Review

Antimicrobial resistance in Cambodia: a review

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ABSTRACT

Objectives: Following the launch of the Global Antimicrobial Resistance Surveillance System (GLASS), antimicrobial resistance (AMR) rates in many countries remain poorly described. This review provides an overview of published AMR data from Cambodia in the context of recently initiated national human and food-animal surveillance.

Methods: PubMed and the Cochrane Database of Systematic Reviews were searched for articles published from 2000 to 2018, which reported antimicrobial susceptibility testing (AST) data for GLASS specific organisms isolated from Cambodia. Articles were screened using strict inclusion/exclusion criteria. AST data was extracted, with medians and ranges of resistance rates calculated for specific bug-drug combinations.

Results: Twenty-four papers were included for final analysis, with 20 describing isolates from human populations. *Escherichia coli* was the most commonly described organism, with median resistance rates from human isolates of 92.8% (n = 6 articles), 46.4% (n = 4), 55.4% (n = 8), and 46.4% (n = 5) to ampicillin, 3rd generation cephalosporins, fluoroquinolones, and gentamicin respectively.

Conclusions: Whilst resistance rates are high for several GLASS organisms, there were insufficient data to draw robust conclusions about the AMR situation in Cambodia. The recently implemented national AMR surveillance systems will begin to address this data gap.

Contents

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Introduction

Antimicrobial resistance (AMR) has emerged as a major threat to human health (WHO, 2015b). Global mortality and the economic burden caused by AMR are anticipated to continue increasing if it is left unchecked, and a "post-antibiotic era" has been predicted (WHO, 2014). Southeast (SE) Asia has been identified as a region of great importance in the development and spread of AMR (Chereau et al., 2017). In Thailand, it has been estimated that 43% of deaths resulting from hospital-acquired bacteraemia were excess mortality due to multi drug resistance (Lim et al., 2016). Similarly, in Cambodia, community-acquired drug-resistant bacteraemia in children is associated with increased mortality, and results in a doubling of hospital admission costs (Fox-Lewis et al., 2018).

Poor hygiene and infection control, lack of sanitation, weak or unenforced medicines regulation, and sub-standard quality drugs have been suggested as some of the main drivers of AMR in SE Asia (Zellweger et al., 2017). In addition, intensification of agriculture and aquaculture may contribute to AMR owing to increased and unregulated use of antibiotics in these sectors as therapeutic, prophylactic, metaphylactic, and growth promotion agents (Zellweger et al., 2017). Acknowledging the diversity of these drivers, a One Health approach to tackling AMR has been encouraged (Robinson et al., 2016), and there is much work to be done to understand clearly the links between agriculture, humans, and the environment in the development and spread of AMR.

In October 2015 the World Health Organisation (WHO) launched the Global Antimicrobial Resistance Surveillance System (GLASS), a necessary contribution to the global action plan against AMR. The surveillance system currently includes eight organisms: *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Salmonella* spp., *Shigella* spp., and *Neisseria gonorrhoeae* (WHO, 2015a). Key drug classes for antimicrobial susceptibility testing (AST) include penicillins, third- and fourth-generation cephalosporins (3GC and 4GC), carbapenems, fluoroquinolones, aminoglycosides, tetracyclines, polymyxins, macrolides, and co-trimoxazole.

Similar to many other low- and middle-income countries, Cambodia has only relatively recently begun to develop diagnostic microbiological facilities, and, as capacity expands, collaboration has led to sharing of AMR data, revision of clinical practice guidelines, and development of infection control policies (Vlieghe et al., 2013c). In addition, there have been early reports of retrospective and prospective AMR surveillance from non-governmental hospitals (Fox-Lewis et al., 2018; Vlieghe et al., 2013b), and a handful of studies on animals and/or meat products (Lay et al., 2011; Nadimpalli et al., 2019a; Strom et al., 2018; Trongjit et al., 2017). To date, however, these data have not been brought together to provide a country level perspective. A national GLASS-compatible AMR surveillance system has been recently implemented in eight sentinel sites (Ministry of Health - Cambodia, 2014), and food animal AMR surveillance has also been initiated nationally (K. Osbjer, Personal Communication). This review aims to describe the recent published AMR data from Cambodia and gives a summary of key AMR patterns in the country. By focusing on the organisms identified by GLASS, and incorporating a One Health approach, the review will provide context to national AMR surveillance systems, and to similar regional initiatives.

Methods

Literature search

Searches were made of PubMed and the Cochrane Database for Systematic Reviews for articles published since 1st January 2000, and until 31st December 2018, in English language (final search date: 6th February 2019). The search query used for the Cochrane database was "Cambodia AND (antibiotic resistance OR antimicrobial resistance OR antibiotic susceptibility OR antimicrobial susceptibility)". The full PubMed search query is included in the Supplementary Methods. Additional articles were identified through manual searches of the reference lists from relevant published papers.

Study selection

The titles and abstracts of all articles retrieved by the search queries were screened by one author (TR). Articles were included for review if they reported bacterial AST on isolates from specimens collected in Cambodia, regardless of source population (e.g. human, animal, food, or environment), or context (i.e. illness or carriage). Articles were excluded if they: (1) addressed only drug resistance in non-GLASS organisms; (2) did not report phenotypic AST data; (3) reported only AST data with a specific resistance phenotype as the denominator; (4) were written as reviews or individual case reports; (5) addressed isolates from travellers or exported food products. Where the fulfilment of inclusion or exclusion criteria was not entirely clear, the paper was included for full text review and excluded at that stage if indicated.

