

## Impact of national interventions to promote responsible antibiotic use: a systematic review

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**Background:** Global recognition of antimicrobial resistance (AMR) as an urgent public health problem has galvanized national and international efforts. Chief among these are interventions to curb the overuse and misuse of antibiotics. However, the impact of these initiatives is not fully understood, making it difficult to assess the expected effectiveness and sustainability of further policy interventions. We conducted a systematic review to summarize existing evidence for the impact of nationally enforced interventions to reduce inappropriate antibiotic use in humans.

**Methods:** We searched seven databases and examined reference lists of retrieved articles. To be included, articles had to evaluate the impact of national responsible use initiatives. We excluded studies that only described policy implementations.

**Results:** We identified 34 articles detailing interventions in 21 high- and upper-middle-income countries. Interventions addressing inappropriate antibiotic access included antibiotic committees, clinical guidelines and prescribing restrictions. There was consistent evidence that these were effective at reducing antibiotic consumption and prescription. Interventions targeting inappropriate antibiotic demand consisted of education campaigns for healthcare professionals and the general public. Evidence for this was mixed, with several studies showing no impact on overall antibiotic consumption.

**Conclusions:** National-level interventions to reduce inappropriate access to antibiotics can be effective. However, evidence is limited to high- and upper-middle-income countries, and more evidence is needed on the long-term sustained impact of interventions. There should also be a simultaneous push towards standardized outcome measures to enable comparisons of interventions in different settings.

### Introduction

Antimicrobial resistance (AMR) is a major threat to global health. Without urgent action, an estimated 10 million annual deaths due to resistant pathogens are expected by 2050.<sup>1</sup> Among antimicrobials, bacterial resistance to antibiotics is a major concern. Antibiotic consumption is a major driver of resistance, and global antibiotic consumption is rising; a recent comprehensive assessment of antibiotic consumption has shown a 65% increase in worldwide antibiotic consumption between 2000 and 2015, from 21.1 billion to 34.8 billion DDD.<sup>2</sup>

To counter the rise in AMR, the WHO's Global Action Plan on Antimicrobial Resistance (2015)<sup>3</sup> has identified responsible use as one of five key priority areas for urgent intervention, endorsing

strategies to reduce both the supply of and demand for antibiotics. These include regulatory measures to reduce and optimize antimicrobial prescribing and dispensing, and campaigns to improve overall awareness and understanding of AMR, among both healthcare professionals and the general public.

Numerous interventions have been proposed and used to reduce antibiotic consumption in different settings, but the extent to which these have been implemented at a national level, and their impact, remain largely unknown. We conducted a systematic review to assess the impact of responsible use initiatives implemented at the national and/or subnational level to reduce unnecessary antibiotic consumption, in order to evaluate the available evidence on the impact of coordinated national implementations.

## Methods

### Inclusion and exclusion criteria

We conducted this review using PRISMA guidelines<sup>4</sup> (Prospero registration number: CRD42017064629). We included studies describing any national-level and/or subnational-level responsible use initiatives to address antibiotic resistance in the community or at the primary, secondary or tertiary care levels. Studies with no reported outcomes relating to antibiotic consumption and/or prescription were excluded. The inclusion and exclusion criteria can be found in Table 1.

### Search strategy

The literature search focused on interventions related to responsible use of antibiotics (Table 2). The search strategy was developed with an information specialist and included Medical Subject Headings (MeSH) terms, keywords and free text (title and abstract) terms relating to AMR, national-level initiatives and their outcomes (Table 2).

The search strategy was used for the databases Medline, Embase and Global Health. To ensure coverage of low- and middle-income countries (LMICs), a simplified search strategy was used for the following databases: Latin American and Caribbean Health Sciences Literature (LILACS), Africa-Wide Information, Index Medicus for the South-East Asian Region (IMSEAR), Index Medicus for the Eastern Mediterranean Region (IMEMR) and Western Pacific Rim Region Index Medicus (WPRIM). In total, seven databases were searched from inception until May 2017. No date or language restrictions were applied; however, searches were conducted in English.

