Plasmid-mediated quinolone resistance; interactions between human, animal, and en...

Health & Medicine

Introduction

Quinolones are fully synthetic and bactericidal antibacterial agents used widely in both human and veterinary medicine. The clinically available quinolones have been classified into several generations based of their spectrum of activity (Ball, 2000). The first generation quinolone (Q1G), nalidixic acid, has been discovered in 1962 (Lesher et al., 1962). Other Q1G, such as pipemidic acid and oxolinic acid, had been developed, the latter being used for in veterinary medicine. The quinolones of the second generation are made of addition of a fluorine atom at position C-6 to the quinolone nucleus, yielding to the fluoroquinolones (FQ; Paton and Reeves, 1988). The early FQ (e. g., norfloxacin, ofloxacin, pefloxacin, ciprofloxacin, or enrofloxacin) achieved higher serum levels and showed potent activity against Gram-negative bacteria, several Gram-positive bacteria (such as *Staphylococcus aureus*), and intracellular bacteria. In addition, ciprofloxacin is active against *Pseudomonas aeruginosa* . Newer FQ (third generation quinolones) were subsequently developed and presented increased activity toward Gram-positive bacteria, in particularly to *Streptococcus pneumoniae* (e. g., sparfloxacin, levofloxacin, or moxifloxacin), and potent activity against anaerobic bacteria (e. g., trovafloxacin, gatifloxacin, or gemifloxacin; Van Bambeke et al., 2005).

Even if the main factors leading to resistance to quinolones and FQ related to chromosomal mutations in the drug target genes, the discovery during the last decade of a series of plasmid-encoded resistance mechanisms has contributed to speculate about the origin and enhancing factors of that

transferable resistance. In particular, the interplay between an environmental and animal source on one side, and the human clinical pathogens on the other side (in which the emergence of resistance to quinolones is a matter of fact) remains to be further explored and understood.

That review aims to present some of the current available data from which speculations can be established.

Mechanism of Quinolone Action

The targets of quinolone molecules are the type II topoisomerases: DNA gyrase (topoisomerase II) and DNA topoisomerase IV (Drlica and Zhao, 1997). As opposed to type I topoisomerases that transiently cleave one strand of the DNA double helix, type II topoisomerases break transiently both strands of a duplex and pass another double-helical segment through the break by ATP hydrolysis (Drlica and Zhao, 1997 ; Hawkey, 2003). The DNA gyrase introduces negative supercoils into DNA whereas topoisomerase IV exhibits a potent decatenation activity. Those enzymes are essential for bacterial growth by controlling the topological status of the chromosomal DNA to facilitate replication, transcription, recombination, and DNA repair (Drlica and Zhao, 1997 ; Hawkey, 2003). The DNA gyrase and the DNA topoisomerase IV are the main targets of quinolones in Gram-negatives and Gram-positives, respectively. Quinolones inhibit the activity of type II topoisomerases by trapping these enzymes on DNA as drug-enzyme-DNA complexes. Ternary complex formation is responsible for inhibition of bacterial growth (bacteriostatic action) by a rapid inhibition of DNA synthesis

and a slower inhibition of RNA synthesis (Drlica and Zhao, 1997 ; Hawkey, 2003). Eventhough these drug–enzyme–DNA complexes block cell growth, they are not directly responsible for the lethal effect of quinolones. Indeed, bactericidal activity is due to the releasing of double-stranded DNA breaks from those complexes, but the detailed mechanism of action of quinolones still needs to be fully understood.

Chromosome-Encoded Resistance

Resistance to quinolones in Enterobacteriaceae most commonly results from the accumulation of mutations primarily in DNA gyrase (GyrA) then in topoisomerase IV (ParC; Hooper, 2000 ; Ruiz, 2003 ; Hopkins et al., 2005 ; Jacoby, 2005). Alterations in GyrA of *E. coli* predominantly occur within the N-terminus of the protein in the so-called quinolone resistance determining region (QRDR) located between amino acids Ala67 and Gln106. Mutations appear most frequently at codons Ser83 and Asp87, which are located near the active sites of enzyme (Tyr122). In addition, quinolone resistance can be associated with a decreased membrane permeability and/or an overexpression of efflux pump systems (Hooper, 2000 ; Hopkins et al., 2005).