All titles that were not excluded through title and abstract review underwent full text review by the same author (TR), with the same inclusion and exclusion criteria applied. Further exclusions were made if the AST data reported was not specific to GLASS bug-drug combinations. Articles that were written by the same research groups were assessed for the likelihood of overlapping or duplicate data sets. These groups were contacted to confirm overlaps and agree on exclusion of papers or ways to prevent duplication bias. Outstanding queries regarding paper selection were resolved by discussion with a second author (PT).

Data extraction and analysis

Data from all remaining papers were entered into a Microsoft Excel 2016 spreadsheet, including general article information (PubMed identification (PMID), first author, year of publication, and duration of data collection), isolate metadata where applicable (specimen type, population type (e.g. human), age group, community acquired infection (CAI) vs. hospital acquired infection (HAI), inpatient vs. outpatient, syndrome, and live or slaughtered animal status) and laboratory methodological information (pathogen identification, AST and breakpoints used, and laboratory accreditation). Further tables were created for the individual GLASS organisms, with resistance data entered from each paper for the GLASS specific antibiotics and antibiotic classes (see Supplementary Table S1). Intermediate susceptibility, where reported, was considered as resistant. Where susceptibility rates were reported, without resistance rates, the resistance rates were calculated as the inverse of the susceptibility rates. For _E. coli_ and _K._

pneumoniae, both gentamicin and amikacin resistance data were also captured, where available. Resistance rates for _Salmonella_ Typhi, _S._ Paratyphi A, and non-typhoidal serovars of _Salmonella enterica_ (NTS) were reported separately given differences in epidemiology and resistance profiles. Resistance rates of _S. aureus_ to cefoxitin and/or oxacillin, and rates of methicillin-resistant _S. aureus_ (MRSA), were entered together as "MRSA". Where AST results were given for more than one GLASS specific antibiotic of the same class (e.g. fluoroquinolones, 3GC, carbapenems), the rate that reflected the highest level of resistance was selected to represent the rate for that respective class. The exception to this was with regard to the aminoglycosides, which were reported individually, since gentamicin and amikacin show markedly different resistance rates. Amikacin, a semisynthetic aminoglycoside, has structural differences that render it refractory to most aminoglycoside modifying enzymes (Ramirez and Tolmasky, 2017). Where articles quoted rates for an antibiotic class, without stating the specific antimicrobial(s) tested, this rate was accepted. As a result of paucity and heterogeneity of data, only the median and range of resistance proportions for each organism-drug combination were reported, as calculated by Excel. Meta-analysis to calculate summary estimates and test for heterogeneity was not feasible, nor was testing for reporting bias.

Results

One-hundred-and-seventy-six articles were identified from the initial literature search. This was reduced to 42 after screening, and then 31 after full text review (Figure 1). After assessment for overlapping or duplicate data sets, seven articles were excluded
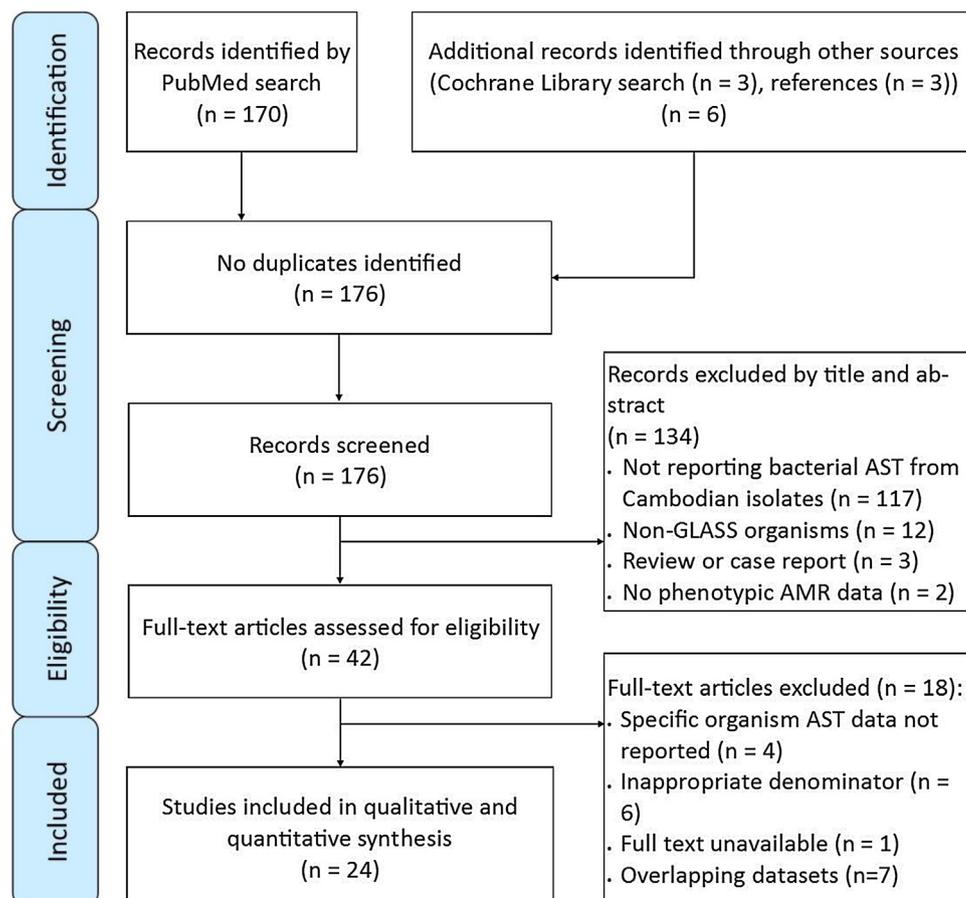

