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REVIEW

A Systematic Review of Multi-decade Antibiotic Resistance Data for Ocular Bacterial Pathogens in the United States

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ABSTRACT

Introduction: Since 2009, the Antibiotic Resistance Monitoring in Ocular Microorganisms (ARMOR) surveillance study has been assessing in vitro antibiotic resistance for bacterial isolates sourced from ocular infections in the US. The main goal of this systematic review was to compare in vitro resistance data for ocular pathogens from published US studies with the most recently published data from the ARMOR study (2009–2018) and, where possible, to evaluate trends in bacterial resistance over time over all studies.

Methods: A literature search was conducted using MEDLINE®, BIOSIS Previews®, and EMBASE® databases (1/1/1995–6/30/2021). Data were extracted from relevant studies and antibiotic susceptibility rates for common ocular pathogens (*Staphylococcus aureus*, coagulase-negative staphylococci [CoNS], *Streptococcus pneumoniae, Pseudomonas aeruginosa*, and *Haemophilus influenzae*), longitudinal changes in susceptibility, and multidrug resistance (MDR) were compared descriptively.

Results: Thirty-two relevant studies were identified. High in vitro resistance was found among *S. aureus* and CoNS to fluoroquinolones, macrolides, and methicillin/oxacillin across studies, with high rates of MDR noted, specifically among methicillin-resistant staphylococci. Data from studies pre-dating or overlapping the early years of ARMOR reflected increasing rates of *S. aureus* resistance to fluoroquinolones, macrolides, methicillin/oxacillin, and aminoglycosides, while the ARMOR data suggested slight decreases in resistance to these classes between 2009 and 2018. Overall, methicillin-resistant *S. aureus* (MRSA) prevalence peaked from 2005 to 2015 with a possible decreasing trend in more recent years.

Discussion and Conclusions: Data from local and regional US datasets were generally consistent with data from the national ARMOR surveillance study. Continued surveillance of ocular bacterial pathogens is needed to track trends such as methicillin resistance and MDR prevalence and any new emerging antibiotic resistance phenotypes. Susceptibility data from

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ARMOR can inform initial choice of therapy, especially in practice areas where local antibiograms are unavailable.

Keywords: Antibiotic resistance; Conjunctivitis; Endophthalmitis; Keratitis; MRSA; Multidrug resistance; Ocular; Surveillance

Key Summary Points

In vitro antibiotic susceptibilities for common ocular pathogens from 32 published US studies spanning multiple decades were reviewed and compared against rates from the first 10 years of the ongoing Antibiotic Resistance Monitoring in Ocular Microorganisms (ARMOR) study (2009–2018), the only currently active nationwide surveillance program specific to ocular pathogens.

Across all studies, high in vitro resistance to fluoroquinolones, macrolides, and methicillin/oxacillin was found among staphylococci, and multidrug resistance was prevalent among methicillin-resistant staphylococci.

Studies pre-dating or slightly overlapping the early years of the ARMOR study reported increasing rates of in vitro resistance among *Staphylococcus aureus* to fluoroquinolones, macrolides, methicillin/oxacillin, and aminoglycosides, while the more recent ARMOR data suggested slight decreases in resistance to these classes between 2009 and 2018.

Other than temporal changes in susceptibility, ARMOR study data were consistent with other locally and regionally reported US susceptibility data validating the use of ARMOR study findings for empiric therapy decision-making in areas with no local antibiograms.

INTRODUCTION

Antibiotic resistance among bacteria is an ongoing concern in all fields of medicine, including ophthalmology. The Centers for Disease Control and Prevention characterizes antibiotic resistance as a leading public health threat and a priority of global significance [1]. While resistance in ocular infections may not be life-threatening, as it may be in other infectious diseases, it can lead to treatment failures that result in morbid consequences, such as blindness or even loss of the affected eye [2–13].

Initial choice of therapy for a bacterial ocular infection is almost always made without the benefit of culture and sensitivity results, because cultures are infrequently obtained as part of routine medical care (e.g., conjunctivitis), because of the costs of culturing and sensitivity testing, and/or because results take time, thus potentially delaying treatment in cases where such delays are unacceptable (e.g., keratitis, endophthalmitis). As a result, it is commonplace for treatment to be selected empirically based on knowledge of likely ocular pathogens for the condition being treated and their antibiotic susceptibility profiles. Antibiotic susceptibility data, whether from local/regional studies or from large nationwide surveillance programs, can be an important tool to monitor clinically relevant resistance profiles and track the emergence of any new resistance phenotypes in response to prescribing habits, thus helping guide the selection of initial therapy.

The Ocular Tracking Resistance in US Today (Ocular TRUST) study was the first nationwide surveillance program to track in vitro resistance specifically for bacterial isolates from ocular tissue sources. Ocular TRUST was conducted in the US for only 4 years (2005–2008) [14–16]. During the study time frame, the data indicated levels of methicillin resistance among *S. aureus* and CoNS isolates ranging from 17 to 54% and from 57 to 62%, respectively, as well as multidrug resistance (MDR) to other antibiotic classes.

The Antibiotic Resistance Monitoring in Ocular micRoorganisms (ARMOR) surveillance study was initiated in 2009. It is the only

ongoing and currently active nationwide surveillance study in the US specific to common ocular bacterial pathogens. The ARMOR study evaluates clinically relevant isolates of *Staphylococcus aureus*, coagulase-negative staphylococci (CoNS), *Streptococcus pneumoniae, Pseudomonas aeruginosa*, and *Haemophilus influenzae* sourced from any ocular tissue as part of routine medical care. On a yearly basis, predefined numbers of ocular isolates are obtained from community hospitals, academic or university hospitals, specialty or ocular centers, and reference laboratories across the US. Detailed methodology of the ARMOR study and various data analyses at different time points have been published [17–24]. Cumulatively over its first 10 years (2009–2018), the ARMOR study analyzed the in vitro antibiotic susceptibility profiles of > 6000 ocular isolates from throughout the US [25].