Plasmid-Mediated Resistance

Although considered as impossible due to the plasmid curing effect of quinolones (Courvalin, 1990), plasmid-mediated quinolone resistance (PMQR) was first reported in 1998 from a *Klebsiella pneumoniae* isolate in the USA (Munshi et al., 1987). Indeed, a plasmid-mediated resistance to nalidixic acid in *Shigella dysenteriae* has been reported previously in 1987 (

Munshi et al., 1987), but the reality of this phenomenon was later rejected (Courvalin, 1990). To date, several PMQR mechanisms have been identified: Qnr proteins, the aminoglycoside acetyltransferase AAC(6′)-Ib-cr, and the efflux pumps QepA and OqxAB.

Qnr Proteins

Qnr structure and nomenclature

The first identified PMQR determinant corresponded to the Qnr protein, lately termed QnrA1 (Martinez-Martinez et al., 1998). The corresponding gene was identified on a broad-host range conjugative plasmid recovered from a ciprofloxacin-resistant *K. pneumoniae* isolate (Martinez-Martinez et al., 1998). QnrA1 is a 218-amino-acid protein that belongs to the pentapeptide repeat family, of which more than 500 members are known, distributed in prokaryotics and eukaryotics (Vetting et al., 2006). Those proteins are made of tandemly repeated amino acid sequences with a consensus sequence [S, T, A, or V] [D or N] [L or F] [S, T, or R] [G] (Vetting et al., 2006). Six other QnrA variants (QnrA2 to QnrA7) have been identified, and differ from QnrA1 by a few amino acid substitutions (Jacoby et al., 2008).

Four distantly related Qnr-like determinants belonging to the pentapeptide repeat family have also been identified in Enterobacteriaceae: QnrB, QnrC, QnrD, and QnrS (Hata et al., 2005 ; Jacoby et al., 2006 ; Cavaco et al., 2009 ; Wang et al., 2009). To date, there are 42 QnrB variants, 1 QnrC, 1 QnrD, and 5 QnrS (http://www. lahey. org/qnrStudies/). QnrB1, QnrC1, and QnrS1 share 40, 60, 47, and 59% amino acid identity with QnrA1, respectively.

In addition, QnrVC-like proteins have been identified in *Vibrio cholerae* , sharing 57% amino acid identity with QnrA1 (Fonseca et al., 2008). Even if the *qnrVC* genes have been identified as acquired resistance genes, they are not plasmid-located, thus not considered as PMQR genes.

Mechanism of action

QnrA1 shares 20 and 19% amino acid identity with McbG and MfpA, respectively, two other members of the pentapeptide repeat family both involved in resistance to gyrase inhibitors (Cattoir and Nordmann, 2009). Qnr proteins may supplement resistance to quinolones due to altered quinolone target enzymes, efflux pump activation, or deficiencies in outer-membrane porins (Martinez-Martinez et al., 2003 ; Jeong et al., 2008). In addition, Qnr proteins facilitate selection of quinolone resistance mutants by raising the level at which they can be selected with a frequency more than 100-fold higher (Martinez-Martinez et al., 1998). The presence of Qnr determinants facilitates the selection of low-level of resistance to quinolones due to chromosome-encoded mechanisms. From a clinical point of view, Qnr determinants may increase the mutant prevention concentration (MPC) of ciprofloxacin by more than 10-fold, facilitating recovery of mutants with higher level of resistance to quinolones (Rodriguez-Martinez et al., 2007). Therefore, Qnr-positive isolates may be a favorable background for an *in vivo* -selection of additional chromosome-borne mechanism(s) of resistance to quinolones after treatment by fluoroquinolones (Poirel et al., 2006).

Epidemiology of Qnr determinants

Qnr in human clinical isolates. All types of Qnr determinants have been identified worldwide in many different enterobacterial species but mostly in *K. pneumoniae* , *Enterobacter* spp., *E. coli* , and *Salmonella enterica* from community and nosocomial isolates (Rodríguez-Martínez et al., 2011). Their overall prevalence may range from 0. 2 to up to 94% depending on selection criteria of studied strains (resistance to ceftazidime, nalidixic acid, FQs,...; Strahilevitz et al., 2009 ; Rodríguez-Martínez et al., 2011). The prevalence of *qnrB* genes seems to be overall higher than that of the other *qnr* genes. However, the *qnrS* genes are very frequently identified in *Salmonella* sp., suggesting that they could represent a significant resistance trait along the food chain. For instance, a recent international survey (13 European countries) identified a *qnrS* gene in 10% of the *Salmonella* sp. collection (Veldman et al., 2011).

