Zoonotic and antibiotic-resistant \textit{Campylobacter}: a view through the One Health lens

Qijing Zhang*, Ashenafi Feyisa Beyi and Yue Yin

Abstract
As a pathogen of a major public health concern with animal health importance, \textit{Campylobacter} constitutes a clear and present threat to One Health. This organism colonizes the intestinal tract and is widely distributed among various animal species, including livestock and poultry, companion animals, and wildlife. As a result of its broad distribution, \textit{Campylobacter} is exposed to antibiotics used in both human and veterinary medicine, which creates antibiotic selection pressure that has driven the development and rising prevalence of antibiotic resistant \textit{Campylobacter}. This is particularly evident with the resistance to fluoroquinolone (FQ), which has become a great concern for public health. However, the increased prevalence of antibiotic-resistant \textit{Campylobacter} cannot be solely attributed to antibiotic usage, as interspecies transmission and subsequent clonal expansion also contribute to the dissemination of antibiotic-resistant \textit{Campylobacter}. This is exemplified by the emergence and expansion of FQ-resistant \textit{Campylobacter} clones in animal production systems where FQ antibiotics were never used, the transmission of extensively drug resistant \textit{Campylobacter} from dogs to human patients, and the spread of antibiotic-resistant and hypervirulent \textit{Campylobacter} from ruminants to humans. Another notable finding from recently published work is the emergence of antibiotic resistance genes of Gram-positive origin in \textit{Campylobacter}, suggesting that genetic exchange between \textit{Campylobacter} and Gram-positive bacteria occurs in the natural environment and is more frequent than previously realized. Once these "foreign" antibiotic resistance genes are presented in \textit{Campylobacter}, they can further disseminate by clonal expansion or horizontal gene transfer among different \textit{Campylobacter} species/strains. These findings indicate that the emergence and transmission of antibiotic-resistant \textit{Campylobacter} in the ecosystem are complex and multidirectional, and are affected by multiple factors. Thus, a holistic and One Health approach is necessary to fully comprehend and mitigate antibiotic resistant \textit{Campylobacter}.

Keywords \textit{Campylobacter}, Antibiotic resistance, Zoonosis, One Health, Pathogen transmission

Introduction
One Health represents both a concept and an approach. As a concept, it emphasizes the interdependence of human, animal, and environmental health, while as an approach it advocates for a systemic and ecological practice that integrates interdisciplinary and transdisciplinary collaborations and unifies regional and global efforts to address issues that threaten human, animal, and environmental health [1]. There are many current challenges that impact One Health, such as emergence of zoonotic infections and new pathogenic variants, transmission of foodborne diseases, spread of antimicrobial resistance (AMR), and climate changes [2–7]. As exemplified by AMR, these challenges are complex and affect
multiple sectors in the ecosystem, and addressing these issues requires a holistic approach to maximize impacts and outcomes.

Owing to their high efficacy and safety, antibiotics have been the key therapeutic agents of bacterial infectious diseases in human and veterinary medicine [8]. The development and spread of AMR have made antibiotic treatments less or ineffective and are particularly problematic with severe and life-threatening infections. This situation is even worse with the emergence of multidrug-resistant bacteria and pathogens that are resistant even to the last-resort antibiotics, such as carbapenem-resistant Enterobacteriales, colistin-resistant Escherichia coli, and oxazolidinone-resistant Gram-positive pathogens [9–12]. Since antibiotics are important for prevention, control, and treatment of animal diseases, AMR also constitutes a major threat to animal production and welfare, food safety, and food security. Additionally, the presence of antibiotics and/or their metabolic products in soil and water systems impacts microbial community and diversity in the ecosystem and selects for the evolution and dissemination of AMR genes in the environment [13]. Moreover, the environment plays a key role in the transmission of AMR to wildlife, domestic animals, and humans.

AMR naturally occurs in microbial community, but the application of antibiotics in human and animal medicine, as well as the use of antibiotics in crop production has driven the rapid evolution and spread of AMR across the entire ecosystem [8]. Thus, the extent and scale of AMR are largely shaped by antibiotic selection pressure originated from antibiotic usage. Bacteria have the natural ability to mutate and adapt under antibiotic selection pressure. Additionally, many AMR determinants are carried by mobile genetic elements, and bacteria can acquire AMR via horizontal gene transfer [14].

