of AMR of *Y. enterocolitica* and *Y. pseudotuberculosis*, found that 100% of *Y. enterocolitica* isolates were resistant to tetracyclines (doxycycline, 2 of 2), 100% to penicillins (amoxicillin–clavulanic acid, 5 of 5; ampicillin, 49 of 49), and 93.6% to first-generation cephalosporins (cefazolin, 44 of 47).[47] In addition, AMR of *Y. enterocolitica* was observed to macrolides (erythromycin) at prevalences of 100% (2 of 2) at one institution and 0% (0/47) at another.[47] No AMR was observed among *Y. pseudotuberculosis* isolates, including a lack of resistance to fluoroquinolones (enrofloxacin),[47] a critically important antimicrobial class in public health.[88] Despite a report that collected recent diagnostic data from approximately 24,650 NHP, few data have been published on AMR of *Yersinia.* Therefore, assessing the prevalence of AMR is difficult; consequently, antimicrobial therapy for *Yersinia*-infected NHP and personnel must be based on individual susceptibility testing.

Comparison of *Yersinia* AMR between humans and NHP. Although most human yersiniosis cases are self-limiting, *Y. enterocolitica* isolates from humans are frequently resistant to penicillins,[34] as are those from NHP. Overall, comparing the prevalence of AMR of *Yersinia* between humans and NHP is challenging due to great temporal and geographic disparities, as well as isolate sources. Many studies investigating AMR and its influence on public health largely examined isolates from food sources rather than patients themselves. And without complete AMR data, we are unable to illustrate the similarities or dissimilarities between *Yersinia* populations in NHP compared with humans. However, likely sources of exposure can be compared. NHP and humans do not commonly share exposure routes to *Yersinia*. Humans are frequently exposed to *Yersinia* through consuming contaminated pork,[34] and pigs in the United States are generally farmed in vertically integrated barns with strict biosecurity procedures,[73] thus minimizing the animals' exposure to wildlife and *Yersinia*. In contrast, wild birds and rodents are 2 reservoirs of *Yersinia*[40,54,76] that can expose NHP in outdoor colonies, which lack barriers similar to those regarding human exposure. Thus, *Yersinia* strains circulating among NHP are more likely to be distinct from strains infecting farmed pigs and subsequently distinct from strains infecting humans through foodborne transmission. However, this distinction is not evident because of the inconsistent sources of AMR data, which otherwise would provide comparable information on resistance patterns and the potential for horizontal transfer of genetic elements between bacterial populations.

Research opportunities. Although many studies have investigated AMR among zoonotic enteric bacteria in NHP, the information available for clinical inferences by NHP veterinarians is limited. First, recent publications (2001 to 2015) are relatively few, and the prevalence of AMR can change substantially quickly.[17] New antimicrobials have been introduced, antimicrobial selective pressure has changed, and, consequently, the development and acquisition of AMR has likely led to evolved AMR genotypes. This evolution can result in the dissemination of new clonal strains and, without regular AMR monitoring, growing and unknown threats to veterinary medicine and occupational health, as seen with the global spread of *Salmonella Tiphimurium* DT104.[36] In addition, many of the studies cited earlier investigated small sample sizes of NHP or isolates, with little or no comparative analysis between NHP and humans or of NHP between institutions. Consequently, despite the AMR data that have been published, veterinarians and physicians require more representative data regarding the prevalence of AMR among zoonotic enteric bacteria in NHP to make better-informed therapy and policy decisions.

Surveillance systems, such as NARMS, have allowed physicians and public health professionals to advance antimicrobial stewardship practices by making more informed decisions to maximize antimicrobial therapy. Additional surveillance programs for food animals exist, such as the National Animal Health Monitoring System and the Food Safety Inspection Service, but in regards to the significant risks of zoonotic diseases, large and important knowledge gaps exist regarding AMR in veterinary medicine, including companion and laboratory animal medicine. Without such surveillance programs, diligent investigation of changes in AMR among zoonotic enteric bacteria is warranted to minimize the associated occupational and public health risks. In addition, the current knowledge gap presents other researchers opportunities to further investigate AMR of zoonotic enteric bacteria in NHP. With AMR data from NHP, veterinarians, as well as physicians, can make more informed

decisions on best antimicrobial practices to maximize antimicrobial therapy and minimize increasing the prevalence of AMR.

