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Effects of laboratory capabilities on combating antimicrobial resistance, 2013–2016: A static model panel data analysis

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ABSTRACT

Objectives: Antimicrobial resistance (AMR) has become a serious global public health problem. The World Health Organization (WHO) and European Union (EU) have taken actions to combat this issue, in which laboratory capability construction is a crucial part. This study aimed to explore the relationship between laboratory capabilities and antimicrobial resistance from a macro perspective.

Methods: The study used annual national level penal data from the EU Laboratory Capability Monitoring System and Antimicrobial Resistance Surveillance Europe 2013–2016. A conventional static panel data analysis was constructed to establish the relationship between the antimicrobial resistance rates and laboratory capabilities.

Results: Laboratory capability on *antimicrobial drug resistance characterisation and monitoring* (LC8) showed a positive effect on *Escherichia coli* (*E. coli*) combined resistance rate (Y5), *E. coli* resistant rate of aminoglycosides (Y4), and *Klebsiella pneumoniae* resistant rate of carbapenems (Y8) (OR = 0.929, 0.957, and 0.861; $P = 0.035$, 0.007, and 0.026, respectively). However, *following the diagnostic testing guidelines* (LC2) caused higher resistance rates of *Klebsiella pneumoniae* to fluoroquinolones (Y6), third-generation cephalosporins (Y7), and aminoglycosides (Y9) (OR = 1.076, 1.093, and1.065; $P = 0.011$, 0.032, and 0.002, respectively).

Conclusions: Antimicrobial drug resistance characterisation and monitoring by laboratories has contributed to minimising antimicrobial resistance, while the mechanism of laboratory capabilities to pose an ineffective or negative impact on AMR remains to be further studied.

1. Introduction

Antimicrobial resistance (AMR) is a serious global public health problem. A global AMR report in 2016 pointed out that >700 000 people worldwide die from drug-resistant strains of common bacterial infections every year [1]. Without effective measures to curb the occurrence and spread of AMR, the number of deaths from AMR each year will be 10 million in 2050 [1]. AMR has also brought a heavy economic burden to countries around the world. For instance, more than 2 million people in the United States (US) are infected with bacteria that are resistant to antibiotics each year [2], causing the US healthcare system an extra $20 billion on advanced drugs because of the commonly used but ineffective first-line antibacterial drugs [3].

As a comprehensive problem, successful containment of AMR requires multi-sectoral involvement and a One Health management approach. The World Health Organization (WHO), European Union (EU), and other countries have taken a series of measures based on the One Health approach, covering multiple fields including medical, agroforestry, animal husbandry, aquaculture and environment [4–6]. These measures involved capacity building of the laboratory, including microbial isolation and identification, determination of antimicrobial susceptibility test, AMR surveillance and outbreak detection. For example, in 2011, the EU lunched the first Action Plan aimed at mitigating the risk of AMR, in which laboratory capacity building was to guide optimal use of antimicrobials by promoting microbiological diagnosis [4]. In 2017, the EU released an Action Plan for AMR governance based on the One Health concept, which intended to improve AMR detection in reference laboratory activities to identify critical control points [6]. The two action plans also stressed the importance of AMR surveillance and establishing laboratory-based surveillance systems, such as the European Antimicrobial Resistance Surveillance Network (EARS-Net), European Surveillance of Antimicrobial

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Consumption Network (ESAC-Net), and Global Antimicrobial Resistance Surveillance System (GLASS) [5].

Since 2012, the EU has also been focusing on strengthening the capability and capacity of the public health microbiology system to identify best practices and address potential vulnerabilities. The EU Laboratory Capability Monitoring System (EULabCap) for monitoring key public health microbiology capabilities and capacity was developed and piloted. So far, four reports have presented the EULabCap survey results as achieved from 2013–2016, respectively [7–10].