Surveillance data, whether local or national, are only useful if considered reliable and if shown to have representative value for a given clinical situation. This review was designed to comprehensively review published ocular pathogen in vitro antibiotic susceptibility data from local and/or regional US studies and compare the study findings against those obtained during the first 10 years of the ARMOR study (2009–2018). The primary goal of this review was to evaluate, at least descriptively, the representativeness of the nationwide ARMOR dataset to the more localized datasets. The analysis also allowed for a broad assessment of ongoing cross-study trends in antibiotic resistance patterns.

METHODS

This review article is based on published studies and does not contain any data from new studies with human participants or animals performed by any of the authors.

Search Strategy

MEDLINE®, EMBASE®, and BIOSIS Previews® databases were used to search the titles and abstracts of studies carried out in human subjects and published in English in scholarly journals between January 1, 1995 through June 30, 2021. The following search terms were used with truncations(*) as indicated: (Polybacteria* OR microbial OR bacteria* OR microbiologic* OR etiology OR epidemiology) AND (antibiotic OR fluoroquinolon* OR aminoglycoside* OR antibacterial OR antimicrobial) AND (resistan* OR susceptibility OR susceptible OR sensitivity* OR spectrum OR minimum inhibitory concentration) AND (ophthalm* OR endophthalmitis OR cornea* OR ocular OR keratitis OR conjunctiv* OR intraocular OR blepharitis) AND (infection* OR infectious OR isolat* OR pathogen* OR microorganism*). News reports and case studies were excluded from search results.

The initial search identified 1109 citations from MEDLINE®, 1688 citations from EMBASE®, and 637 citations from BIOSIS Previews®. Following the removal of duplicates across databases, abstracts, and full papers when necessary, were then reviewed to exclude publications with any of the following characteristics: non-US studies; studies focused solely on bacterial organisms and/or antibiotics not included in ARMOR; studies without organism-specific susceptibility data; studies focused on non-clinically relevant (non-pathogenic) bacterial organisms (e.g., normal flora); studies that did not have a minimum of 20 isolates for at least one bacterial species included in ARMOR; studies that separated data by, or limited data to, unique patient or organism characteristics or situations (e.g., prior use of antibiotics or purposeful selection of organisms with certain resistance characteristics such as fluoroquinolone or vancomycin resistance); studies in which more than half of the data collection years preceded 1995; review papers; and ARMOR-related datasets that were published prior to the 10-year analysis [25]. Reference lists in relevant publications were reviewed to identify additional articles for inclusion.

Data Analysis

Published surveillance data from local/regional studies were compared descriptively against corresponding data from the 10-year ARMOR

dataset. The primary focus was cross-study antibiotic susceptibility patterns for *S. aureus*, CoNS, *S. pneumoniae, P. aeruginosa,* and *H. influenzae* isolates, the bacterial pathogens that are specifically collected in ARMOR. Wherever possible, cross-study susceptibility data were compared within categories of the same ocular tissue or clinical diagnosis corresponding to that tissue (e.g., conjunctivitis/conjunctiva; keratitis/cornea; endophthalmitis/intraocular [aqueous or vitreous humor]).

Secondary cross-study analyses included MDR among staphylococci, longitudinal changes in susceptibility over time, and minimum inhibitory concentration (MIC) data. Other than in vitro antibiotic susceptibility data, which were a prerequisite for study inclusion, not every study reported data relevant for all secondary analyses.

Antibiotic susceptibility analyses were limited to drugs and classes of drugs assessed in ARMOR, including fluoroquinolones, macrolides, chloramphenicol, the beta-lactam oxacillin, tetracycline, aminoglycosides, trimethoprim, and vancomycin. For studies reporting susceptibility data for multiple drugs per class, the default drug chosen was aligned with that used in the ARMOR study to define class resistance, namely: ciprofloxacin for fluoroquinolone resistance (moxifloxacin if ciprofloxacin was not reported); azithromycin for macrolide resistance (erythromycin if azithromycin was not reported); and tobramycin for aminoglycoside resistance. In the analysis of all published data, including ARMOR, methicillin resistance was defined by resistance to oxacillin or methicillin. Multidrug resistance was defined as resistance to at least one antimicrobial agent in at least three or more drug classes.