Figure 1. PRISMA diagram of article selection procedure.

(Chheng et al., 2013; Emary et al., 2012; Moore et al., 2016a; Stoesser et al., 2013b; Vlieghe et al., 2015; Vlieghe et al., 2013a; Wijedoru et al., 2012), leaving a final count of 24 papers. Details of these papers are summarised in Table 1, and Supplementary Table S2. Among these, 20 reported isolates from human populations and four reported isolates from animals and/or meat products. Of the human population papers, nine reported isolates from children only, and seven reported isolates from sterile sites only (e.g. blood, cerebrospinal fluid). Three articles described isolates associated with both CAI and HAI, however, only in one article was it possible to separate these isolates (Fox-Lewis et al., 2018). Three articles described isolates from CAI only, and no articles stated that their isolates were associated with HAI only. Assessment of study methodology showed that 11 articles either did not state, or did not explain in detail, organism identification

methods used. AST was done by disk diffusion method in 18 studies, with 14 studies determining minimum inhibitory concentration (MIC) in addition to susceptibility by disk diffusion. MIC testing was largely done by the E-test method (n = 11). Four studies did not state which AST interpretative criteria were used (e.g. Clinical and Laboratory Standards Institute breakpoints). Of the remaining papers that did, all but one stated the specific edition used.

The earliest published article identified was from 2007 (Augustin et al., 2007). The most commonly reported organism was *E. coli*, with AST data reported by 11 papers. In contrast, AST data was reported by one paper for *Shigella* spp. (Meng et al., 2011), and two papers for *N. gonorrhoeae* (Khauv et al., 2014; Vernel-Pauillac et al., 2010). Four studies reported isolates from non-human populations, specifically, *E. coli* and NTS.

Table 1
Summary of individual papers included in review.

Reference	Duration of data collection	Population	Specimens	Age group	HAI vs CAI	Syndrome	GLASS Organism(s) included
Augustin et al. (2007)	Not stated	Human	Urine	Child	Not stated	Not stated	*E. coli, K. pneumoniae*
Caron et al. (2018)	Jan 2012– Dec 2015	Human	Blood, pulmonary, urine, genital, stool, other	All	Both	Not stated	*E. coli, K. pneumoniae*
Fox-Lewis et al. (2018)	2007–2016	Human	Blood, CSF	Child	Both	Febrile	*E. coli, K. pneumoniae, A. baumannii, S. aureus, S. pneumoniae, Salmonella* spp.
Hout et al. (2015)	2011–2013	Human	Wound swab	Child	Not stated	Wound exudate	*E. coli, K. pneumoniae, A. baumannii, S. aureus*
Inghammar et al. (2018)	2005–2014	Human	Blood, CSF, BAL, pleural fluid, sputum	All	Not stated	Not stated	*S. pneumoniae*
Kasper et al. (2010)	Dec 2006–Apr 2009	Human	Blood	All	Not stated	Fever	*Salmonella* spp.
Khauv et al. (2014)	Mar 2012– Oct 2012	Human	Ophthalmic	Child	Not stated	Ophthalmic infection	*S. aureus, S. pneumoniae, N. gonorrhoeae*
Kuijpers et al. (2017)	2008–2015	Human	Blood	All	Not stated	Enteric fever	*Salmonella* spp.
Lay et al. (2011)	Mar 2006– Feb 2007	Poultry carcass	Poultry skin	N/A	N/A	N/A	*Salmonella* spp.
Meng et al. (2011)	Nov 2004– Oct 2006	Human	Stool	Child	Not stated	Diarrhoea	*E. coli, Salmonella* spp., *Shigella* spp.
Moore et al. (2016b)	Jan 2007– Dec 2011	Human	Urine	Child	Not stated	Not stated	*E. coli, K. pneumoniae*
Phe et al. (2013)	Jan 2009– Dec 2011	Human	Blood	Adult	CAI	Systemic inflammatory response	*E. coli, S. aureus*
Rammaert et al. (2012)	Apr 2007– Dec 2009	Human	Blood, sputum, nasopharyngeal swab	All	CAI	Acute lower respiratory infection	*K. pneumoniae*
Ruppe et al. (2009)	Jan 2004– Dec 2005	Human	Urine	All	CAI	UTI	*E. coli*
Srun et al. (2013)	Oct 2010– Feb 2011	Human	Wound swab	Adult	Not stated	Surgical wound infection	*S. aureus*
Stoesser et al. (2013a)	2011	Human	Nasal swab	Child	N/A	Carriage	*S. aureus*
Stoesser et al. (2013c)	Jan 2007– Jul 2011	Human	Synovial fluid	Child	Not stated	Bone/joint infection	*S. aureus*
Strom et al. (2018)	Jan 2017– Feb 2017	Pigs	Stool, rectal swab	N/A	N/A	N/A	
Trongjit et al. (2016)	Jul 2014– Jan 2015	Pigs, poultry, meat products	Stool, rectal swab, carcass swab	N/A	N/A	N/A	*E. coli*
Trongjit et al. (2017)	Jul 2014– Jan 2015	Pigs, poultry, meat products	Stool, rectal swab, carcass swab	N/A	N/A	N/A	*Salmonella* spp.
Turner et al. (2015)	Aug 2013– Jul 2014	Human	Nasopharyngeal swabs, blood	Child	N/A	Admission or minor illness	*S. pneumoniae*
Vernel-Pauillac et al. (2010)	Oct 2006– Oct 2007	Human	Cervical/urethral swab	Not stated	Not stated	Not stated	*N. gonorrhoeae*
Vlieghe et al. (2012)	Jul 2007– Jun 2011	Human	Blood	Adult	Not stated	Systemic inflammatory response	*Salmonella* spp.
Vlieghe et al. (2013)	Jul 2007– Dec 2010	Human	Blood	Adult	Both	Systemic inflammatory response	*E. coli, K. pneumoniae, A. baumannii*