Several studies have paid attention to the significance of microbiology laboratory capacity in combating AMR from micro perspectives. Along with the development of diagnostic technology, molecular typing plays an important role in the early detection of drug-resistance pathogens [11] and determination of the epidemiological pathways in increasing antimicrobial resistance [12], especially whole-genome sequencing (WGS) [13]. Harris et al. identified the transmission of methicillin-resistant *Staphylococcus aureus* (MRSA) using rapid WGS in a special baby unit, and to some extent, WGS-led intervention brought the outbreak to a halt [14]. Meanwhile, the significance of microbiology laboratory diagnostic capability is not limited to identifying drug-resistance pathogens, but also extends to other AMR combating strategies. Denning et al. presented a case illustrating that misdiagnosis and inappropriate use of antimicrobials and antifungals arising from a lack of fungal diagnostic capability in laboratories compromises AMR control [15]. Surveillance is also critical to understanding the status and trends of AMR [16]. Active participation of medical microbiology laboratories in Netherlands gives a good example of national AMR surveillance [17], and several studies have used the surveillance results for early detection and containment of specific resistant pathogens of public health concern [18,19].

However, from macro perspectives, the impact of comprehensive laboratory capabilities on antimicrobial resistance has not been conducted. This study aimed to: explore the relationship between laboratory capabilities and AMR from a macro level, use the existing monitoring data to discover new knowledge, and provide macro evidence for stakeholders such as policymakers and implementers in resource allocation use and management under the EU's One Health approach.

2. Material and methods

2.1. Data sources

This study used annual national level penal data from the EU Laboratory Capability Monitoring System 2013–2016 [7–10] and Antimicrobial Resistance Surveillance Europe in 2016, which covered resistance rate data from 2013–2016 [20]. The former assessed the laboratory capabilities with 12 performance indicators based on 60 items, and the latter performed surveillance of AMR in eight bacterial pathogens of public health importance.

2.2. Measures of variables

The variables on antimicrobial resistance rates were 14 combinations of antimicrobials and bacterial organisms, which were selected based on Antimicrobial Resistance Surveillance Europe [20], the WHO's list of antibiotic-resistant 'priority pathogens' [21], and the two major extended-spectrum β-lactamase-producing Gram-negative bacilli as *Escherichia coli* (*E. coli*) and *Klebsiella pneumoniae* (*K. pneumoniae*) (Table 1). The antimicrobial resistance rates were expressed as the percentage of resistance isolates out of all isolates with antimicrobial susceptibility testing (AST) information on that specific combinations of classes of antimicrobial and bacterial organism.

The variables on laboratory capabilities were measured by 12 indicators (Table 1). Each indicator consisted of five items and all values of indicators were displayed on a scale of 0–10. Each item was scored at three levels: low (0, 'no or limited capability/capacity'), intermediate (1, 'partial capability/capacity', e.g. below the EU target or partial compliance) or high (2, 'complete capability/capacity', e.g. EU target reached or high compliance). Items for which data were not available or that were not applicable (NA) to the country were not scored [7–10]. Because NA (not available or not applicable) was not included in the calculation of the specific indicator, the laboratory capabilities scores were

Table 1
Variable definitions.

Variables	Definitions
LC1	*Provision and regulation of clinical microbiology services*
LC2	*Diagnostic testing guidelines*
LC3	*Diagnostic testing utilization*
LC4	*Antimicrobial drug susceptibility testing*
LC5	*Provision and regulation of national reference microbiology services*
LC6	*Reference diagnostic confirmation and pathogen identification*
LC7	*Molecular typing for surveillance*
LC8	*Antimicrobial drug resistance characterization and monitoring*
LC9	*Support to national surveillance networks*
LC10	*Active participation in EU disease networks*
LC11	*National outbreak response support*
LC12	*(Re)-emerging diseases laboratory preparedness and response support*
Y1	*Escherichia coli* resistance rate of aminopenicillins
Y2	*Escherichia coli* resistant rate of fluoroquinolones
Y3	*Escherichia coli* resistant rate of third-generation cephalosporins
Y4	*Escherichia coli* resistant rate of aminoglycosides
Y5	*Escherichia coli* combined resistance rate of fluoroquinolones, third-generation cephalosporins and aminoglycosides
Y6	*Klebsiella pneumoniae* resistant rate of fluoroquinolones
Y7	*Klebsiella pneumoniae* resistant rate of third-generation cephalosporins
Y8	*Klebsiella pneumoniae* resistant rate of carbapenems
Y9	*Klebsiella pneumoniae* resistant rate of aminoglycosides
Y10	*Klebsiella pneumoniae* combined resistance rate of fluoroquinolones, third-generation cephalosporins and aminoglycosides
Y11	*Pseudomonas aeruginosa* resistant rate of carbapenems
Y12	*Acinetobacter spp.* resistant rate of carbapenems
Y13	*Staphylococcus aureus* resistant rate of methicillin (MRSA)
Y14	*Enterococcus faecium* resistant rate of vancomycin