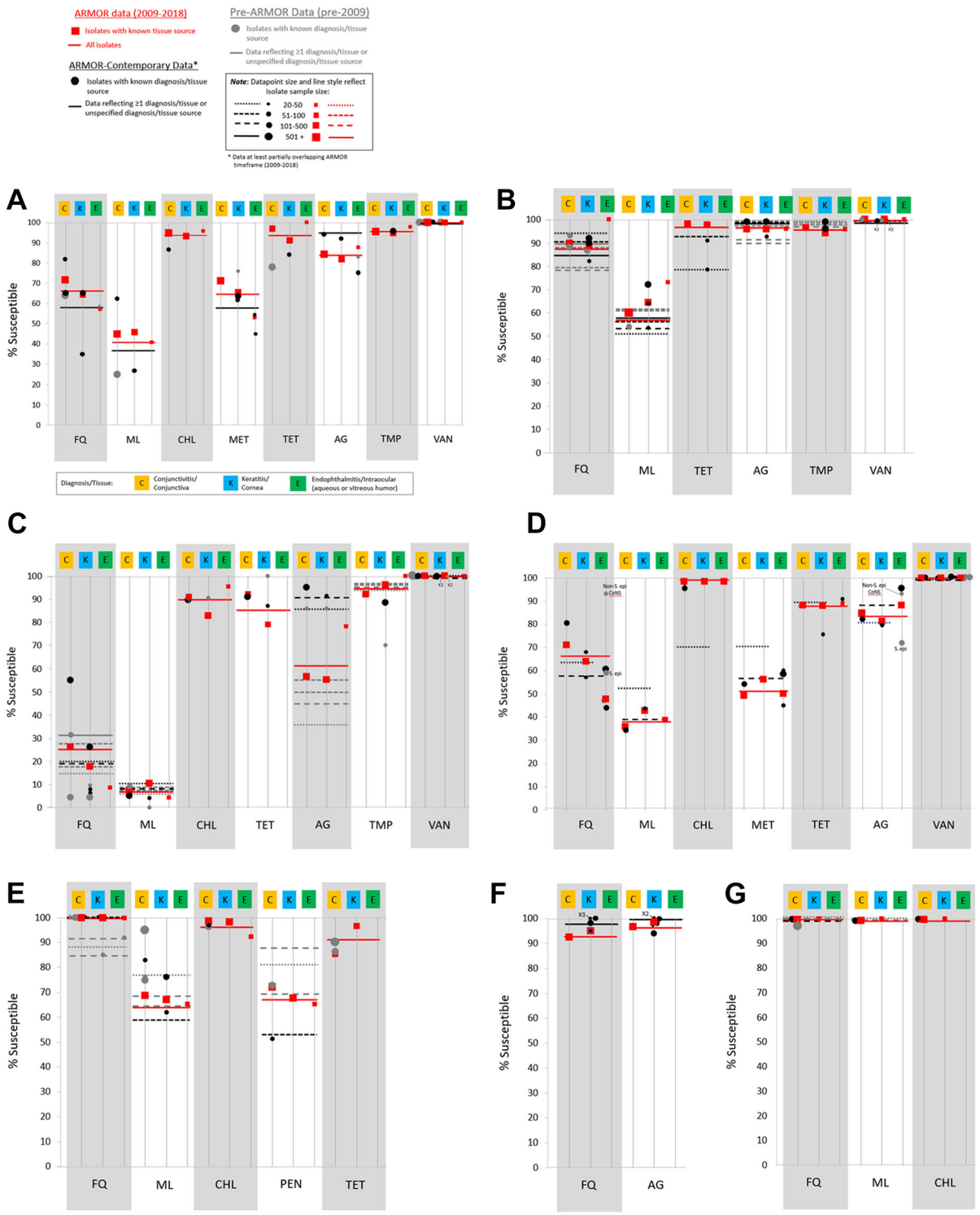
RESULTS

Antibiotic Class Susceptibility

The literature search identified 32 studies with relevant in vitro antibiotic susceptibility data that could be compared to data from the ARMOR study [8, 14–16, 26–53]. Figure 1 illustrates antibiotic class in vitro susceptibilities by ocular pathogen and diagnosis/ocular tissue source, where available, for these US studies and the ARMOR study. Numerical values for each data point can be found in Table S1 in the Supplemental Material. Note that in the 10-year ARMOR dataset, the ocular tissue source (conjunctiva, cornea, aqueous humor/vitreous humor) was known for 51% of isolates. Thus, Fig. 1 presents ARMOR data both for all isolates overall regardless of tissue source and by ocular tissue source where known. Also, unless stated otherwise, ARMOR data cited in the following paragraphs reflect that for the overall ARMOR dataset (i.e., regardless of diagnosis/tissue source).

In the ARMOR dataset, 66.5% of *S. aureus* isolates were susceptible to fluoroquinolones; other studies reported percentages ranging from 34.7 to 81.8% (Fig. 1A). For ARMOR isolates with known tissue source, susceptibility to these antibiotics varied by tissue source: endophthalmitis (57.1%), keratitis (64.3%), and conjunctivitis (71.6%). In ARMOR, 40.3% of *S. aureus* isolates overall were susceptible to macrolides, with other studies ranging from 25 to 62.1%. As for methicillin resistance, 65.1% of *S. aureus* isolates in ARMOR were susceptible to oxacillin, while other studies ranged from 45.0 to 76%. Methicillin-resistant *S. aureus* (MRSA) rates tended to be higher among ARMOR isolates from endophthalmitis (46.9%) and keratitis (34.3%) compared to conjunctivitis (28.9%). ARMOR and other studies consistently indicated high susceptibility of *S. aureus* to chloramphenicol (ARMOR, 94.3%; others, 86.4%), tetracycline (ARMOR, 93.9%; others, 78.0–84.0%), aminoglycosides (ARMOR, 84.4%; others, 75.0–95.0%), trimethoprim (ARMOR, 95.7%; others, 95.7%), and vancomycin (ARMOR, 100%; others, 99–100%).

Susceptibility data for methicillin-susceptible *S. aureus* (MSSA) isolates (Fig. 1B) showed a high degree of cross-study similarity with high susceptibility to most antibiotics reported, including fluoroquinolones (ARMOR, 88.6%; others, 79.9–96.0%), tetracycline (ARMOR, 97.1%; others, 78.6–94.1%), aminoglycosides (ARMOR, 96.7%; others, 91.9–100%), trimethoprim (ARMOR, 96.3%; others, 96.0–100%), and


ARMOR data (2009-2018)
Isolates with known tissue source
All isolates
ARMOR-Contemporary Data*
Isolates with known diagnosis/tissue source
Data reflecting ≥1 diagnosis/tissue or unspecified diagnosis/tissue source
Pre-ARMOR Data (pre-2009)
Isolates with known diagnosis/tissue source
Data reflecting ≥1 diagnosis/tissue or unspecified diagnosis/tissue source
Note: Datapoint size and line style reflect isolate sample size:
20-50
51-100
101-500
501 +
* Data at least partially overlapping ARMOR timeframe (2009-2018)
A
B
C
D
E
F
G
% Susceptible
FQ
ML
CHL
MET
TET
AG
TMP
VAN
PEN
Diagnosis/Tissue:
C Conjunctivitis/ Conjunctiva
K Keratitis/ Cornea
E Endophthalmitis/Intraocular (aqueous or vitreous humor)