Escherichia coli

There were nine papers that reported *E. coli* among human populations (Table 2). Fluoroquinolone and co-trimoxazole AST were reported in all these studies. Median resistances were calculated as 92.8% (n = 6, IQR 86.1–94.3), 46.4% (n = 4, IQR 44.8–53.8), 55.4% (n = 8, IQR 40.2–69.8), 79.9% (n = 8, IQR 72.6–83.3), 46.4% (n = 5, IQR 44.7–51.7), for ampicillin, 3GC, fluoroquinolones, co-trimoxazole, and gentamicin respectively. No carbapenem resistance was found in the three studies that reported AST data for this antibiotic class. 4GC (cefepime) resistance was reported as 22.2%–46.2% by two studies (Hout et al., 2015; Vlieghe et al., 2013b), and colistin resistance was reported as 0.8%, (n = 1/130) in one study (Vlieghe et al., 2013b).

Two studies describing *E. coli* isolates from pigs and chickens were identified (Strom et al., 2018; Trongjit et al., 2016). Both reported resistance rates to ampicillin (75.0%–86.0%), 3GC (2.0%–8.4%), fluoroquinolones (0.7%–59.0%), and gentamicin (6.6%–25.0%) (Supplementary Table S3). One study reported resistance rates from 261 isolates to colistin (20.0%,) and to carbapenems (0.0%) (Strom et al., 2018). Neither of these papers reported AST data for co-trimoxazole, amikacin, or 4GC.

Klebsiella pneumoniae

Antimicrobial susceptibility data was reported for *K. pneumoniae* isolates in seven studies (Table 2), all of which were from humans. Fluoroquinolone and co-trimoxazole resistance data were reported in all papers, with 3GC resistance data reported in four papers. The median resistance rate was 64.4% (n = 4, IQR 49.2–80.2), 21.9% (n = 7, IQR 11.7–44.8), 50.0% (n = 7, IQR 40.4–76.3), and 51.1% (n = 4, IQR 37.0–66.3) for 3GC, fluoroquinolones, co-trimoxazole, and gentamicin respectively. 4GC (cefepime) resistance was reported as 22.0-28.1% by two papers (Hout et al., 2015; Vlieghe et al., 2013b), and colistin resistance was reported as 3.1% (n = 1/32 isolates), by one paper (Vlieghe et al., 2013b).

Acinetobacter baumannii

Three papers reported resistance data for *A. baumannii* in humans (Fox-Lewis et al., 2018; Hout et al., 2015; Vlieghe et al., 2013b) (Supplementary Table S4). All three reported resistance rates for carbapenems (median 13.5%, range 5.9%-33.3%). Gentamicin resistance was reported by two papers with rates of 66.7% (n = 2/3 isolates) (Hout et al., 2015), and 58.8% (n = 10/17 isolates) (Vlieghe et al., 2013b). The same two papers also reported amikacin resistance as 66.7% (n = 2/3 isolates) (Hout et al., 2015), and 41.2% (n = 7/17 isolates) (Vlieghe et al., 2013b). One paper reported rates for colistin (17.6%, n = 3/17 isolates) (Vlieghe et al., 2013b). None of the studies tested GLASS-specific tetracyclines (minocycline or tigecycline), although one paper did report resistance rates of 66.6% (n = 2/3 isolates) to tetracycline (Hout et al., 2015).

Salmonella spp

In total, seven papers were identified for inclusion of AST data for *Salmonella* spp., including two studies of isolates from animals and/or their meat products (Lay et al., 2011; Trongjit et al., 2017). Data from the human papers are summarised in Table 3. Fluoroquinolone resistance was reported in all papers, with much higher rates seen in *S.* Typhi (range 88.0%–96.9%, n = 3) than in *S.* Paratyphi A (range 11.5%-22.7%, n = 2) or NTS (range 0.6%-63.4%, n = 3). Resistance to 3GC was uncommon in all *Salmonella* spp. isolates (0.0%-8.1%) and, in the three studies reporting data, carbapenem resistance was not detected.