AMR does not respect boundaries, and its transmission is multi-directional. AMR developed in one sector can spill over to another. For example, AMR developed in animal reservoirs may be transmitted to humans via food, water, and environmental routes, while human sewage, animal manures, and agricultural runoff can spread AMR to soil, water systems, and the environment [13]. Additionally, reverse zoonotic transmission of AMR from humans to animals may also occur [15]. Thus, AMR truly represents a One Health challenge.

Campylobacter is a major zoonotic and foodborne pathogen [16], and is increasingly resistant to antibiotics used for human and veterinary medicine [17]. Due to its importance in public health and its rising resistance to antibiotics, particularly fluoroquinolones (FQ), Campylobacter has been recognized as one of the serious antibiotic resistant threats of high priority by both WHO and the CDC [18]. Thus, antibiotic resistant Campylobacter presents a clear and imminent challenge to One Health. In this review, we will examine development and transmission of antibiotic-resistant Campylobacter from a One Health perspective and will use some examples to illustrate the relevance of antibiotic-resistant Campylobacter to One Health. It should be pointed out that this paper is not intended to provide a comprehensive review on Campylobacter antibiotic resistance mechanisms and trends. For such a topic, we would refer readers to some recent review articles [17, 19–21].

**Campylobacter distribution and transmission in the ecosystem**

Campylobacter has extensive animal reservoirs and is commonly present in the intestinal tracts of food-producing animals and companion animals [22]. Additionally, Campylobacter may be carried by wildlife, flies, and other insects, which serve as transmission vectors spreading Campylobacter to and across farms and to the environment including surface water [23–26]. The common presence of Campylobacter in animals and wildlife and the variety of means by which it can disseminate contribute to the broad distribution of Campylobacter in the ecosystem. A single animal species may be colonized by multiple Campylobacter spp., but there are some notable differences in species distribution. For example, chickens and ruminants tend to harbor more Campylobacter jejuni than Campylobacter coli; pigs tend to carry more C. coli than C. jejuni; and cats and dogs primarily carry C. jejuni and Campylobacter upsaliensis [27–29]. Campylobacter spp. are generally commensals in animal reservoirs; however, they can be pathogenic in some animal species. One example is C. jejuni induced abortion in sheep [22]. Transmission of Campylobacter from animal reservoirs to humans mainly occurs through contaminated food, milk, and water [30]. Contact with animals, such as petting zoo and companion animals, is another transmission route [31–33]. Thus, Campylobacter is both a zoonotic and a foodborne pathogen. In developed countries, campylobacteriosis is mainly manifested as foodborne enteritis, occurring as sporadic cases and outbreaks, while in developing countries, Campylobacter is endemic and a significant burden of diarrhea in children [34]. Although the primary clinical condition induced by Campylobacter in humans is enteritis, it is also associated with extraintestinal diseases and other complications such as bacteremia and Guillain Barrie Syndrome [30].

**Fluoroquinolone (FQ) resistance in Campylobacter: a One Health case study**

As a zoonotic pathogen, Campylobacter is exposed to antibiotics used for both human and veterinary medicine. Its resistance to FQ antimicrobials is of particular
concern to public health because FQs (e.g., ciprofloxacin) are an important class of antimicrobials used for clinical therapy of campylobacteriosis and other enteric infections [35]. The prevalence of FQ-resistant Campylobacter is continuing to rise on a global scale and has reached alarming levels in some countries [17, 21, 36–38]. This has led WHO to list FQ-resistant Campylobacter as a high-priority for research and development of new antibiotics [18]. Part of the reason for this high rate of FQ resistance in Campylobacter is due to the fact that DNA gyrase mutations that confer resistance to FQ antibiotics readily occur in this organism and these mutants are rapidly selected and enriched under FQ treatment, which was shown by both in vitro and in vivo studies as well as observations from clinical trials with human patients [39, 40].