### Search and retrieval of studies

Two reviewers (J. M. L. and S. R. S.) independently conducted the literature search and identified relevant articles based on title and/or abstract. If either reviewer considered a study potentially eligible, the two reviewers would independently assess the full text to determine whether it met the inclusion criteria. Full text articles in languages other than English were translated into English for screening. Any disagreements were resolved by discussion with a third reviewer (D. M. C.).

**Table 1.** Inclusion and exclusion criteria

Category	Criteria
Inclusion criteria	Peer-reviewed articles that described any national- and/or subnational-level responsible antibiotic use initiatives (i.e. interventions to reduce subtherapeutic consumption or prescription of antibiotics)
Setting	All healthcare settings (primary, secondary, tertiary care) as well as in the community
Outcomes	Any outcomes (externally measured, self-reported or observed changes) relating to antibiotic consumption and/or prescription
Exclusion criteria	<p>Studies that only describe implementation of an intervention with no reported outcomes relating to antibiotic consumption and/or prescription</p> <p>Studies that target antimicrobials other than antibiotics</p> <p>Studies that only describe interventions not related to antibiotic stewardship/responsible antibiotic use (e.g. infection control, vaccines, surveillance, etc.)</p> <p>Studies that only describe interventions for antibiotic use in animals and/or the environment</p>

### Data synthesis

Three reviewers (J. M. L., S. R. S. and D. M. C.) independently extracted data from included studies. Data were extracted on the following: (i) study characteristics (study design, setting); (ii) type of intervention; and (iii) results and type of outcome measure (e.g. antibiotic consumption, prescription, compliance with prescription guidelines, resistance rates). Differences in data extraction or study interpretation were resolved by discussion and consensus. Included studies were then grouped based on type of intervention conducted.

### Risk of bias assessment

Three reviewers (J. M. L., S. R. S. and D. M. C.) independently assessed risk of bias. We used the Cochrane Risk of Bias Tool for Non-Randomized Studies of Interventions (ACROBAT-NRSI), since most of the intervention studies adopted a time-series design.<sup>5</sup> We classified studies that had low risk of bias in all domains as low overall risk of bias. Studies that had high or unclear risk of bias in one or more domains were classified as overall high or unclear risk of bias.

## Results

We identified 12 718 records from the database search, and two additional records from forward searching. After removing duplicate records, 7952 articles remained. These were screened for relevance by title and abstract, yielding 68 articles that were retrieved as full texts (Figure 1). Thirty-four articles met the inclusion criteria, all of which were journal articles and were published in English, Chinese, French, Croatian and Spanish. We did not conduct a meta-analysis owing to heterogeneity of study design, interventions, participants and outcomes, but instead present a qualitative summary of interventions, results and outcomes.

### Countries and interventions (characteristics of included studies)

The 34 included studies used quantitative methods and were conducted in 21 countries (Figures 2 and 3). Twenty-two studies were carried out in high-income and 12 in upper-middle-income countries as defined by World Bank classification.<sup>6</sup> Eight studies had high risk of bias, 20 studies had moderate risk of bias and 6 studies had low risk of bias. We classified studies into two broad domains: (i) interventions to reduce the inappropriate access to antibiotics; and (ii) interventions to reduce demand for antibiotics.

Full details of the included studies, including study design, setting and key findings, can be found in Table 3.

### Reducing inappropriate access to antibiotics

Interventions within this domain included the institution of antibiotic-specific regulations (12 studies), prescribing restrictions (10 studies), separation of drug prescribing from dispensing (2 studies) and educational campaigns for healthcare professionals (6 studies).

### Institution of regulation (antibiotic committees and clinical guidelines)

Eleven studies in seven countries described establishment of national hospital antibiotic management teams as an intervention to address AMR. Responsibilities of hospital antibiotic management