◀**Fig. 1** Antibiotic class in vitro susceptibility of common ocular bacterial pathogens (US studies). Data points represent the percentages of pathogens susceptible to the antibiotic classes indicated along the bottom of the figure. Where reported as such, data are presented by ocular diagnosis/tissue source (top labels C, K, E; see explanatory legend below panel A). Data without a known ocular diagnosis/tissue source and/or data inclusive of multiple diagnoses/tissue sources are depicted by horizontal lines spanning the antibiotic category. Red squares/lines represent ARMOR data[a]; black circles/lines represent other published data with time frames at least partially contemporary with ARMOR (2009–2018); gray circles/lines represent other published data with time frames exclusively older than ARMOR (pre-2009). For studies reporting resistance rates by individual year only, most recent year data are reflected. Only studies with pathogen samples consisting of $\geq$ 20 isolates per species are included. Source data can be viewed in Table S1 of the Supplemental Material. *AG* aminoglycosides, *CHL* chloramphenicol, *CoNS* coagulase-negative staphylococci, *FQ* fluoroquinolones, *MET* methicillin/oxacillin, *ML* macrolides, *MRSA* methicillin-resistant *Staphylococcus aureus*, *MSSA* methicillin-susceptible *Staphylococcus aureus*, *PEN* penicillin, *TET* tetracycline, *VAN* vancomycin. [a]Note: For the ARMOR study, the horizontal data lines reflect *all* ARMOR data for that pathogen/antibiotic class combination and include the tissue source-specific data represented by the red square plot points in the same categories. Tissue source was unknown for about half (49%) of all isolates collected in ARMOR. **A** *S. aureus*. **B** MSSA. Note: Markers labeled "X2" indicate the presence of 2 data points with identical values at the indicated plot point. **C** MRSA. Note: Markers labeled "X2" indicate the presence of 2 data points with identical values at the indicated plot point. **D** CoNS. S. epi = *Staphylococcus epidermidis*. **E** *S. pneumoniae*. **F** *P. aeruginosa*. Note: Markers labeled "X2" or "X3" denote the presence of 2 or 3 data points, respectively, with identical values at the indicated plot point. **G** *H. influenzae*

vancomycin (ARMOR, 100%; others, 99.0–100%). For the macrolide class, MSSA isolates demonstrated relatively lower susceptibility percentages (ARMOR, 58.2%; others, 52.0–72.0%).

Data for MRSA isolates showed low susceptibility to fluoroquinolones (ARMOR, 25.5%; others, 4.3–55.0%) and macrolides (ARMOR, 7.1%; others, 0–10.7%) across studies (Fig. 1C). Conversely, susceptibilities were uniformly high for chloramphenicol (ARMOR, 90.4%; others, 90.0–90.5%), tetracycline (ARMOR, 85.0%; others, 87.2–100%), trimethoprim (ARMOR, 94.5%; others, 70—96.1%), and vancomycin (ARMOR, 100%; others, 99.0–100%). Susceptibility data for MRSA isolates to aminoglycosides showed a high degree of variability among studies, with ARMOR data being approximately mid-range between susceptibility data points from other studies (ARMOR 61.6%; others, 36.4—95.0%).

For CoNS isolates, the collective data indicated moderate susceptibility to fluoroquinolones (ARMOR, 65.8%; others, 44–93.0%), macrolides (ARMOR, 38.6%; others, 34.3–52%), and methicillin/oxacillin (ARMOR, 50.7%; others, 45–70.4%) (Fig. 1D). In the ARMOR study, susceptibility to fluoroquinolones appeared to be impacted by tissue source, with endophthalmitis isolates (47.8%) showing lower susceptibility to these antibiotics compared to keratitis (63.9%) or conjunctivitis (70.8%) isolates. Overall, susceptibility was high to chloramphenicol (ARMOR, 98.8%; others, 70–95.5%), tetracycline (ARMOR, 87.6%; others, 75.7–90.9%), aminoglycosides (ARMOR, 82.5%; others, 72–95.3%), and vancomycin (ARMOR, 100%; others, 99–100%). In two non-ARMOR studies, susceptibility rates of *Staphylococcus epidermidis* endophthalmitis isolates were notably lower than those for non-*S. epidermidis* CoNS isolates for fluoroquinolones and aminoglycosides (Fig. 1D).

Data for *S. pneumoniae* isolates suggested a high degree of susceptibility to fluoroquinolones (ARMOR, 99.8%; others, 85.0–100%), chloramphenicol (ARMOR, 96.9%; others, 96.4–97.1%), and tetracycline (ARMOR, 91.3%; others, 86.4–90.0%), while macrolides (ARMOR, 63.7%; others, 59.0–95.0%) and penicillin (ARMOR, 67.8%; others, 51.4–88%) were characterized by moderate to high susceptibility and less congruence between studies (Fig. 1E). For the macrolides and penicillin, lower susceptibility percentages were noted among published studies at least partially contemporary with ARMOR compared to those with exclusively pre-2009 data.

For *P. aeruginosa* isolates, published susceptibility percentages for fluoroquinolones

(ARMOR, 92.8%; others, 95.0–100%) and aminoglycosides (ARMOR, 97.1%; others, 94–100%) were high and consistent between studies (Fig. 1F).

Published data for *H. influenzae* isolates showed uniformly high susceptibility, with almost all studies reporting close to 100% susceptibility to fluoroquinolones, macrolides, and chloramphenicol (Fig. 1G).

Multidrug Resistance

Including the ARMOR study, only five studies reported data pertaining to the prevalence of MDR. Three studies reported rates of MDR among MRSA isolates within overlapping time frames, ranging from 42.9% (2010–2015 data from New York) [44] to 91.5% (2006–2016 data from Florida) [46] compared with 75.4% reported in the ARMOR study [25]. Furthermore, while a specific percentage was not cited, Asbell et al. reported that "MRSA was resistant to almost every agent, including the newer fluoroquinolones" in The Surveillance Network nationwide study conducted in the US from 2000 to 2005 [27]. The ARMOR study (2009–2018) noted MDR in 41.2% of all CoNS isolates and 73.7% of all methicillin-resistant CoNS (MRCoNS) isolates nationwide [25]. Schechter et al. [48] reported that 30% of *S. epidermidis* isolates and 75% of methicillin-resistant *S. epidermidis* (MRSE) isolates were multidrug-resistant (2017 data).