calculated as follows:

$$Laboratory\ \ Capability\ \ = \frac{actual\ \ score}{\text{ideal}\ \ \text{score}} \times 10$$

$$ideal\ \ score\ \ = \ \ 2 \times (5 - n)$$

Actual score gathered the scores of five items, and n referred to the number of 'NA' of the items.

2.3. Analysis of the variables

Considering that the distribution of variables was skewed, the median and inter-quartile range were combined to descriptive statistics. The relationship between antimicrobial resistance rates and laboratory capabilities was evaluated using Spearman's correlation coefficient, with $P < 0.05$ being taken as statistically significant. The study considered a logit transformation of antimicrobial resistance rates to make an expansion in the scale from [0,1] to [± infinity] [22]. A country-fixed and year-fixed effect model was used to eliminate the effects of unobservable country-invariant and year-invariant confounders. A conventional static panel data analysis was constructed to establish the relationship between the antimicrobial resistance rates and laboratory capabilities, employing a two-way fixed-effect model [23] as following:

$$\text{logit}\ \ Y_{it}\ \ = \ \ \beta_0 + \ \ \sum_{m=1}^{12} \beta_m\ \ LC_{mit}\ \ + \ \ \eta_i + \lambda_t + \ \ \varepsilon_{it}$$

The subscript denoted country i ($i = 1, 2, \ldots, 30$) and time t ($t = 1, 2, 3, 4$) and m was the number of laboratory capability indicator; η_i controlled for the unobserved differences across countries, while λ_t controlled for all unmeasured differences within years; ε_{it} was the random error. All statistical analysis was performed with STATA (Version 12.0, Stata Cop., College Station, Texas, USA).

3. Results and discussion

3.1. Summary statistics

The medians of the laboratory capabilities were between 6–10. The values of inter-quartile range concentrated from 2–4.25, showing little variation, and the minimum values ranged from 0–4, with a maximum of 10 (Table 2).

Table 3 shows that the top three high drug resistance rates are *E. coli resistance rate of aminopenicillins* (Y1), *K. pneumoniae resistant rate of fluoroquinolones* (Y6), and *K. pneumoniae resistant rate of third-generation cephalosporins* (Y7) (56.6%, 29.6%, and 28.7%, respectively). The resistance rates of *E. coli* to four drugs (Y1–Y4) were between 9.9–56.6%. The resistance rates of *K. pneumoniae* to four drugs (Y6–Y9) were between 0.6–29.6%, with variation (0.023–0.417) slightly larger than the first one (0.076–0.151), suggesting that *K. pneumoniae* had a large difference in drug resistance rates between years or countries.

Table 2
Statistics of laboratory capabilities.

Variable	Median	IQR[a]	Min	Max
LC1	7.00	3.00	2.00	10.00
LC2	6.00	4.00	0.00	10.00
LC3	6.00	4.00	0.00	10.00
LC4	9.00	3.00	4.00	10.00
LC5	8.00	2.00	2.00	10.00
LC6	7.50	2.08	3.00	10.00
LC7	6.00	4.25	0.00	10.00
LC8	8.00	2.75	0.00	10.00
LC9	8.00	3.00	0.00	10.00
LC10	10.00	2.00	3.33	10.00
LC11	7.50	3.00	1.25	10.00
LC12	8.00	3.00	2.00	10.00

[a] IQR referred interquartile range.

Table 3
Summary statistics of the antimicrobial resistance rates.