FQs are not only used in human medicine but also for the control and treatment of animal diseases in many countries [41]. In food producing animals, the use of FQ antimicrobials are not intended for curing Campylobacter but for the control and treatment of other bacterial infections such as respiratory diseases in poultry, swine, and cattle [42, 43]. Thus, the selection and enrichment of FQ-resistant Campylobacter in these animals represent an unintended consequence of FQ application. However, FQ-resistant Campylobacter developed in food producing animals may be transmitted to humans via the food chain or environmental route. Use of FQs in poultry is of particular concern as Campylobacter is highly prevalent in poultry, and administration of FQ antibiotics to poultry results in the rapid emergence of FQ-resistant Campylobacter [44–46]. Given that contaminated poultry meat serves as a major vehicle for transmission of Campylobacter to humans, use of FQs and consequential development of FQ-resistant Campylobacter in poultry pose a major risk for food safety and public health. Indeed, there were many epidemiological observations that demonstrated a temporal link between approved use of FQ antimicrobials in food producing animals, particularly in poultry, and the increased prevalence of FQ-resistant Campylobacter in both animal reservoirs and humans [47–49]. Additionally, comparison of conventional production practices and organic operations in the U.S. showed a significantly higher rate of FQ-resistant Campylobacter in conventional production systems than in organic operations [39, 50], further suggesting the contribution of FQ use to the high prevalence of FQ-resistant Campylobacter. Arising from the concern with FQ resistance in Campylobacter, the FDA elected to withdraw the approval of FQ antibiotics for poultry in the U.S. in 2005 [51].

Antibiotic selection pressure is not the only factor influencing the emergence and transmission of FQ-resistant Campylobacter. In contrast to many other countries, FQ antimicrobials were never used in poultry production in Australia, where the prevalence of FQ-resistant Campylobacter in human patients and poultry was historically at a very low level [52, 53]. However, recent studies have identified the emergence of FQ-resistant Campylobacter in both poultry production and human clinical cases in Australia [54, 55]. Among the poultry isolates, the FQ resistance rates were reported to be 15% in C. jejuni and 5% in C. coli, while the FQ resistance rate among the human C. jejuni isolates was 14%. Notably, FQ resistance appears to be associated with a limited number of genotypes: three sequence types (STs) for C. jejuni and a single ST for C. coli. Similarly, FQ antibiotics are prohibited for use in poultry in New Zealand, where FQ-resistant Campylobacter was rarely reported until recently [56]. A recent study identified the emergence and rapid expansion of a FQ- and tetracycline-resistant C. jejuni clone (ST6964) in both human and poultry [57]. This clone was first detected in New Zealand in 2014 and became widely disseminated in both chickens and human patients by 2015. The emergence and dissemination of these FQ-resistant Campylobacter clones in both Australia and New Zealand cannot be explained by the use of FQ antibiotics in poultry and suggest that they were initially introduced into poultry from a different source. As suggested by the authors, this could be wildlife (such as wild birds) or even reverse zoonotic transmission from human to chickens [54]. Regardless of the original sources of these FQ-resistant Campylobacter, their rapid expansion suggest that they have a fitness advantage in the ecosystem.

Another example of the emergence of FQ resistance due to clonal expansion is the recent discovery of a FQ-resistant C. coli clone in sheep in the U.S. [58]. FQ antimicrobials were never approved for use in sheep production in the U.S., and Campylobacter from sheep was generally susceptible to this class of antibiotics [59]. However, a 2019 study found that 95% of the C. coli isolates from two commercial sheep farms were resistant to ciprofloxacin [58]. This high FQ resistance rate could not be explained by selection pressure derived from FQ usage as they were never used on sheep farms in the U.S. Additionally, the C. jejuni isolates derived from the same sheep farms were largely susceptible to ciprofloxacin (only 1.7% resistant to ciprofloxacin), further suggesting the absence of FQ antimicrobial selection in the sheep. Thus, the FQ-resistant C. coli in sheep was likely introduced from another source. Notably, all the C. coli isolates identified in the study belonged to a single predominant genotype (ST902), suggesting that host adaptation and clonal expansion contributed to its dissemination in sheep. How ST902 was introduced into sheep and what made it predominant remains unknown. Given that wild birds on livestock farms are known to...
carry FQ-resistant *Campylobacter* [23, 60], it is possible that ST902 was initially transmitted to sheep by birds and subsequently expanded in the production system.