Longitudinal Changes in Antibiotic Susceptibilities

Including the ARMOR study, nine studies reported statistically significant longitudinal changes in antibiotic susceptibilities for specific pathogens (Table 1). For *S. aureus,* earlier studies suggested increasing resistance to multiple classes of antibiotics over time, including fluoroquinolones, macrolides, the beta-lactams methicillin/oxacillin, and aminoglycosides, while the ARMOR 2009–2018 study found decreasing resistance to each of these antibiotic classes [25]. Marangon et al. [39] reported an increase in resistance to fluoroquinolones from 7.5 to 39.6% between 1990–2001. An increase in resistance of *S. aureus* isolates to fluoroquinolones from 6 to 36% was observed between 1997 and 2008 (change of 2.57% per year) by Adebayo et al. [26]. In the ARMOR study, fluoroquinolone resistance among *S. aureus* isolates decreased 2.24% per year between 2009 (38.5%) and 2018 (30.0%) [25]. Macrolide resistance among *S. aureus* isolates increased 3.74% per year between 1997 (~ 20%) and 2008 (~ 75%) in one study [26] but was shown to decrease 1.4% per year between 2009 (61.5%) and 2018 (56.3%) in the ARMOR dataset [25].

Increases in *S. aureus* resistance to beta-lactam antibiotics (generally oxacillin) were reported in the time periods from 1993–1996 (18.4%) to 2009–2012 (38.3%) (+ 19.9%) [29], from 1992–1996 (23%) to 2007–2011 (55%) (+ 32%) [32], from 2000 (29.5%) to 2005 (41.6%) (+ 12.1%) [27], and from 1997 (~ 2%) to 2008 (~ 40%) (+ 3.69% per year) [26]. In the ARMOR study, oxacillin resistance among *S. aureus* isolates decreased by 2.16% per year between 2009 (39.0%) and 2018 (29.3%) [25]. Figure 2 presents data points pertaining to reported prevalence of MRSA (resistance to oxacillin or methicillin) as a proportion of *S. aureus* isolates by year. Overall, reported prevalence was highest during the periods from 2005 to 2015 and shows some signs of decreasing in most recent years.

Aminoglycoside resistance among *S. aureus* isolates increased by 0.36% per year from 1997 (~ 7%) to 2008 (~ 10%) as reported by Adebayo et al. [26] but decreased by 1.84% per year from 2009 (23.5%) to 2018 (10.7%) in the ARMOR study [25].

For MRSA isolates, older studies reported trends of increasing resistance among MRSA to fluoroquinolones, including a 27.9% increase between 1990 (55.8%) and 2001 (83.7%) [39] and an increase from approximately 10% during 1993–1996 to approximately 45% during 2009–2012 [29]; the ARMOR study noted no significant changes among MRSA in resistance rates to fluoroquinolones, macrolides, chloramphenicol, or tetracycline between 2009 and 2018, and found decreasing resistance in MRSA

Table 1 Studies reporting significant[a] longitudinal changes in bacterial resistance over time, sorted by end date of data collection, most recent to least recent

	Time frame	FQ	ML	CHL	MET/PEN	TET	AG
S. aureus							
Asbell et al. (2020) [25] (ARMOR)	2009–2018	↓ 2.24% PY (CIP) 2009: 38.5% 2018: 30.0%	↓ 1.44% PY (AZI) 2009: 61.5% 2018: 56.3%	↓ 0.54% PY 2010: 6.6% 2018: 4.6%	↓ 2.16% PY (OXA) 2009: 39.0% 2018: 29.3%	No change	↓ 1.84% PY (TOB) 2009: 23.5% 2018: 10.7%
Oydanich et al. (2017) [44]	2010–2015				No change		
Hsu et al. (2019) [36]	1993–2013				No change		
Chang et al. (2015) [29]	1993–2012				↑ 19.9% (OXA) 1993–1996:18.4% 2012: 38.3%		
Gentile et al. (2014) [32]	1987–2011				↑ 37% (MET/OXA[b]) 1987–1991: 18% 2007–2011: 55%		
Adebayo et al. (2011) [26]	1997–2008	↑ 2.57% PY (CIP) 1997: ~ 6% 2008: ~ 36%	↑ 3.74% PY (ERY) 1997: ~ 20% 2008: ~ 75%		↑ 3.69% PY (OXA) 1997: ~ 2% 2008: ~ 40%		↑ 0.36% PY (TOB) 1997: ~ 7% 2008: ~ 10%
Asbell et al. (2008) [27]	2000–2005				↑ 12.1% (unknown) 2000: 29.5% 2005: 41.6%		
Marangon et al. (2004) [39]	1990–2001	↑ 32.1% (CIP) 1990: 7.5% 2001: 39.6%					
MRSA							
Asbell et al. (2020) [25] (ARMOR)	2009–2018	No change (CIP)	No change (AZI)	No change		No change	↓ 2.53% PY (TOB) 2009: 53.8% 2018: 27.4%
Chang et al. (2015) [29]	1993–2012	↑ ~ 35% (MXF) 1993–1996: ~ 10% 2009–2012: ~ 45%					
Marangon et al. (2004) [39]	1990–2001	↑ 27.9% (CIP) 1990: 55.8% 2001: 83.7%					
CoNS							