Very few studies have been performed to evaluate the prevalence of the *qnrC* and *qnrD* genes since those genes have been recently identified. However, the *qnrC* has been identified from a *Proteus mirabilis* isolate from China, and its prevalence seems to be very low, at least in China (Wang et al., 2009). The *qnrD* gene has been identified in 22 out of 1215 *Salmonella* isolates obtained from different European countries, being either of human or animal isolates (Veldman et al., 2011).

Qnr in animal isolates. QnrS1 was first identified from a transferable plasmid carried by a clinical isolate of *Shigella flexneri* 2b as a source of a foodborne outbreak in Aichi prefecture, Japan (Hata et al., 2005). As described for the

qnrA1 gene, the *qnrS1* gene has been identified from several enterobacterial isolates (particularly in *Salmonella* spp.) in many countries. It has been identified in porcine *E. coli* (Szmolka et al., 2011) in Hungary, in equine *E. coli* in Czech Republic (Dolejska et al., 2011), and in poultry *E. coli* in China (Yue et al., 2011). The *qnrS2* gene was identified in a single non-Typhi *Salmonella* clinical isolate from the USA (Gay et al., 2006). Finally, the *qnrS3* variant has been identified in a single veterinary clinical *E. coli* isolate from China (GenBank accession no. EU077611).

In an interesting study including 1215 *Salmonella* and 333 *E. coli* isolates, six variants of *qnrB* were identified from 138 *qnrB* -positive isolates, most of them being obtained from turkeys (Veldman et al., 2011). The *qnrD* gene was identified in 22 *Salmonella* of eight different serovars, being mostly identified in Spain but also in Italy.

Whereas there is so far no report of *qnrA* -like genes in non-enterobacterial species, *qnrB* - and *qnrS* -like genes have been identified for instance in *Pseudomonas fluorescens* and *Aeromonas* spp. isolates, respectively (Ahmed et al., 2007 ; Cattoir et al., 2008b ; Sanchez-Cespedes et al., 2008). Interestingly, *qnrS* and mostly *qnrB* genes were identified from zoo animals, mostly including reptiles (Ahmed et al., 2007).

Qnr determinants in aquatic environments. Overall, the *qnrS* -type genes seem to be the most commonly identified acquired *qnr* genes in the environment. They have been mainly identified from waterborne species, and in particular *Aeromonas* spp. The *qnrS2* gene was identified from a mobilizable IncQ-related plasmid (pGNB2) isolated from an activated sludge

bacterial community of a wastewater treatment plant in Germany (Bonemann et al., 2006), in two strains of *Aeromonas* spp. (*Aeromonas punctata* and *A. media*) isolates from the Seine river in France (Cattoir et al., 2007b), and lately in a single clinical *Aeromonas veronii* isolate from Spain (Sanchez-Cespedes et al., 2008). In Italy, a *Citrobacter freundii* strain producing the ESBL TEM-116 was recovered from a sewage effluent (Forcella et al., 2010). This ESBL gene was encoded on a plasmid that co-harbored the *qnrB9* gene. This constitutes one of the few example showing the occurrence of a *qnr* gene from an enterobacterial isolate recovered from the environment.

The environmental species that have been found to carry *qnr* genes were mainly *Aeromonas* spp. or *Vibrio* spp. In China, an *A. punctata* strain recovered from a wastewater sample in the Shandong province carried the *qnrVC4* gene on a plasmid (Xia et al., 2010). That strain was resistant to nalidixic acid but susceptible to fluoroquinolones.

Mobile genetic vehicles

All the *qnr* genes have been identified on plasmids that vary in size ranging from ca. 7 to 320 kb (Cattoir and Nordmann, 2009 ; Strahilevitz et al., 2009) Those plasmids, and especially the *qnrA*- and *qnrB* -positive ones, often harbor other antibiotic resistance genes conferring resistance to β-lactams, aminoglycosides, chloramphenicol, tetracycline, sulfonamides, trimethoprim, and rifampin.