Variable	Median	IQR[a]	Min	Max
Y1	0.566	0.132	0.341	0.780
Y2	0.237	0.151	0.068	0.519
Y3	0.114	0.080	0.017	0.416
Y4	0.099	0.076	0.029	0.348
Y5	0.050	0.057	0.000	0.221
Y6	0.296	0.348	0.000	0.708
Y7	0.287	0.417	0.000	0.750
Y8	0.006	0.023	0.000	0.669
Y9	0.226	0.405	0.000	0.682
Y10	0.170	0.292	0.000	0.633
Y11	0.160	0.179	0.000	0.663
Y12	0.283	0.683	0.000	0.954
Y13	0.134	0.188	0.000	0.645
Y14	0.071	0.168	0.000	0.463

[a] IQR referred interquartile range.

The correlation analysis in Table 4 indicated that the variables *Molecular typing for surveillance* (LC7), *Antimicrobial drug resistance characterization and monitoring* (LC8), *National outbreak response support* (LC11) and *(Re)-emerging diseases laboratory preparedness and response support* (LC12) have the greatest negative correlation with all antimicrobial resistance rates, followed by *Active participation in EU disease networks* (LC10), *Antimicrobial drug susceptibility testing* (LC4) and *Support to national surveillance networks* (LC9). It showed that the higher the laboratory capabilities, the lower the resistance rates.

3.2. Positive effect of laboratory capabilities on AMR

The correlation analysis and country-and-year fixed-effect model revealed that the higher laboratory capability on *antimicrobial drug resistance characterisation and monitoring* contributed to the lower antimicrobial resistance rates. Table 5 shows that a one-point increase in *antimicrobial drug resistance characterisation and monitoring* (LC8) was associated with a 7.1% decrease in *E. coli* combined resistance rate (Y5), 4.35% decrease in *E. coli* resistant rate of aminoglycosides (Y4) and 13.96% decrease in *K. pneumoniae* resistant rate of carbapenems (Y8) (OR = 0.929, 0.957, and 0.861; $P = 0.035$, 0.007, and 0.026, respectively). In addition to LC8, higher laboratory capability on *(Re)-emerging diseases laboratory preparedness and response support* (LC12) also had a positive effect on *MRSA* (Y13) (OR = 0.995; $P = 0.031$).

Similar results can be seen in the US, where the central laboratory conducting the AMR characterisation acted as a cornerstone of the Antimicrobial Resistance Monitoring and Research Program, and the result showed that incidence rates of carbapenem-resistant Enterobacteriaceae (CRE) per 100 000 patient-years significantly declined by about 42% [24]. Another case that distinguished mechanisms of carbapenem resistance to promote the rapid generation of accurate data achieved a 10-fold reduction in the transmission of CRE [25]. To some extent, identification of the type of carbapenemase contributed to controlling the outbreak of carbapenemase-producing Enterobacteriaceae (CPE) [26–28].

The positive effects of laboratory capabilities on AMR stem from the willingness and expectations of many experts and other stakeholders, especially policymakers and implementers of nosocomial infection control [7–10]. For instance,

Table 4
Relationship between antimicrobial resistance rates and laboratory capabilities (r*).