The two non-human studies, describing NTS isolates from chickens and pigs, both reported AST data for fluoroquinolones (0.0%-2.5%), and 3GC (0.0%-6.0%) (Lay et al., 2011; Trongjit et al., 2017) (Supplementary Table S5). Neither study reported carbapenem resistance data.

Shigella spp

One study reported AST data for *Shigella* spp., with no resistance found to ciprofloxacin or azithromycin among 41 isolates (Meng et al., 2011) (Supplementary Table S6). This paper did not report AST data for 3GC.

Neisseria gonorrhoeae

Two papers reported AST data for *N. gonorrhoeae* (Supplementary Table S7). One reported ciprofloxacin (93.3%) and penicillin (100%) resistance rates on 15 isolates from Cambodia, as part of a larger multi-country study (Vernel-Pauillac et al., 2010). The other reported AST data for 3GC (0%) and ciprofloxacin (100%) from two isolates (Khauv et al., 2014). Resistance rates were not reported for azithromycin, spectinomycin, or gentamicin in either paper.

Staphylococcus aureus

MRSA rates ranged from 0% to 52.5%, with a median of 20.0% (n = 7, IQR 8.7%–35.8%) (Table 4). All *S. aureus* isolates were from studies of humans, with one study reporting isolates from hospital screening.

Streptococcus pneumoniae

Four papers reporting AST data for *S. pneumoniae* were included (Table 5). All papers reported resistance rates for penicillin (median 46.6%, IQR 31.8%–58.1%), co-trimoxazole (median 75.2%, IQR 74.5%–79.3%), and 3GC (median 4.8%, IQR 3.4%–8.0%). One of the papers reported isolates from a study of nasopharyngeal carriage of *S. pneumoniae* in children (Turner et al., 2015), whereas the others reported isolates from unwell patients.

Discussion

This review provides a summary of all the published GLASS-organism AMR data for Cambodia over the last 19 years. To date, there are few published AMR datasets but the rate at which manuscripts are appearing has increased: only two publications were identified prior to 2010, compared with 10 from 2016–2018. The small number of isolates and lack of classification metadata (e.g. age groups, hospitalization status) make it difficult to draw firm conclusions from the data. However, resistance rates to several key clinically-important antibiotics were found to be alarmingly high.

The best represented GLASS organisms in this review were *Enterobacteriaceae*, with *E. coli, K. pneumoniae,* or *Salmonella* spp. being described by two thirds of the papers (15/22). *Shigella* spp. were an exception to this, with only one paper. Another striking lack of data was with regard to *N. gonorrhoeae*, with only two papers, both describing small numbers of isolates, and with resistance rates reported to only two of the five GLASS specific antibiotics. The level of representation for each GLASS organism may partly be a reflection of their respective burdens on healthcare. A study at a tertiary hospital in Hanoi showed that *K. pneumoniae* and *E. coli* were responsible for 17.5% and 17.3% of blood stream infections (BSI) respectively (Dat et al., 2017), and, in a paediatric setting in Cambodia, *Salmonella* spp. were shown to be responsible for 30.4% of BSI (Fox-Lewis et al., 2018). Microbiology

Table 2
Resistance rates for *E. coli* and *K. pneumoniae* isolates from humans.

	Specimen type(s)	Ampicillin		3GC[c]		4GC[d]		Carbapenem[e]		Fluoroquinolone[f]		Co-trimoxazole		Gentamicin		Amikacin		Colistin	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
E. coli																			
Fox-Lewis et al. (2018)	Blood & CSF	101/107	94.4	53/107	49.5	-	-	0/98	0.0	48/105	45.7	89/105	84.8	51/106	48.1	-	-	-	-
Caron et al. (2018)	Multiple types[b]	-	-	-	-	-	-	-	-	560/789	71.0[g]	580/789	73.5	-	-	206/789	26.0	-	-
Hout et al. (2015)	Wound swab	33/36	91.7	24/36	66.7	8/36	22.2	0/36	0.0	25/36	69.4	28/36	77.8	22/36	61.1	1/36	2.8	-	-
Moore et al. (2016b)	Urine	164/170	96.5	68/170	40.0	-	-	-	-	77/170	45.3	147/170	86.5	76/170	44.7	-	-	-	-
Vlieghe et al. (2013b)[a]	Blood	122/130	93.8	-	-	60/130	46.2	-	-	-	-	-	-	-	-	-	-	1/130	0.8
Phe et al. (2013)[a]	Blood	-	-	70/151	46.4	-	-	0/151	0.0	113/151	74.8	125/151	82.8	78/151	51.7	3/151	2.0	-	-
Meng et al. (2011)	Stool	295/323	91.3	-	-	-	-	-	-	6/ 323	1.9	288/323	89.2	40/323	12.4	-	-	-	-
Ruppe et al. (2009)	Urine	-	-	-	-	-	-	-	-	68/93	63.0	75/93	70.0	-	-	-	-	-	-
Augustin et al. (2007)	Urine	12/16	75.0	-	-	-	-	-	-	4/16	25.0	6/16	37.5	-	-	-	-	-	-
K. pneumoniae																			
Fox-Lewis et al. (2018)	Blood & CSF	N/A		115/146	78.8	-	-	1/142	0.7	86/142	60.6	111/143	77.6	90/145	62.1	-	-	-	-
Caron et al. (2018)	Multiple types[b]	N/A		-	-	-	-	-	-	71/243	29.0[g]	118/243	48.5	-	-	47/243	19.5	-	-
Hout et al. (2015)	Wound swab	N/A		5/10	50.0	2/10	20.0	0/10	0.0	2/10	20.0	5/10	50.0	4/10	40.0	0.0	0.0	-	-
Moore et al. (2016b)	Urine	N/A		16/19	84.2	-	-	-	-	12/19	63.2	18/19	94.7	15/19	78.9	-	-	-	-
Vlieghe et al. (2013b)	Blood	N/A		15/32	46.9	9/32	28.1	0/32	0.0	7/32	21.9	24/32	75.0	9/32	28.1	0.0	0.0	1/32	3.1
Augustin et al. (2007)	Urine	N/A		-	-	-	-	-	-	1/30	3.3	9/30	30.0	-	-	-	-	-	-
Rammaert et al. (2012)	Blood & respiratory	N/A		-	-	-	-	-	-	1/46	2.2	10/46	32.3	-	-	-	-	-	-