**Table 2.** Search terms

	MeSH terms	Keywords
Antimicrobial	anti-infective agents anti-bacterial agents	anti-infective agent* OR anti-bacterial agent* OR antibiotic* OR antimicrobial* OR anti-microbial* OR antibacterial* OR anti-bacterial* OR antiinfective* OR anti-infective*
Resistance	drug resistance drug resistance, multiple drug resistance, multiple, bacterial drug resistance, microbial	drug resistance OR drug resistance, multiple OR drug resistance, multiple, bacterial OR drug resistance, microbial OR resistance OR resistant OR resist
Policy/programme	health policy health care reform national health policy policy making health promotion government programmes	health policy OR health care reform OR national health policy OR policy making OR health promotion OR government program* OR policy OR policies OR program OR programme OR programs OR programmes OR campaign OR campaigns OR intervention OR interventions OR government OR governance OR govern OR governing OR national policy
Outcome	prescription drug misuse prescription drug overuse inappropriate prescribing drug prescriptions drug utilization practice patterns, physicians	consume OR consumption OR usage OR utilization OR utilisation OR stewardship OR rationale OR responsible OR guidance OR guideline OR guidelines prudent OR unnecessary OR underprescribe OR under-prescribe OR underprescribing OR under-prescribing OR underprescription OR under-prescription OR overprescribe OR over-prescribe OR overprescribing OR over-prescribing OR overprescription OR over-prescription OR prescribe OR prescribing OR prescription OR prescriptions OR practice pattern OR drug misuse OR reduce OR reduction OR decrease

teams included training of healthcare professionals, surveillance of antibiotic consumption, prescription review, evaluation of hospital resources for infection control and development of clinical guidelines for antibiotic prescription. Additionally, two studies in two countries described the strengthening and dissemination of clinical guidelines for the prescription of antibiotics in both inpatient and outpatient settings.

Of the 11 studies, 10 found overall reductions in antibiotic use, while 1 found mixed results in terms of consumption levels; a decrease in consumption of third-generation cephalosporins after implementation of an antibiotic restriction programme was accompanied by an increase in consumption of penicillins.<sup>7</sup> Other outcome measures included reductions in the number of antibiotic packages consumed and/or prescribed,<sup>8,9</sup> seasonal variation in fluoroquinolone use,<sup>9</sup> grams consumed per year,<sup>10</sup> antibiotic sales value and volume,<sup>11,12</sup> percentage of antibiotic use by inpatients<sup>13</sup> as well as DDD.<sup>13-16</sup> Three studies evaluated the link between antibiotic consumption and antibiotic resistance rates, calculated as the percentage of bacterial isolates displaying resistance,<sup>10,15,17</sup> and found mixed results. At the institutional level, two studies found increased compliance with national antibiotic prescribing guidelines as well as better key structural resources for antibiotic management and infection control in hospitals.<sup>18-20</sup>

### Restriction of prescribing practices

Two types of prescribing restrictions were described in 11 studies representing nine countries. The first was restrictions on reimbursement of antibiotic prescription (e.g. when antibiotics were prescribed as first-line treatment, or reduced reimbursement in general). These were described in six countries and covered the following antibiotics: methicillin,<sup>21</sup> amoxicillin/clavulanic acid,<sup>22,23</sup> third- and fourth-generation cephalosporins,<sup>22,24</sup>

fluoroquinolones,<sup>22,24-26</sup> aminoglycosides, macrolides<sup>21-24</sup> and tetracyclines.<sup>21,23</sup> Although all six studies found significant overall decreases in antibiotic consumption (as expressed by DDD and number of weekly antibiotic prescriptions), one study<sup>24</sup> found increases in macrolides and penicillin prescriptions. Of the six studies, two investigated the link between antibiotic consumption with resistance rates of *Streptococcus pneumoniae* and *Helicobacter pylori*, and found mixed results.