Occupational risk. The presence of AMR zoonotic isolates affects not only NHP patients but also poses a risk to personnel. After several documented exposures of zoonotic pathogens from NHP to occupational personnel, the Centers for Disease Control and Prevention recommended improved biosafety standards with PPE and engineering controls.[14,15,20,60]Although these exposures—along with other reports[8,13,28,46,52,75,78,80,86]—involve zoonotic viral exposures, the Centers for Disease Control and Prevention recommendations also improved biosafety against zoonotic bacteria. Occupational shigellosis has been noted,[45,51] and few zoonotic bacterial exposures have been reported. However, the frequency of exposures may be underestimated, considering the likely risk of exposure to zoonotic bacteria[27] given that enteric bacteria are common sources of NHP illness.[29] Nevertheless, the cited reports, in association with literature recommending standardized biosafety protocols,[1,23,61] dramatically decreased—but did not eliminate—the incidence of exposure. However, it is important to emphasize that both PPE and engineering controls are not completely preventive and are subject to damage and noncompliance.

A cross-sectional survey among attendees of the 2009 American Society of Primatology revealed that 11 (9.5%) of the participants experienced a needlestick, 69 (59.5%) had a scratch, 48 (41.1%) were bitten, and 83 (71.6%) experienced a mucosal splash from NHP throughout their careers.[27] Although the authors did not differentiate fecal–oral exposure, the reports of mucosal splashes illustrate the potential for fecal–oral transmission. In addition, 54 (69.2%) of the study participants had been exposed in a laboratory setting.[27] Although the authors addressed several limitations, including selection and recall biases,[27] their study nonetheless highlights the substantial risk of occupational exposure. Such risk combined with the reasonably high prevalences of *Shigella*, *Campylobacter*, and *Yersinia* and their ability to be horizontally transmitted among people,[17,32,70,71] a public health risk undoubtedly exists. Because of recent biosafety advancements, the occupational and public health risks are likely low. Despite all possible efforts to mitigate risk in the work place through engineering controls and PPE, this risk cannot be eliminated, and a single exposure to AMR isolates can lead to multiple human illnesses. This concern is heightened due to the low infectious doses of *Shigella* and *Campylobacter*.[3,10,32] Furthermore, occupational exposures to potentially zoonotic bacteria are commonly underreported, with one group revealing that 36% (10 of 28) of exposures were not communicated to associated supervisors.[86] In addition, the incidence of occupational-related sicknesses likely is insufficient to initiate documented outbreak investigations. The combination of underreported, underdiagnosed, and undocumented occupation-related cases results in an unquantifiable risk, but prior studies clearly show that risk is present, even with key improvements in the hierarchy of hazard controls to reduce that risk. Monitoring AMR among NHP not only allows veterinarians to make informed decisions on antimicrobial therapy and policy, thereby improving animal welfare, but it also informs physicians in the event of occupational exposure. Such diligence improves health outcomes for both research animals and personnel.

Conclusion

NHP are critically important animals in biomedical research, acting as models for important human diseases. Because of the continued use of NHP and their frequent colonization and infection with antimicrobial-resistant zoonotic enteric bacteria, research involving NHP poses important occupational and public health risks. In humans, comprehensive surveillance data from NARMS have been invaluable, allowing physicians to monitor changes in AMR. However, except for *Shigella*, a NARMS-like source that provides veterinarians with AMR data on *Campylobacter* and *Yersinia* isolated from NHP is unavailable, creating undetermined occupational and public health risks. Although valuable, NARMS is a limited resource for veterinarians to assess occupational risk. Some similarities in the prevalences of AMR between NHP and humans are evident, but the comparative data available are insufficient for veterinarians and physicians to target AMR epidemiologically and minimize its associated occupational and public health risks. This dearth emphasizes the necessity for proactive AMR monitoring of NHP zoonotic enteric bacterial isolates. Otherwise, the considerable present knowledge gap will continue to grow and force veterinarians and physicians to make poorly informed policy and treatment decisions. Adopting simple and routine susceptibility tests will allow veterinarians to quantitatively track trends in AMR, ultimately maximizing the effectiveness of antimicrobial therapy of both NHP patients and their human colleagues, in the event of occupational exposure.

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