The *qnrA* -like genes are usually dentified as part of complex *sul1* -type class 1 integrons, that exhibit duplicated 3′-conserved sequences (3′-CS)

containing the *qacEΔ1* and *sul1* genes. Immediately upstream of *qnrA* genes, the *orf513* gene which constitutes the transposase gene of insertion sequence IS *CR1* is systematically identified (Toleman et al., 2006). The *qnrB* -like genes have been associated with either the *orf1005* gene encoding a putative transposase for *qnrB1* (Jacoby et al., 2006), the IS *CR1* element for *qnrB2* (Garnier et al., 2006 ; Jacoby et al., 2006 ; Minarini et al., 2008), *qnrB4* (Cattoir et al., 2007b ; Hu et al., 2008), *qnrB10* (Quiroga et al., 2007), and *qnrB12* (Kehrenberg et al., 2008), or an IS *Ecp1* element for *qnrB19* (Cattoir et al., 2008a). Although *qnrS* -like genes are not embedded in *sul1* -type integrons, two different genetic environments have been described, with the *qnrS1* genes being identified in association with Tn *3* -like transposon structures or the insertion sequence IS *Ecl2* (Poirel et al., 2007), and the *qnrS2* gene being part of a transposon-like structure, named mobile insertion cassette (MIC), and inserted in an ORF coding for a zinc metalloprotease (MpR) in *Aeromonas* spp. (Cattoir et al., 2008b ; Sanchez-Cespedes et al., 2008).

The *qnr* genes originate from environmental species

By screening for a collection of 48 Gram-negative clinical and environmental bacterial species (Enterobacteriaceae, Aeromonadaceae, Pseudomonadaceae, Xanthomonadaceae, Moraxellaceae, and Shewanellaceae), the origin of the *qnrA* gene was identified as being the chromosome of *Shewanella algae* (Poirel et al., 2005b). Indeed, three QnrA-like determinants (termed QnrA3, QnrA4, and QnrA5) have been identified in *S. algae* , and differ by a few amino acid substitutions from QnrA1. *S. algae* is widely distributed in aquatic environments and rarely involved in human

infections. As opposed to what it has been described for the plasmid-mediated *qnrA1* gene, the chromosomal *qnrA* -like genes were not associated with the IS *CR1* element in the chromosome of *S. algae* (Poirel et al., 2005b). Finally, The G + C content (52%) of the *qnrA* -like of *S. algae* matched exactly that of the genome of *S. algae* (Poirel et al., 2005b).

It has been shown that *Vibrio splendidus* is a source of QnrS-like determinants since chromosomal-encoded Qnr-like proteins shared about 84 and 88% amino acid identity with the plasmid-mediated determinants QnrS1 and QnrS2, respectively (Cattoir et al., 2007a). In addition, the G + C contents of *qnrS* -like genes from *V. splendidus* (ca. 45%) are close to those of *qnrS1* and *qnrS2* (ca. 44%). Although the exact progenitor species of the plasmid-encoded QnrS determinant remains unknown, the bacterial species should be closely related to *V. splendidus* and likely waterborne.

Recently, the progenitor of the *qnrB* -like genes was identified to be *Citrobacter* spp. which are enterobacterial species known to be widely present in the aquatic environment, being either human commensal bacteria or opportunistic pathogens depending on the species (Jacoby et al., 2011).

Noteworthy, it has been shown that some bacterial species belonging to the Vibrionaceae family (such as *Vibrio vulnificus* , *Vibrio parahaemolyticus* , or *Photobacterium profundum*) also possess intrinsically chromosome-encoded Qnr-like determinants (sharing 40–67% identity with the plasmid-mediated Qnr determinants) and conferring resistance to quinolones (Poirel et al., 2005a). That means that those waterborne species may also constitute potential sources of emerging PMQR genes.

Several Qnr-like pentapeptide repeat proteins have been identified in the chromosome of Gram-positive bacteria (*Enterococcus faecalis* , *Enterococcus faecium* , *Listeria monocytogenes* , *Clostridium perfringens* , *Clostridium difficile* , *Bacillus cereus* , and *Bacillus subtilis* ; Arsene and Leclercq, 2007 ; Rodriguez-Martinez et al., 2008). Amino acid sequences of these Qnr-like proteins are identical from 16 to 22% with the PMQR determinants QnrA1, QnrB1, and QnrS1 (Rodriguez-Martinez et al., 2008). Similarly, those Gram-positive species could also constitute a reservoir for Qnr-like although none of these genes has been yet identified as plasmid-located determinants.