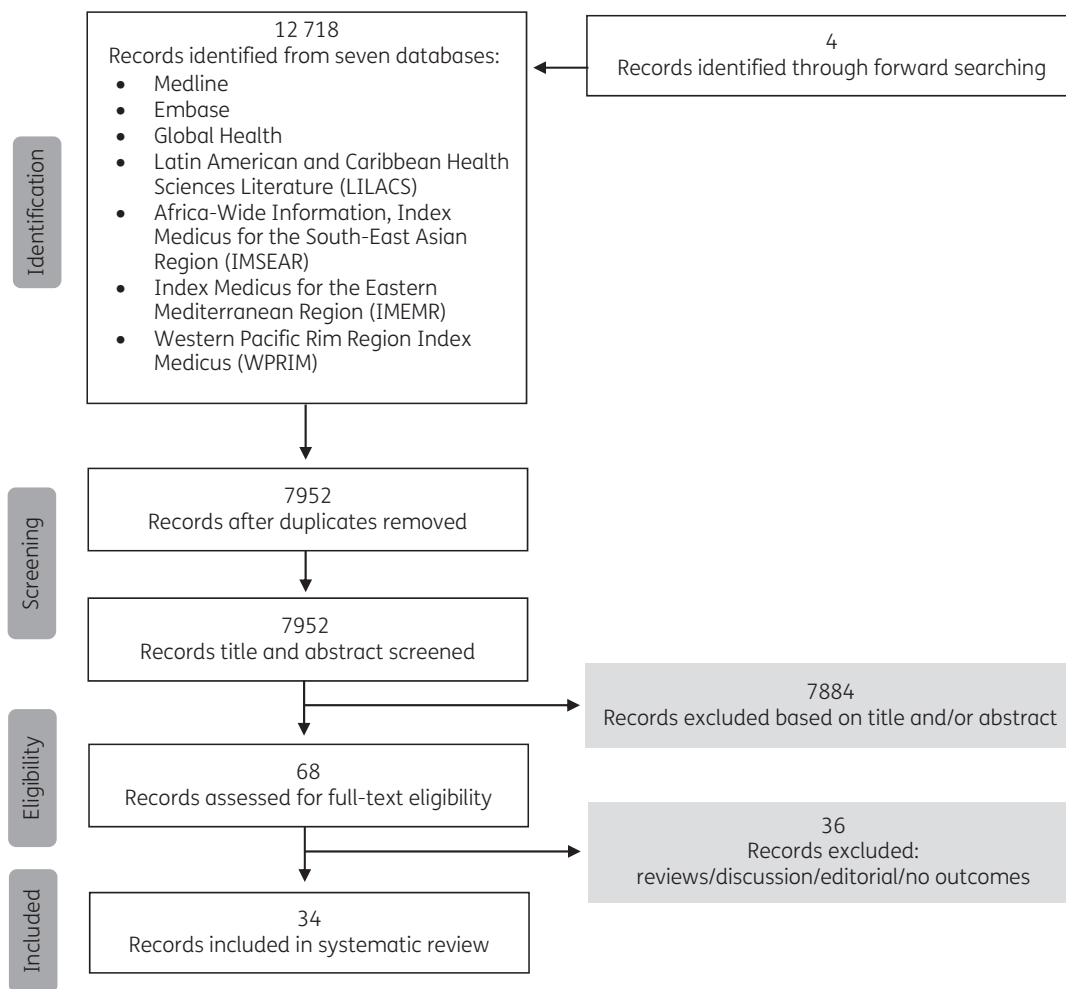
The remaining five studies evaluated the restriction of antibiotic purchases without a prescription. Four of the studies found reductions in antibiotic consumption after implementation,<sup>11,12,16,27</sup> while one study found no changes in antibiotic consumption.<sup>28</sup> All results were expressed in DDD.

### Separation of antibiotic prescribing from dispensing

Two studies reported the impact of separating drug prescribing from drug dispensing in primary care to disincentivize profit making from prescribing.<sup>29,30</sup> After implementation of the separation policy in both countries, reductions in antibiotic use, measured in DDD, and prescription were observed. However, in one study, this effect diminished over time and there was no significant reduction in overall antibiotic expenditure.

### Campaigns for healthcare professionals

Six studies described campaigns for healthcare professionals in five countries. Campaigns included disseminating flyers and toolkits,<sup>18,22,31,32</sup> conducting workshops and seminars on antibiotic prescription,<sup>22,31,33,34</sup> providing individual prescribing feedback,<sup>31-33</sup> promoting antibiotic prescribing guidelines in medical school education<sup>32</sup> and sharing experiences among healthcare professionals.<sup>34</sup> Outcome measures to evaluate the effectiveness of these campaigns included the number of