Variables	LC1	LC2	LC3	LC4	LC5	LC6	LC7	LC8	LC9	LC10	LC11	LC12
Y1	−0.0630	0.249*	−0.1300	−0.421*	−0.0620	−0.1000	−0.328*	−0.300*	−0.432*	−0.228*	−0.399*	−0.357*
Y2	−0.0680	0.1080	−0.1950	−0.385*	−0.0450	−0.1990	−0.436*	−0.273*	−0.385*	−0.248*	−0.467*	−0.394*
Y3	0.0550	0.2120	−0.1010	−0.402*	0.1280	−0.1750	−0.476*	−0.257*	−0.1790	−0.299*	−0.329*	−0.339*
Y4	−0.0290	0.220*	−0.1630	−0.390*	0.0110	−0.1430	−0.430*	−0.236*	−0.263*	−0.327*	−0.345*	−0.382*
Y5	0.0440	0.1260	−0.0990	−0.321*	0.0330	−0.1880	−0.474*	−0.300*	−0.267*	−0.327*	−0.352*	−0.377*
Y6	−0.0130	0.264*	−0.310*	−0.1500	−0.1410	−0.1010	−0.595*	−0.316*	−0.228*	−0.480*	−0.458*	−0.466*
Y7	0.0240	0.308*	−0.304*	−0.249*	−0.0450	−0.1380	−0.599*	−0.306*	−0.253*	−0.510*	−0.450*	−0.494*
Y8	−0.1730	0.0590	−0.1640	−0.343*	−0.0110	−0.1140	−0.216*	−0.277*	−0.376*	−0.1670	−0.401*	−0.230*
Y9	0.0720	0.353*	−0.303*	−0.239*	−0.0490	−0.1190	−0.634*	−0.297*	−0.1990	−0.528*	−0.423*	−0.499*
Y10	0.0610	0.355*	−0.298*	−0.1860	−0.1040	−0.1150	−0.629*	−0.280*	−0.1530	−0.487*	−0.403*	−0.458*
Y11	−0.0690	0.2140	−0.387*	−0.235*	−0.265*	−0.2150	−0.651*	−0.397*	−0.251*	−0.451*	−0.472*	−0.346*
Y12	−0.315*	0.0390	−0.405*	−0.350*	−0.246*	−0.229*	−0.524*	−0.391*	−0.417*	−0.361*	−0.476*	−0.407*
Y13	−0.1240	0.340*	−0.2060	−0.328*	−0.0820	0.0100	−0.346*	−0.218*	−0.247*	−0.290*	−0.321*	−0.339*
Y14	−0.2010	0.0210	−0.1210	−0.302*	0.0000	−0.0190	−0.479*	−0.493*	−0.331*	−0.305*	−0.353*	−0.313*
n[b]	1	0	6	12	2	1	14	14	11	13	14	14

[a]Significance: *$P < 0.05$.
[b] n: the number of significant negative correlation coefficient.

Table 5
Fixed-effect model of laboratory capabilities effect on antimicrobial resistance rates (OR).

Variables	logitY1	logitY2	logitY3	logitY4	logitY5	logitY6	logitY7	logitY8	logitY9	logitY10	logitY12	logitY13	logitY14
LC1	0.995	0.973	0.973	1.009	1.015	0.947	0.956	1.011	0.970	0.963	1.077	0.983	0.894
LC2	0.996	0.990	0.996	0.945	0.970	1.076*	1.093**	1.133	1.065*	1.089	0.888	1.034	1.050
LC3	1.002	1.036**	1.034**	1.023	1.019	1.034	0.988	0.964	1.015	1.011	1.102*	1.008	1.057
LC4	1.000	1.021	1.008	0.982	0.967	0.988	0.976	0.892	0.997	0.967	1.060	0.974	1.009
LC5	0.980	0.982	0.995	1.024	1.023	1.010	1.033	1.103	1.016	1.027	1.079	1.044	1.006
LC6	0.992	0.991	1.026	1.007	1.033	1.002	1.024	0.944	0.966	1.004	0.908	1.000	0.972
LC7	1.016	0.984	0.998	0.998	1.001	0.982	0.996	1.085	0.990	0.975	0.931	1.008	0.935
LC8	1.009	0.976	0.972	0.957**	0.929*	1.000	1.014	0.861*	1.010	1.026	1.043	0.999	0.965
LC9	1.020	1.029	1.010	1.023	0.989	0.989	0.977	0.917	0.990	0.950	0.969	0.969	1.077
LC10	0.998	1.037	1.038	1.009	1.004	1.025	1.013	1.083	1.046	1.053	1.022	1.006	1.078
LC11	1.009	1.008	1.052*	1.024	1.068*	1.031	1.014	1.192	0.968	1.026	0.980	1.036	0.961
LC12	1.004	1.002	0.982	0.991	0.976	1.015	1.007	0.998	1.030	0.993	0.974	0.945*	1.041
Year													
2014	0.952	0.982	1.017	1.033	1.096	1.035	0.994	1.182	1.082	1.182	0.730	1.008	1.510
2015	0.969	0.989	1.030	1.044	1.163	1.014	0.973	0.859	0.991	1.075	0.966	0.922	1.629
2016	0.996	1.046	1.108	1.035	1.140	1.022	1.034	1.161	1.003	1.132	0.838	0.921	2.024*