Aminoglycoside Acetyltransferase AAC(6′)-Ib-cr

The AAC(6′)-Ib- *cr* enzyme is a PMQR determinant that has been discovered from *qnrA* -positive *E. coli* from Shanghai, China (Robicsek et al., 2006). The *aac(6′)-Ib-cr* (for *c* iprofloxacin *r* esistance) gene encodes a variant of the widespread aminoglycoside acetyltransferase AAC(6′)-Ib usually responsible for resistance to kanamycin, tobramycin, and amikacin (Strahilevitz et al., 2009). This variant possesses two substitutions at codons 102 (Trp → Arg) and 179 (Asp → Tyr) compared to the wild-type AAC(6′)-Ib, both mutations seem to be required to confer reduced susceptibility to several FQ molecules (Robicsek et al., 2006). The protein AAC(6′)-Ib-cr is able to acetylate kanamycin, tobramycin, and amikacin, but also ciprofloxacin conferring slightly higher MIC values (twofold to fourfold increase). Nevertheless, it acetylates more efficiently aminoglycosides than ciprofloxacin. Since acetylation occurs at the amino nitrogen on the piperazinyl substituent, only FQs harboring an unsubstituted piperazinyl group (such as ciprofloxacin and

norfloxacin) are substrates of AAC(6′)-Ib-cr (Robicsek et al., 2006). Although the *aac(6′)-Ib-cr* gene by itself confers low-level resistance to certain FQs, it may facilitate survival of target-site mutants with a 10-fold increase of their MPC (Cattoir and Nordmann, 2009).

The overall prevalence of *aac(6′)-Ib-cr* may range from 0. 4 to up to 34% depending on the studied human clinical strains (Robicsek et al., 2006). This gene has been reported mostly from *E. coli* and *K. pneumoniae* clinical isolates. However, it has also been identified in *Aeromonas* spp. collected in 2006 from feces of zoo animals in Japan (Ahmed et al., 2007). Recently, it has been identified in *Salmonella* spp. recovered from chickens in Japan, and in *E. coli* of poultry origin in Spain or of pig origin in China (Liu et al., 2011 ; Soufi et al., 2011 ; Du et al., 2012). Since this gene seems to be geographically widespread, stable over the time, and equally prevalent in ciprofloxacin-susceptible and -resistant strains (Park et al., 2006), its significance remains debatable. Its occurrence could also result from human contamination, as suggested with a study from Gibson et al. (2010) identifying this gene in companion animals.

The *aac(6′)-Ib-cr* gene has been identified as a form a gene cassette into *sul1* -type class 1 integrons, and has been identified both among ESBL-positive and ESBL-negative enterobacterial isolates (Cattoir and Nordmann, 2009). Its occurrence in animals and in the environment is likely frequent, but extensive surveys are still required to better evaluate their prevalence in environmental habitats.

Efflux Pump QepA

Whereas efflux pumps are chromosome-encoded, a novel PMQR determinant, *qepA* (for *q* uinolone *e* fflux *p* ump), has been identified in *E. coli* human clinical isolates from Japan and Belgium (Perichon et al., 2007 ; Yamane et al., 2007). This gene encodes a 511-amino-acid deduced protein (53 kDa) that shares significant identity with various 14-transmembrane-segment (14-TMS) putative efflux pump belonging to the major facilitator superfamily (MFS) of proton-dependent transporters (Perichon et al., 2007 ; Yamane et al., 2007). This protein confers significant decreased susceptibility to the hydrophilic quinolones (e. g., norfloxacin, ciprofloxacin, and enrofloxacin) with an 8- to 32-fold increase of MICs as compared to a wild-type susceptibility profile (Yamane et al., 2007). On the opposite, QepA protein does not significantly modify MICs of moderately hydrophilic (e. g., pefloxacin, sparfloxacin, levofloxacin, moxifloxacin) and hydrophobic (e. g., nalidixic acid) quinolones (Perichon et al., 2007 ; Yamane et al., 2007).