**Figure 1.** Study flow diagram.

annual primary care antibiotic prescriptions per physician,<sup>31</sup> antibiotic prescriptions per 1000 inhabitants per year or month,<sup>32,33</sup> DDD,<sup>22,34</sup> percentage of patients receiving antibiotic prescriptions<sup>32,33</sup> and expenditure on antibiotic prescriptions per 1000 inhabitants per month.<sup>32</sup>

Four studies showed overall decreases in the number of antibiotic prescriptions per physician at the primary care level,<sup>22,31–33</sup> especially in prescribing for respiratory tract infections. One study found no significant changes in overall physician antibiotic prescribing post intervention, although there were increases in prescriptions for both amoxicillin and penicillin.<sup>34</sup>

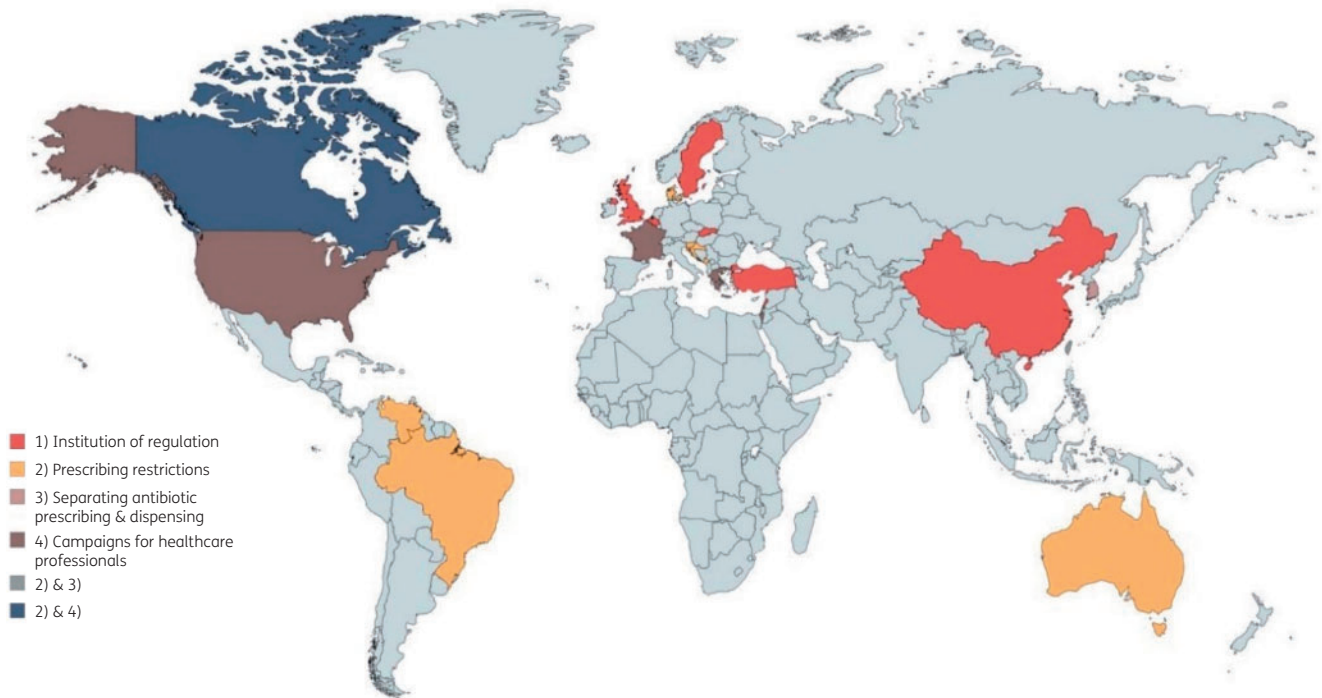
### Decreasing the demand for antibiotics

We found 13 studies from 10 countries describing national public education campaigns to increase awareness about appropriate antibiotic use, hand hygiene and vaccination. These included media campaigns using booklets, exhibits, flyers, posters, websites, newspapers, television or radio spots.<sup>18,19,31,32,35–39</sup> Other platforms were also used to raise awareness about antibiotics, such as health information workshops and seminars in the community,<sup>18,22,32,40</sup> childcare centres, primary schools and