[a]Significance: *$P < 0.05$, **$P < 0.01$.
[b]Model with poorly fitted results were not included in the table.

identification of type of carbapenemase (the main resistance characterisation of carbapenem-resistant pathogens) with various characteristics in carbapenemase-producing Gram-negative bacilli isolates, especially CPE, was mandatory to prevent the spread of highly resistant pathogens [29]. The key issues with CPE arose because higher levels of resistance were produced by acquired carbapenemases (typically KPC, VIM, IMP, NDM and OXA-48 types); the organisms can easily be transmissible and they have the potential for horizontal gene transfer between related bacteria [30–32]. Therefore, in clinical practice, antimicrobials that were active against CRE relied on carbapenemase types, which would have influenced choice of antimicrobial therapy; proper identification of the type of carbapenemase could reduce the transmission of CRE and emergence of resistance [29].

In addition to EULabCap, The European Survey of CPE (EuSCAPE) also aimed to build national capabilities across Europe for standardised laboratory detection, identification, and surveillance of CPE [33] and the results revealed that the establishment of a surveillance system for CPE, supported by reference laboratory confirmation and identification, as well as molecular typing services were the cornerstones of efficient monitoring and controlling of the spread of CPE [34–36].

3.3. Negative effect of laboratory capabilities on AMR

Several laboratory capabilities had significant but negative influences on antimicrobial resistance rates (Table 5). For instance, following the *diagnostic testing guidelines* (LC2) caused higher resistance rates of *K. pneumoniae* to fluoroquinolones (Y6), third-generation cephalosporins (Y7), and aminoglycosides (Y9) (OR = 1.076, 1.093, and 1.065; $P = 0.011$, 0.032, and 0.002, respectively).

Following the National Guidelines for screening CPE, Berry et al. confirmed that there was marked heterogeneity in CPE screening [37]. Unfortunately, an audit showed that high-risk patients may not be screened for CPE or isolated as a consequence of the poor risk assessment of CPE on hospital admission, which may rely on reactive control measures rather than proactive strategies when CPE cases are confirmed to have further spread [38]. Besides, compared with the Clinical and Laboratory Standards Institute (CLSI), Hombach et al. found that applying breakpoints of European Committee on Antimicrobial Susceptibility Testing (EUCAST) 2011 led to significantly more isolates of Gram-negative species being reported as resistant to extended-spectrum cephalosporins (ceftriaxone, cefepime), carbapenems and fluoroquinolone [39,40]. All the above show that the mechanism of laboratory capabilities to combat AMR needs to be explored.

3.4. Limitations

This study had some limitations. First, the relatively small data size may have limited the robustness and statistical significance of the estimates. Second, due to the short duration, the study could not employ a dynamic approach, which considered the dynamic nature of panel data and feedback effects to estimate the relationship between antimicrobial resistance rates and laboratory capabilities. Third, several laboratory capabilities showed no or augmenting effects on AMR. Other factors may help to explain it. For instance, samples that are not properly collected and transported may lead to false results; good laboratory capability [41] and effective communication are critical for the microbiology laboratory procedures [42]. However, the mechanism of laboratory capabilities to pose an ineffective or augmenting impact on AMR remains to be further studied.

4. Conclusions

In general, laboratory capability on AMR characterisation and monitoring plays a significant role in reducing the rate of resistance. Based on this finding, reducing the rates of resistance needs to strengthen laboratory capabilities building.

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Competing interests

None.

Ethical approval

Not required.

Authorship

YC was involved in data collection, data analysis, data interpretation and manuscript draft. XZ made significant contributions to the data interpretation and manuscript writing. JL aided in design of the study and interpretation of data. All authors approved the final version of the manuscript to be submitted.

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