Similar to the situation in sheep, FQ-resistant *Campylobacter* are increasingly detected in cattle in the U.S. For example, a study published by Tang et al. in 2017 reported that 74% *C. coli* and 35% *C. jejuni* isolated from feedlot cattle in five different states were resistant to ciprofloxacin [61]. Although the FQ-resistant *C. jejuni* isolates were genetically diverse, most of the FQ-resistant *C. coli* strains belonged to a single genotype, ST1068, suggesting clonal expansion was involved in the dissemination of FQ-resistant *C. coli* in cattle. Another recent study reported that 87% of the calves obtained from a commercial farm were naturally colonized by FQ-resistant *C. jejuni* [62], further indicating the high prevalence of FQ-resistant *Campylobacter* in the ruminant host. Different from sheep production where the use of FQ antimicrobials is prohibited, FQs are used for the treatment and control of respiratory diseases in cattle [63]. The use of FQ antimicrobials could serve as a selection force for the spread of FQ-resistant *Campylobacter*, but a recent FQ treatment study suggested that subcutaneous injection of FQ antimicrobials did not result in the de novo development of FQ-resistant mutants from the inoculated FQ-susceptible *C. jejuni* in the cattle intestinal tract [64]. As explained by the authors, this might be due to the relatively low density of *Campylobacter* in cattle feces and the high concentration of the antimicrobial excreted into the intestine [65], which could have exceeded the mutant selection window and prevented the emergence of FQ-resistant mutants. Although the exact factors contributing to the increased prevalence of FQ-resistant *Campylobacter* in cattle remain unclear, it constitutes a risk for food safety and public health as ruminant *Campylobacter* has been increasingly recognized as a significant reservoir for human campylobacteriosis and for environmental contamination such as surface water [66–72].

Clinical use of FQ antimicrobials in human patients also selects for FQ-resistant *Campylobacter*, which was shown in clinical trials [40, 73]. Since human-to-human transmission of *Campylobacter* is rare in developed countries, the foodborne and environmental routes play a major role in the transmission of FQ-resistant *Campylobacter* to humans. However, in developing countries, where *Campylobacter* is endemic and people may carry *Campylobacter* asymptptomatically, community-based transmission of FQ-resistant *Campylobacter* may also occur. Additionally, antibiotic-resistant *Campylobacter* developed in humans may spill over to domestic animals, wildlife, and the environment by reverse zoonotic transmission [54, 74]. Together, the examples discussed above illustrate that the transmission and dissemination of FQ-resistant *Campylobacter* are complex and multi-directional, and constitute a threat to One Health.

### The shared AMR gene pool between *Campylobacter* and other organisms in the One Ecosystem

*Campylobacter* shares the same “One Ecosystem” with many other bacteria in the animal intestinal tract and the environment and has the ability to acquire AMR determinants from other bacteria via horizontal gene transfer. Recent studies have discovered a plethora of antibiotic resistance determinants that were horizontally transferred to *Campylobacter*. Some examples include *erm*(B) and *erm*(N) for macrolide resistance [75–79], *fexA*, *optrA*, and *cfr*(C) for florfenicol resistance [80–84], and *tet*(L) for tetracycline resistance [85]. The emergence and spread of these AMR genes in *Campylobacter* were likely driven by the use of antibiotics in food producing animals. These genes are either associated with multidrug-resistance genomic islands or carried by conjugative plasmids. Sequence analysis strongly suggest that they were originated from Gram-positive bacteria, such as *Enterococcus*, *Staphylococcus*, and *Streptococcus*. These recent discoveries, plus previously identified horizontally acquired AMR genes, such as *cat* (chloramphenicol resistance) [86], *aphA-3* (kanamycin resistance) [87, 88], and *tet*(O) (tetracycline resistance) [89], imply that gene transfer between *Campylobacter* and Gram-positive bacteria frequently occurs in the natural environment. It remains unclear how gene exchange occurs between *Campylobacter* and other bacteria, but it has been speculated that AMR genes were first introduced into *Campylobacter* from a Gram-positive origin by conjugation and then integrated into *Campylobacter* chromosome or plasmids [90]. Subsequent spread among different *Campylobacter* species and strains could be facilitated by natural transformation, which was shown under laboratory conditions. The sharing and transfer of AMR genes between *Campylobacter* and Gram-positive bacteria have both direct and indirect consequences for public health. For instance, macrolide is the drug of choice for therapeutic treatment of campylobacteriosis in humans. Thus, the spread of *erm*(B) and *erm*(N) may undermine the efficacy of this important class of antibiotics. Some of the florfenicol resistance genes, such as *optrA* and *cfr*(C), not only confer resistance to florfenicol but also to the oxazolidinone class [91], which is critical for treating infections caused by multidrug resistant Gram-positive pathogens [12]. Although oxazolidinones are not used for treating *Campylobacter* infections, gene exchange may lead to dissemination of these AMR genes from *Campylobacter* to other Gram-positive pathogens that share the same niche with *Campylobacter*. 
Sharing of multidrug resistant *Campylobacter* between companion animals and humans