Table 1 continued

	Time frame	FQ	ML	CHL	MET/PEN	TET	AG
Asbell et al. (2020) [25] (ARMOR)	2009–2018	↓ 1.38% PY (CIP) 2009: 45.8% 2018: 33.6%	No change (AZI)	No change	No change (OXA)	No change	↑ 0.71% PY (TOB) 2009: 19.4% 2018: 22.1%
Stringham et al. (2017) [51]	1995–2016	↑28% (CIP) 1995–1999: 28% 2010–2016: 56%					
Gentile et al. (2014) [32]	1987–2011				↑ 24% (S epi) (MET/OXA[a]) 1987–1991: 31% 2007–2011: 55%		
P. aeruginosa							
Asbell et al. (2020) [25] (ARMOR)	2009–2018	No change (CIP)					No change (TOB)
S. pneumoniae							
Asbell et al. (2020) [25] (ARMOR)	2009–2018	No change (MXF)	No change (AZI)	No change	No change (PEN)	No change	
Adebayo et al. (2011) [26]	1997–2008		↑ 0.38% PY (ERY) 1997: ~ 1% 2008: ~ 5%			↑ 0.85% PY 1997: ~ 1% 2008: ~ 10%	
H. influenzae							
Asbell et al. (2020) [25] (ARMOR)	2009–2018	No change (CIP)	No change (AZI)	No change		No change	
Adebayo et al. (2011) [26]	1997–2008					↑ 2.18% PY 1997: ~ 3% 2008: ~ 25%	

For drug class categories, the specific drug reflected by the data is indicated. Change values (beginning and end of reporting period) are provided for context. Changes are shown as the absolute percent change over the indicated time period or as annualized per year (PY) changes

"Arrows only" reflect studies that reported a significant change in resistance but did not provide data

AG aminoglycosides, *AZI* azithromycin, *CHL* chloramphenicol, *CIP* ciprofloxacin, *CoNS* coagulase-negative staphylococci, *ERY* erythromycin, *FQ* fluoroquinolones, *MET* methicillin/oxacillin, *ML* macrolides, *MRSA* methicillin-resistant *Staphylococcus aureus*, *MXF* moxifloxacin, *OXA* oxacillin, *PEN* penicillin, *PY* per year, *TET* tetracycline, *TOB* tobramycin

[a] $P < 0.05$

[b] Methicillin 1987–1992; Oxacillin 1992–2011

isolates to aminoglycosides between 2009 and 2018 [25].

For CoNS isolates, one study reported a 28% increase in CoNS resistance to fluoroquinolones between the time periods 1995–1999 (28%) to 2010–2016 (56%) [51]. In addition, data from the Bascom Palmer Eye Institute reported CoNS resistance to ciprofloxacin increased from 10.3% during the period 1990–1994 to 60.5% during the period 2005–2011 [49, 54] (no statistics provided, thus not included in Table 1). In contrast, the ARMOR study revealed

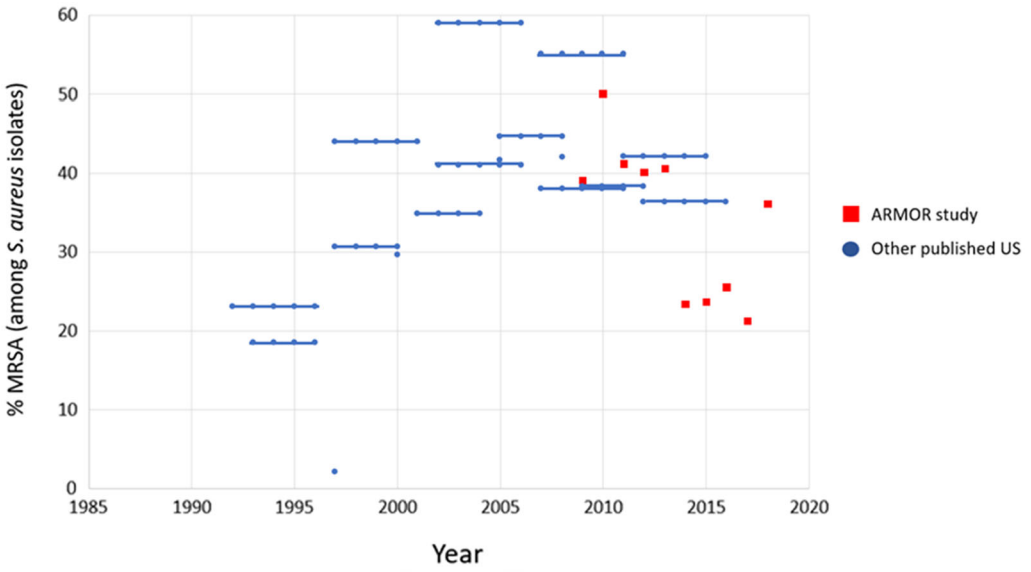


Fig. 2 Published data on prevalence of MRSA among *S. aureus* isolates by year (US studies) [25–27, 29, 32, 40, 46]. Points connected by lines reflect a single percentage reported for a range of years

decreasing resistance to fluoroquinolones by a rate of –1.38% per year between 2009 (45.8%) and 2018 (33.6%) [25]. The ARMOR study found no significant changes in CoNS resistance to oxacillin from 2009 to 2018 but did indicate a slight increase in resistance to aminoglycosides of + 0.71% per year [25]. There were no other published longitudinal findings for CoNS except a small study by Gentile et al. [32], which reported a 24% increase in *S. epidermidis* resistance to oxacillin between the periods 1987–1991 (31% resistant) and 2007–2011 (55% resistant).

For *P. aeruginosa, S. pneumoniae,* and *H. influenzae* isolates, the ARMOR 10-year data did not demonstrate any significant changes in resistance to any of the antibiotic classes tested. In one other published study that reported longitudinal data for these organisms between 1997 and 2008 [26], small increases were noted for *S. pneumoniae* resistance to macrolides (1997, ~ 1%; 2008, ~ 5%; + 0.38% per year) and tetracycline (1997, ~ 1%; 2008, ~ 10%; + 0.85% per year) and for *H. influenzae* resistance to tetracycline (1997, ~ 3%; 2008, ~ 25%; + 2.18% per year).

Minimum Inhibitory Concentrations (MICs)

Table S2 in the Supplemental Material provides MIC data that were presented in several of the studies [14, 25, 33–35, 38, 44]. Among staphylococcal isolates, where reported, vancomycin MICs were consistently low whereas macrolide MICs were consistently high. A comparison of susceptibility rates for individual fluoroquinolones reported in various published studies did not reveal many differences between individual agents (ciprofloxacin, levofloxacin, gatifloxacin, moxifloxacin; Fig. S1 in the Supplemental Material), even though reported MICs varied between them, particularly for staphylococcal isolates, with 8-methoxy fluoroquinolones demonstrating better in vitro potency in general (Table S2 in the Supplemental Material).