CSF, cerebrospinal fluid.
[a] Papers with overlapping datasets: Ampicillin, 4GC, and Colistin resistance rates taken from Vlieghe et al., 2013. All other resistance rates taken from Phe et al., 2013, as larger numbers of isolates.
[b] Specimens include blood, stool, pulmonary, pus, genito-urinary, and other body fluid samples.
[c] 3GC, third generation cephalosporin: ceftriaxone, ceftazidime.
[d] 4GC, fourth generation cephalosporin: cefepime.
[e] Carbapenems: meropenem.
[f] Fluoroquinolones: ciprofloxacin.
[g] Resistance rate stated for antibiotic class only, without stating specific antibiotic.

Table 3
Resistance rates for *Salmonella* spp. isolates from humans.

	Specimen type(s)	Fluoroquinolone[b]		3GC[c]		Carbapenem[d]	
		n	%	n	%	n	%
S. Typhi							
Fox-Lewis et al. (2018)	Blood & CSF	308/322	95.7	1/173	0.6	-	-
[a]Kuijpers et al. (2017)	Blood	62/64	96.9	0/64	0.0	0/64	0.0
Kasper et al. (2010)	Blood	36/41	88.0	0/41	0.0	-	-
S. Paratyphi A							
Fox-Lewis et al. (2018)	Blood & CSF	10/44	22.7	0/44	0.0	-	-
[a]Kuijpers et al. (2017)	Blood	21/183	11.5	0/183	0.0	0/183	0.0
Non-typhoidal salmonellae (NTS)							
Fox-Lewis et al. (2018)	Blood & CSF	26/41	63.4	3/37	8.1	-	-
[a]Vlieghe et al. (2012)	Blood	12/37	32.0	1/37	2.7	0/37	0.0
Meng et al. (2011)	Stool	1/178	0.6	-	-	-	-

[a] Papers with overlapping datasets: Data used from Kuijpers et al. 2017 for *S.* Typhi and *S.* Paratyphi due to higher number of isolates, and likewise for Vlieghe et al., 2012 for NTS.
[b] Fluoroquinolones: ciprofloxacin.
[c] 3GC, third generation cephalosporin: ceftriaxone, cefotaxime.
[d] Carbapenems: meropenem. NTS, non-typhoidal salmonella. CSF, cerebrospinal fluid.

Table 4
Methicillin resistance rates for *S. aureus* isolates.

	Specimen type(s)	MRSA	
		n	%
S. aureus			
Fox-Lewis et al. (2018)	Blood & CSF	24/185	13.0
Hout et al. (2015)	Wound swab	52/99	52.5
Khauv et al. (2014)	Ophthalmic	1/23	4.3
Stoesser et al. (2013a)	Nasal swab	1/5	20.0
Phe et al. (2013)	Blood	11/51	21.6
Srun et al. (2013)[a]	Wound swab	1/2	50.0
Stoesser et al. (2013c)	Synovial fluid	0/4	0.0

MRSA, methicillin resistant *Staphylococcus aureus*: cefoxitin, oxacillin.
[a] Specific AST not stated.

laboratories and clinical services prioritise much of their diagnostic capabilities on the most unwell patients who require management in hospital, rather than on infections based in the community setting, such as diarrhoeal illness and genito-urinary infection. Nevertheless, *Shigella* spp. account for 12.5% of diarrhoeal deaths globally (GBD Diarrhoeal Diseases Collaborators, 2017), and *N. gonorrhoeae* causes high levels of morbidity in LMICs, with both known for rapid development of AMR (Kotloff et al., 2018; Unemo et al., 2016). Future surveillance and research outputs in Cambodia and SE Asia should not neglect these organisms.