Dogs and cats harbor many different *Campylobacter* spp., particularly *C. jejuni*, *Campylobacter upsaliensis*, and *Campylobacter helveticus*, and their prevalence is higher in younger dogs than in older dogs [29]. These animals may carry *Campylobacter* asymptomatically, but *Campylobacter*-induced clinical diseases, such as enteritis, bacteremia, and abortion, have been reported in dogs [29]. Due to the intimate interaction between companion animals and their owners, transmission of *Campylobacter* may occur between them. Indeed, there have been multiple reports of transmission of *Campylobacter* between dogs and humans [92–94]. In these reported cases, epidemiological investigation and the use of genetic typing methods confirmed human-to-pet or pet-to-human transmission. Of particular note are the recent reports on a large outbreak associated with extensively drug-resistant *C. jejuni* that occurred in the U.S. from 2016 to 2021 [95–97]. Over the course, more than 160 people were infected, and multiple patients were hospitalized. Epidemiological investigation and whole genome sequence analysis conducted by the CDC linked the outbreak cases to contact with pet store puppies. Notably, the *C. jejuni* isolates implicated in the outbreak were extensively resistant to antibiotics and belonged to a single ST type (ST2109). Whole genome sequence analysis revealed the presence of multiple antibiotic resistance genes and resistance-conferring mutations in the outbreak isolates, explaining the extensively drug resistance phenotype. Additionally, ST2109 harbors a functionally enhanced multidrug efflux transporter CmeB (RE-CmeB), which was known to work with other AMR mechanisms to confer exceedingly high-level resistance to various antibiotics [98]. Interestingly, *C. jejuni* ST2109 was rarely reported in other animal species, and the reasons for its prevalence in commercial dog breeding facilities remain unknown. Furthermore, how ST2109 was introduced into dogs and how it became multidrug resistant are intriguing and warrant further investigations.

Ruminant-to-human transmission of hypervirulent and antibiotic-resistant *C. jejuni*: a case study with clone SA

Secondary to poultry, ruminants are major reservoirs for *C. jejuni*, and there are many different strains and genotypes of *C. jejuni* in bovine and small ruminants [99–102]. Molecular typing and source attribution studies have increasingly recognized the role of ruminants in human campylobacteriosis [66, 71, 103–105]. Ruminant *Campylobacter* may be transmitted to humans via unpasteurized milk and other routes such as petting zoo or environmental contamination. *Campylobacter* reside in the intestinal tract of ruminant animals typically as commensals, but some strains may be pathogenic and induce clinical abortion [22]. For example, a single *C. jejuni* clone named SA (for sheep abortion), has emerged as the major cause of sheep abortion in the U.S., responsible for more than 90% of *Campylobacter*-induced abortion cases [106]. Based on multi-locus sequence typing, all clone SA isolates belonged to a single sequence type (ST8). One of the distinct features of *C. jejuni* clone SA is that all the isolates derived after the year 2000 were resistant to tetracycline, the only antibiotic approved for the control of sheep abortion in the U.S. [106]. Early clone SA isolates (derived before the year 2000) carried the tet(O) gene on a plasmid, but later isolates had the antibiotic resistance gene inserted into the chromosome [107]. Clone SA is well adapted in the intestinal tract and gall bladder of sheep and is commonly detected in healthy animals [108]. However, *C. jejuni* clone SA is hypervirulent in pregnant ewes, as orally inoculated clone SA is able to translocate across the intestinal epithelium, produce systemic infection, and infect placenta, causing clinical abortion [109, 110]. This distinguishes clone SA from many other *C. jejuni* strains that typically stay in the intestinal tract. The genomes of clone SA isolates are highly homologous and harbor unique amino acid substitutions in the major outer membrane protein encoded by the *porA* gene, which were shown to be responsible for its hypervirulence in abortion induction [107]. In addition to being present in sheep, clone SA was also widely distributed on cattle farms (both feedlot and dairy cattle) in the U.S. and was also detected in goats [102, 108, 111, 112]. However, *C. jejuni* clone SA is uncommon in other animal species, indicating ruminant animals are the major reservoirs for *C. jejuni* clone SA.