The occurrence of QepA among human clinical isolates seems to be quite limited according to the few studies that have been conducted on this subject worldwide. However, its occurrence in animals might be significant. A study performed on *E. coli* isolates from pigs in China showed that 28 (58. 3%) out of 48 16S rRNA methylase RmtB-producing *E. coli* isolates were *qepA* -positive suggesting a strong linkage between *qepA* and *rmtB* genes (Liu et al., 2008). RmtB confers resistance to all aminoglycosides (except streptomycin) by decreasing the affinity of the ribosome for the antibiotic after N7-methylation at the G1405 within the 16S rRNA (Perichon et al., 2007).

Other *E. coli* isolates from pigs in China have been reported as co-expressing the *qepA* , *qnrS2* , and *aac(6′)-Ib-cr* genes (Liu et al., 2008). This co-expression of several PMQR determinants may facilitate the selection of mutants under selective pressure of antimicrobial agents. QepA-producing enterobacterial isolates were also identified from pets in China (Deng et al., 2011). In Nigeria, an *E. coli* strain recovered from chicken co-harbored a *qepA* and a *qnrB* gene (Fortini et al., 2011).

The natural reservoir of *qepA* remains unknown. However, it may be *Actinomycetales* species since QepA had significant amino acid identity with likely membrane transporters of the members of the order of *Actinomycetales* (such as *Streptomyces globisporus* , *Streptomyces coelicolor* , *Nocardia farcinica* , or *Polaromonas* spp.), and its high GC% content (72%) is compatible with this origin.

Efflux Pump OqxAB

The OqxAB multidrug resistance mechanism was initially identified from *E. coli* strains recovered from swine manure (Hansen et al., 2004). The identified plasmid harbored the *oqxA* and *oqxB* genes that are similar to genes encoding resistance–nodulation–cell-division efflux systems. That plasmid conferred resistance to olaquindox that is a veterinary growth promoter. Then, it was shown to mediate resistance to other molecules, such as chloramphenicol, nalidixic acid, and ciprofloxacin (Hansen et al., 2007). In Denmark, a retrospective study showed that nine out of 156 *E. coli* strains isolated from pigs were positive for the *oqxA* gene (Hansen et al., 2005). Recently, a Chinese study showed that 39% of the *E. coli* isolates recovered from sows, piglets, weaners, and boars in swine farms, and chicken in

chicken farms harbored the *oqxAB* gene (Zhao et al., 2010). An OqxAB-positive *E. coli* strain was also identified from a liver sample of a diseased chicken in China (Liu et al., 2008). Interestingly, another Chinese study reported a series of *K. pneumoniae* isolates in which the *oqxAB* genes were actually chromosomally located (Kim et al., 2009).

Discussion

The discovery of a series of PMQR determinants within the last 10 years further raised out a novel issue regarding resistance to quinolones. Indeed, whereas such resistance was supposed to be only vertically transmitted, the occurrence of those PMQR encoding genes show that it may be also horizontally mediated. Noteworthy, and even if the first research interests focused on the impact and relevance of PMQR genes among human clinical isolates, subsequent studies rapidly showed that they were also of main concern in animal and environmental strains. Such observation raises out several questions: are there relationships between quinolones in the environment that are poorly biodegraded and the prevalence of those resistance mechanisms? Are those resistance mechanisms really new and emerging? Which is the extend of the interplay between the situation observed in the environment and the current clinical concerns?

The heavy use of quinolones in animals and in particular in fish farming might likely have played a role in the selection of some resistance mechanisms. This may have impacted the fauna itself, and as a consequence the environment through contamination of aquatic habitats, but that speculation remains debatable. A recent study showed that there

was no correlation between the occurrence of FQ-resistant bacteria in aquatic environments and the FQ contamination in Vietnam and Thailand (Takasu et al., 2011). However, the authors designed their study by selecting FQ-resistant bacteria with high level of resistance (more than 16 mg/l), that is not a correct criteria when focusing on PMQR only conferring decreased susceptibility to FQ.

The fact that most if not all PMQR encoding genes originate from bacterial species that are naturally present in the environment, and in particular in the aquatic one, likely suggests that this latter may represent the main source of the problem. This is indeed probable that genetic events leading to the mobilization of the resistance gene from the natural reservoir (the progenitor or the donor) to the recipient (the target plasmid or the target strain) occur in those environments where the donor is numerous.

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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