Our review has demonstrated the particularly high levels of resistance among *Enterobacteriaceae* to many of the most accessible and widely used antibiotics in Cambodia, including ampicillin, gentamicin, 3GC, fluoroquinolones, and co-trimoxazole. The rise in prevalence of ESBL producing organisms in Cambodia has been raised as a concern (Caron et al., 2018). In

Phnom Penh, among fish, pork, and chicken samples, bacterial plasmids carrying CTX-M type ESBL genes also carry resistance genes for multiple other classes of antibiotic, including aminoglycosides, fluoroquinolones, and co-trimoxazole (Nadimpalli et al., 2019a). Furthermore, a link has been made between CTX-M type ESBL producing *E. coli* isolated from fish, pork, and chicken in markets from Phnom Penh, and isolates colonising humans (Nadimpalli et al., 2019b). A subsequent concern is that injudicious use of any of these classes of antibiotic will co-select for resistance genotypes against the others. If resistance rates among *Enterobacteriaceae* worsen, management of their associated infections will become increasingly dependent upon more expensive, and less readily available antibiotics.

AMR rates in Cambodia appear to be in keeping with the limited number of reports of regional AMR rates. Surveillance of GLASS organisms in Thailand has shown high resistance rates among *E. coli* and *K. pneumoniae* to 3GC, and ciprofloxacin, with well-preserved sensitivity to meropenem and cefepime (Sirijatuphat et al., 2018). A review of antibiotic susceptibilities in Africa and Asia also demonstrated high 3GC, co-trimoxazole, and gentamicin resistance among Asian *E. coli* and *K. pneumoniae* isolates (Ashley et al., 2011). There are, however, some clear differences to elsewhere in the world. Increased ciprofloxacin resistance rates among *Salmonella* spp. are of particular concern, when compared to countries outside of Asia. A recent systematic review of antimicrobial resistance in Africa showed that 28 studies describing AST in *S.* Typhi had a median resistance to ciprofloxacin of 0% (Tadesse et al., 2017). In contrast, our review shows high levels of fluoroquinolone resistance in *S.* Typhi in Cambodia, with a range of 88.0%–95.7%. This finding adds weight to the argument that the region is a "hotspot" for the development of AMR in enteric fever,

Table 5
Papers reporting resistance rates for *S. pneumoniae* isolates.

	Specimen type(s)	Penicillin		Co-trimoxazole		[b]3GC	
		n	%	n	%	n	%
S. pneumoniae							
Fox-Lewis et al. (2018)	Blood & CSF	73/144	50.7	101/134	75.4	6/134	4.5
Inghammar et al. (2018)	Multiple types[a]	70/165	42.4	149/164	90.9	8/157	5.1
Turner et al. (2015)	Nasopharyngeal swab	779/972	80.1	711/972	73.1	163/972	16.8
Khauv et al. (2014)	Ophthalmic	0/4	0.0	3/4	75.0	0/4	0.0

[a] Specimens include blood, pleural fluid, sputum, bronchoalveolar lavage, and cerebrospinal fluid (CSF).
[b] 3GC, third generation cephalosporin: ceftriaxone.

particularly *gyrA* mediated fluoroquinolone resistance (Vlieghe et al., 2012; Wong et al., 2015). Resistance to fluoroquinolones appears less prevalent among *S.* Paratyphi A isolates (11.5%–22.7%), however increasing rates of decreased-ciprofloxacin-sensitivity were reported in Phnom Penh throughout the recent outbreak (Kuijpers et al., 2017). Continuing use of ciprofloxacin as a first line treatment of uncomplicated enteric fever in Cambodia can reasonably be expected to lead to prolonged fever clearance times, treatment failures, and increased carriage rates of *S.* Typhi and *S.* Paratyphi A. Azithromycin may be considered an affordable and accessible alternative therapy for uncomplicated enteric fever, but AST reporting to this drug is not currently a GLASS requirement for *Salmonella* spp., a decision that may need to be revisited. Sensitivity to 3GC seems quite well preserved among *Salmonella* spp., and no resistance to carbapenems was reported in these papers. ESBL producing *Salmonella* spp. have been described in Cambodia (Nadimpalli et al., 2019a; Trongjit et al., 2017), and the emergence of an extensively drug resistant dominant strain of *S.* Typhi or *S.* Paratyphi A, as recently seen in Pakistan (Klemm et al., 2018), could herald a regional disaster. Resistance to 3GC in *Salmonella* spp. should be monitored closely in the region.

There are widely accepted differences in organisms and AMR patterns between hospital acquired infections (HAI) and community acquired infections (CAI) (Cardoso et al., 2015). One study from a paediatric hospital in Cambodia clearly demonstrated this difference, with higher rates of resistance seen amongst BSI isolates from HAI compared to those from CAI (Fox-Lewis et al., 2018). In this study, rates of MRSA associated with HAI were 40.0% (n = 8/20), compared with 9.7% (n = 16/165) in those from CAI. Few other studies in this review clearly delineated between these different categories of infection, however this rate of MRSA associated with HAI correlates closely to the rate of MRSA from wound swabs in another paediatric inpatient population in Cambodia (52.5%, n = 52/99) (Hout et al., 2015). GLASS uses inpatient status as a proxy for hospital acquired infection, and while this is an imperfect method, inpatient and outpatient status was more widely reported, and this approach may provide at least some insight into the differences between HAI and CAI in Cambodia and elsewhere.