DISCUSSION

The ARMOR study is the only currently active nationwide surveillance program that monitors in vitro bacterial resistance to antibiotics among common ocular pathogens. Given the

importance of reliable surveillance data for guiding empiric therapy in ocular infections, the representativeness of the ARMOR data is an important consideration. In this analysis, antibiotic susceptibility data specific to ocular bacterial pathogens from US studies published in the past 25 years were compared against susceptibility data from the first ten years of the ARMOR program. Of the 32 comparative reports included in this review, all were single-center and/or regional US studies except one that was also comprised of national data, namely the Ocular TRUST study [14–16] but was conducted in the years prior to initiation of ARMOR.

Across all studies, high levels of in vitro resistance were found among *S. aureus* and CoNS to fluoroquinolones, macrolides, and methicillin/oxacillin. As expected, MSSA isolates showed high susceptibility to all antibiotic classes evaluated in all studies, except for moderate susceptibility to macrolides, while MRSA isolates were shown to have generally low susceptibility to fluoroquinolones and macrolides. In contrast to findings for staphylococci, high levels of susceptibility were observed across studies to fluoroquinolones, chloramphenicol, and tetracycline among *S. pneumoniae*, to fluoroquinolones and aminoglycosides among *P. aeruginosa*, and to fluoroquinolones, macrolides, and chloramphenicol among *H. influenzae*. Overall, ARMOR 10-year cumulative susceptibility data were generally mid-range of, or similar to, other published US susceptibility data for common ocular pathogens. Furthermore, there was generally a high degree of concordance among resistance rates across studies by ocular diagnoses/tissue sources (conjunctivitis/conjunctiva, keratitis/cornea, endophthalmitis/aqueous or vitreous humor), with few exceptions. For instance, in the ARMOR study, MSSA intraocular isolates ($n = 26$) had greater susceptibility to macrolides compared to most other studies and compared to isolates from other ocular sources in ARMOR; however, the isolates in this subset only constitute about 2% of the total ARMOR MSSA dataset. Additionally, among *S. aureus* and CoNS, there was an observed trend for lower susceptibility to fluoroquinolones among endophthalmitis/intraocular-sourced isolates than among those from other diagnoses/ocular sources. These findings may reflect greater exposure of staphylococcal intraocular isolates to the fluoroquinolone class as these antibiotics are widely used for prophylaxis of endophthalmitis, either as topical eye-drops applied before and after an intraocular procedure or as intracameral injections in the cataract surgery setting [55].

Multidrug resistance can pose a major obstacle to effective treatment, yet few of the studies reviewed reported on this phenomenon. Methicillin resistance is often a hallmark of resistance to other antibiotic classes [14, 29], and indeed three out of four MRSA and MRCoNS isolates from the ARMOR study exhibited MDR. Other relatively recent data reviewed here also reported high rates of MDR among MRSA [44, 46] and MRSE [48]. Together, these data underscore the potential challenges to the management of ocular infections caused by methicillin-resistant staphylococci, as these organisms are highly resistant to the first line of antibiotics commonly used in ophthalmology. This adds to the importance of the availability of reliable and contemporary susceptibility data. On the other hand, MRSA isolates were shown in most studies to have reasonably high rates of susceptibility to chloramphenicol, tetracycline, trimethoprim, and vancomycin. One may expect similarly high susceptibilities to these drugs among the subset of MRCoNS isolates; however, there were insufficient studies with data on this resistance phenotype group for comparison.

For *S. aureus,* the collective data from all studies suggested increasing in vitro resistance to multiple antibiotic classes over time in the 1990s and 2000s. Studies reporting data from ocular isolates collected more recently suggested a plateau and even decreasing resistance among *S. aureus* since then, most notably for methicillin/oxacillin, a finding in line with the decreasing incidence of systemic MRSA infections observed in recent years by the Center for Disease Control and a similar decreasing MRSA rate in the global SENTRY surveillance study [56, 57]. The ARMOR study, which provides the most recent data (2009–2018) of the published studies, demonstrated small but statistically significant decreases in antibiotic resistance of

S. aureus to fluoroquinolones, oxacillin, macrolides, chloramphenicol, and aminoglycosides. With the exception of chloramphenicol, these decreasing trends appear to have persisted through 2019 as reported in an interim analysis of ARMOR data [58]. Furthermore, for MRSA isolates, studies with datasets reflecting the time periods from 1990–2001 [39] and 1993–2012 [29] noted significant increases in resistance to fluoroquinolones, whereas ARMOR study isolates collected from 2009–2018 did not demonstrate any significant changes in MRSA resistance to fluoroquinolones over that time frame, which suggests that such resistance may have stabilized during those years. For CoNS, one study reported a 28% increase in CoNS resistance to fluoroquinolones from 1995 to 2016 [51], whereas the ARMOR study demonstrated a small but significant yearly decrease in CoNS resistance to fluoroquinolones for the more recent time period of 2009 to 2018 [25]. Furthermore, a 24% increase in *S. epidermidis* resistance to oxacillin was noted in one study between the time periods 1987–1991 and 2007–2011 [32], while the more recent ARMOR study found no significant change in CoNS resistance to methicillin/oxacillin between 2009 and 2018. While the comparator studies that included organisms collected prior to or in the early years of the ARMOR program found increasing rates of resistance to clinically relevant antibiotics, ARMOR findings suggest potential recent reductions (or stabilization) in antibiotic resistance among staphylococci. It is important to note that most of the comparator studies reported rates of resistance, especially to topical fluoroquinolones, in subsets of isolates recovered from specific groups of diseases where these antibiotics are widely used empirically for treatment (e.g., keratitis) or prophylaxis (e.g., endophthalmitis), while the ARMOR data on resistance trends over time were not stratified by infection type to allow evaluation of any potential disease/tissue-specific trends in the population analyzed. If the slight decreases in resistance suggested by the more recent ARMOR data are true, these positive trends might reflect improved antibiotic stewardship in clinical practice, but clearly further study is necessary to confirm these trends.