Importantly, *C. jejuni* clone SA is also a foodborne hazard that is transmitted to humans via contaminated raw milk and other routes, causing foodborne enteritis [108]. Molecular evidence has linked multiple outbreaks and sporadic cases to this clone in the U.S. [108]. A known route for zoonotic transmission of *C. jejuni* clone SA is raw milk, but ruminant animals may also contaminate environmental water systems, which may also facilitate the dissemination of this pathogenic clone to humans. Analysis of the *Campylobacter* genomic sequences deposited in NCBI indicated that clone SA is primarily isolated from ruminants and humans, further suggesting the transmission between the ruminant reservoir and humans. The analysis also indicated that *C. jejuni* clone SA was primarily reported in North America, but it was also found in other countries, such as China, Japan, Switzerland, and the UK (Zhang, unpublished data). The emergence of *C. jejuni* clone SA in the U.S. appears to be a relatively recent event as molecular clock analysis
estimates that it initially occurred around mid 1970s [107]. What has driven the emergence and spread of clone SA is not entirely clear, but computer analysis of genomic sequence data suggested the specific amino acid changes in the major outer membrane protein contributed to the evolution and expansion of clone SA. Additionally, the use of tetracycline in sheep production and insertion of the tet(O) gene into the chromosome may have also helped the clone to expand on sheep farms and in other ruminant hosts.

Conclusion and future perspectives
The examples discussed above illustrate several key aspects of Campylobacter that are important to One Health. As a zoonotic pathogen, Campylobacter has broad animal reservoirs, and its transmission in the ecosystem is multidirectional and often crosses species boundaries. This pathogenic organism has the ability to rapidly evolve in response to antibiotic selection pressure and the conditions in various animal hosts and the environment, leading to the emergence of new variants with multidrug resistance and/or hypervirulence (e.g., ST2109 and ST8). The use of FQ antimicrobials in human and veterinary medicine has driven the rapid rise of FQ resistance in Campylobacter worldwide, but recent studies suggest that interspecies transmission and subsequent clonal expansion have also contributed to the dissemination of FQ-resistant Campylobacter (such as ST6964 in poultry in New Zealand and ST902 in sheep in the U.S.). What has promoted the rapid expansion of these FQ-resistant clones in the absence of FQ selection is unknown but intriguing, and answering these questions will facilitate the mitigation of FQ resistance. Thus, further investigations are warranted to understand the bacterial, host, and environmental factors that contribute to the establishment and thriving of these FQ-resistant clones in different animal species. Additionally, many of the recently identified AMR genes in Campylobacter appear to be the result of horizontal gene transfer from Gram-positive bacteria, which share the same niche with Campylobacter in the animal intestine. The mechanisms underlying the initial trans-Gram genetic exchange and subsequent integration of the transferred AMR genes into Campylobacter chromosome (e.g., multidrug resistance genomic islands) or plasmids remain to be defined. This needs to be examined beyond laboratory conditions, ideally in the natural environment (e.g., animal intestine) where Campylobacter resides. With the recent technological advancement, it is now possible to elucidate the transfer of AMR genes in complex niche systems. Although poultry remains the primary source of human Campylobacter infections, the role of ruminants and companion animals in transmitting Campylobacter to humans is being increasingly recognized, but has been understudied. Thus, heightened efforts should be taken to understand the complex and broader interactions of various animal reservoirs with humans and the environment in transmission of antibiotic-resistant Campylobacter. A holistic and One Health approach that emphasizes the interconnection of animal reservoirs, humans, and the environment will likely lead to the optimal control of zoonotic Campylobacter and its resistance to clinically important antibiotics.


Publisher's Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:
- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

Learn more biomedcentral.com/submissions

At BMC, research is always in progress.