Significant variation was observed in specific AST reported for each organism. Fluoroquinolone AST was reported universally for the *Enterobacteriaceae*, and the only papers that did not report cotrimoxazole AST, where indicated by GLASS, were non-human studies. On the other hand, both colistin and 4GC resistance rates were reported by only two of the twelve papers addressing *E. coli*, *K. pneumoniae,* or *A. baumannii*, and fewer than 50% (7/17) of papers reported carbapenem resistance, where indicated by GLASS. The fact that antimicrobial susceptibilities for colistin, 4GC, and carbapenems are under reported or not tested, may reflect the lack of availability of these drugs to clinicians. Nevertheless, they are considered "reserve" or "watch" antibiotics, and it is of great importance to know the resistance patterns of their target pathogens (Sharland et al., 2018).

AMR in non-humans has been relatively neglected to date. Only four papers from this review addressed AMR in animals or meat products, and no studies were identified looking at environmental isolates. However, the fact that three of these were published within the last three years may represent the beginning of a shift towards a multi-sector approach to AMR research in Cambodia. Antibiotics, including colistin, are frequently used for prophylaxis and growth promotion in SE Asian agriculture (Nhung et al., 2016). It is of concern that colistin resistance was found in 20% of porcine *E. coli* isolates from Phnom Penh (Strom et al., 2018). Genetic testing was not done in this study, but subsequent investigation has confirmed a link with the *mcr-1* gene (Strom Hallenberg et al., 2019), and reflects similar regional rates of *mcr-1* associated

colistin resistance in food animals (Nguyen et al., 2016). The *mcr-1* gene has been reported in human isolates collected in Cambodia in as early as 2012 (Stoesser et al., 2016) and has also been identified in *Salmonella* spp. and *E. coli* isolated from market food in Phnom Penh (Nadimpalli et al., 2019a; Nadimpalli et al., 2019b). The transmission pathways have not yet been clarified, but the role of food and food animals in the human acquisition of *mcr-1* carrying *Enterobacteriaceae* is believed to be significant, and raises fears for the future of one of our "last-resort" antibiotics (Nhung et al., 2016).

While providing a useful overview of AMR in Cambodia, this review had some limitations. Paper quality was not assessed, but clearly study methodology and presentation of AST data was highly variable. This has been noted elsewhere in previous similar reviews, and there are calls for better standardisation of AMR data presented in published manuscripts (Ashley et al., 2018). It should be hoped that, with the adoption of such tools as the Microbiology Investigation Criteria for Reporting Objectively (MICRO) checklist, high quality AMR data will be seen more consistently in future (Turner et al., 2019). Some specific resistance mechanisms, including ESBL and methicillin resistance, may have been underrepresented, as several studies used laboratory methodology that selected for specific resistance phenotypes, and therefore had inappropriate denominators for inclusion. Other studies were also excluded as they presented only genotypic resistance data, without phenotypic description. The expansion of both clinical and research microbiological capacity in Cambodia will result in newer technologies being used, including whole genome sequencing, to determine and control AMR (Koser et al., 2014). Future reviews and surveillance should reflect these changes.

Globally, important steps are being made to reduce further development and spread of AMR. Accurate reporting of AMR in clinical isolates from humans is one key step. In addition to harmonisation between national and global surveillance systems, efforts need to be made to standardise methodology data in published research outputs and embrace a broader One Health approach, including surveillance in plants and the environment. Capture of patient-level data will be critical to understand the impacts of AMR. In Cambodia, the fledgling national AMR surveillance systems for humans and food animals will contribute to the generation of multi-sectoral data, allowing a stronger One Health approach in tackling AMR. Furthermore, standardised microbiological and clinical data will be used by GLASS, and will inform public health policy at country, regional, and global levels.

Conclusion

Availability of AMR data for Cambodia is limited but improving. From the data published to date, the AMR rates for GLASS organisms appear to be similar to those of other countries in the region. High resistance rates are seen to many first-line antibiotics, especially among *Enterobacteriaceae*. The recently commenced national AMR surveillance systems in humans and food animals will bring together data from across the country, in a uniform manner, to improve clarity of the AMR situation in Cambodia.

Member organisations of the Cambodia Technical Working Group on Antimicrobial Resistance

Ministry of Health — Department of Communicable Diseases Control; Ministry of Health – Department of Health Services / Bureau of Medical Laboratory Services; Ministry of Health – Department of Drugs and Food; Ministry of Agriculture, Forestry and Fisheries; Angkor Hospital for Children; Battambang Provincial Hospital; Calmette Hospital; Kampong Cham

Provincial Hospital; National Paediatric Hospital; Siem Reap Provincial Hospital; Sihanouk Hospital Center of Hope; Takeo Provincial Hospital; Royal University of Agriculture; University of Health Sciences; Cambodia Oxford Medical Research Unit; Diagnostic Microbiology Development Program; Fondation Merieux; Institut Pasteur du Cambodge; National Institute of Public Health / National Public Health Laboratory; United States Centers for Disease Control and Prevention; United States Naval Medical Research Unit-2; Food and Agriculture Organization; World Health Organization.

CDC and FAO disclaimer

The findings and conclusions of this report are those of the authors and do not necessarily represent the official positions of the Food and Agriculture Organization of the United Nations (FAO), or the Centers for Disease Control and Prevention (CDC).

Conflict of interest statement

No competing interest declared.

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Not required.

Appendix A. Supplementary data

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