Minimum inhibitory concentrations for a given ocular isolate can be useful for comparing relative in vitro potency of specific agents, particularly for different compounds within the same drug class. Studies have suggested a correlation between MICs and clinical outcomes in patients with corneal infections [13, 59, 60], indicating that MIC data that have not been interpreted further (as susceptible, intermediate, or resistant) could also have value in choosing empiric treatment. A comparison of available MIC data in reviewed studies found that fluoroquinolone agents had similar in vitro potency against gram-negative organisms, although the newer-generation 8-methoxy fluoroquinolones (moxifloxacin and gatifloxacin) generally exhibited higher in vitro potency (lower MICs) compared to older fluoroquinolones (ciprofloxacin and levofloxacin) against gram-positive isolates, especially staphylococci. While only evaluated in ARMOR and two other studies reviewed herein, MICs for besifloxacin, an 8-chloro-fluoroquinolone FDA-approved in 2009, were typically among the lowest of the fluoroquinolones. In the 10-year ARMOR dataset, besifloxacin MICs that inhibited growth of 90% of isolates in the studied population (MIC_{90}s), were at least fourfold lower than moxifloxacin and gatifloxacin and at least 16-fold lower than ciprofloxacin and levofloxacin for gram-positive bacteria including *S. aureus*, CoNS, and *S. pneumoniae* [25]. Marketed exclusively as an ocular formulation, besifloxacin has no CLSI systemic breakpoints and was therefore not included in any susceptibility assessments in the studies reviewed here.

Although not the primary focus of this review, pathogen distributions by diagnosis/ocular tissue in identified studies were examined (**Table S3** in the Supplemental Material). While distributions by diagnoses/ocular tissues were observed to differ across studies, *S. aureus* and CoNS/*S. epidermidis* were cited as "prevalent" (one of the top five most prevalent pathogens) in all diagnoses (conjunctivitis, keratitis, and endophthalmitis) in almost every study with relevant data. As endophthalmitis often results from introduction of organisms originating from the ocular microbiota secondary to penetration of the ocular surface

through surgery or trauma [61, 62], a high rate of infection with these organisms is not surprising. *Haemophilus influenzae* was prevalent in conjunctivitis sources but not in keratitis or endophthalmitis cases. *Pseudomonas aeruginosa* was consistently reported as prevalent in keratitis; it was noted as prevalent in conjunctivitis in fewer than half of relevant studies and in none of the studies with endophthalmitis data. Thus, data from the published studies with prevalence data confirm that the bacterial pathogens selected for study in ARMOR (*S. aureus,* CoNS*, S. pneumoniae, P. aeruginosa*, and *H. influenzae*) do appear to be among the most common species isolated from various eye infections in US patients. Also, although a formal analysis was not conducted, there were no apparent differences in pathogen distribution by geography.

Among the limitations of this review is that the studies evaluated were not uniform with regard to antibiotics tested, bacterial pathogens included, and ocular diagnoses. Data included were limited to the bacterial pathogens and antibiotics tested in ARMOR, thereby excluding information on other, albeit less common, bacterial species involved in ocular infections. There were also differences in methodologies used to determine resistance profiles (e.g., MIC vs. E-test vs. disk diffusion), which could introduce slight variations in data between studies. CLSI breakpoints are occasionally updated, allowing for the possibility that isolates categorized at one time point as susceptible might have been categorized as non-susceptible at a different time point, or vice versa. As well, patient age-associated differences in ocular pathogen distributions and antibiotic susceptibilities have been observed in ARMOR analyses and other studies [17, 18, 22, 44, 63–66]; however, very few of the studies included in this review provided patient age data, thus precluding cross-study comparisons adjusting for this confounding factor and likely contributing to some of the between-study variabilities observed. Yet, it could be argued that the similarities found among much of the findings, regardless of cross-study methodology differences and control for confounding variables, add to the strength of the observations. Finally, this analysis evaluated in vitro data only, and almost none of the studies included information on clinical outcomes of microbial eradication or clinical resolution. For ocular infections, susceptibility classifications should be interpreted with an understanding of how they are determined. CLSI breakpoints used for susceptibility determinations are based on pharmacokinetics and pharmacodynamics of antibiotics when administered systemically. As there are no specific ocular breakpoints for susceptibility, systemic breakpoints are currently all that are available for assessing in vitro susceptibility even though topical ocular administration of medication is a distinct and very different milieu. Antibiotics administered topically to the eye would be expected to achieve much higher initial concentrations than concentrations achieved in the blood with systemic administration, but factors such as tear dilution and elimination from the eye can lower concentrations on the eye very rapidly. Accordingly, the clinical relevance of in vitro susceptibility data for ocular infections is unclear.

CONCLUSIONS

Overall, this review of published studies featuring in vitro susceptibility data for common ocular bacterial pathogens found high levels of in vitro resistance to fluoroquinolones, macrolides, and methicillin/oxacillin among staphylococci, as well as prevalent MDR in these pathogens, particularly among methicillin-resistant staphylococci. The collective data reviewed herein also reveal a longitudinal pattern of increasing in vitro resistance rates for ocular staphylococci to multiple classes of antibiotics over past decades, but that this trend may be potentially showing signs of reversing or stabilizing. Overall findings suggest that the ongoing national ARMOR study reports resistance data that are generally consistent with that from other studies reporting local and regional US data. As such, it lends support to the reliability of the ARMOR findings for identifying trends in susceptibility and its clinical usefulness in informing empiric therapy decision-

making, especially where local and/or current antibiograms are not available. Continued monitoring of antibiotic susceptibility data in ocular bacteria is critical to track these trends and maintain vigilance for the emergence of important resistance phenotypes.

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