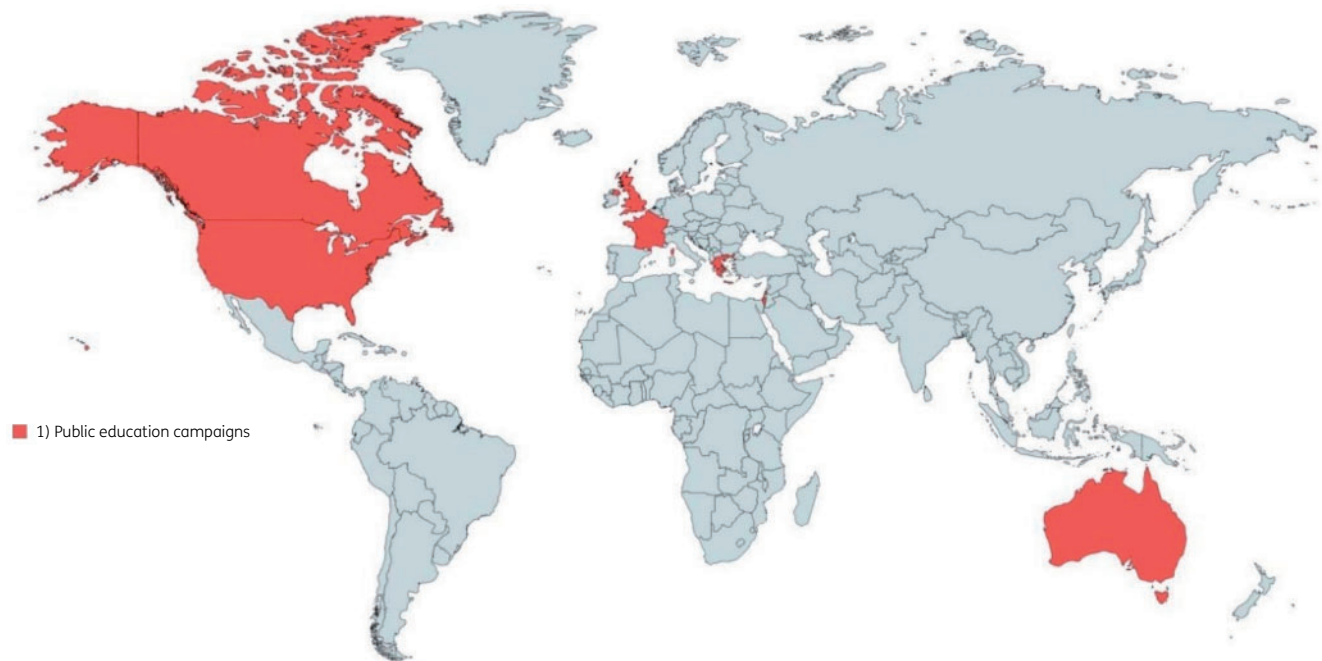
nursing homes.<sup>31,34</sup> In addition to messages about antibiotic awareness, there were also hand hygiene campaigns for the prevention of nosocomial infections,<sup>19</sup> and introduction of influenza vaccines for children.<sup>33</sup>

Outcome measures used to evaluate these campaigns included the number of reimbursed antibiotic packages, number of prescriptions per physician, volume of antibiotics distributed to retail outlets per capita, percentage of consultations resulting in antibiotic prescriptions and DDD. Using these measures, 10 studies found overall decreases in antibiotic consumption. Of these, two studies found notable decreases only during and immediately after the intervention period,<sup>35,40</sup> two studies found decreases in antibiotic prescriptions for upper respiratory tract infections,<sup>39</sup> including nasopharyngitis and influenza,<sup>33</sup> and one study showed that the overall decrease was driven mostly by penicillin, macrolides and cephalosporins.<sup>38</sup>

One study<sup>34</sup> found no overall change in antibiotic consumption (in DDD), but reported decreased consumption of macrolides, offset by increased consumption of amoxicillin and penicillin. Only one study<sup>19</sup> linked antibiotic consumption with resistance rates and found reductions in penicillin-, tetracycline- and macrolide-resistant *S. pneumoniae*.



**Figure 2.** Countries where interventions to reduce inappropriate access to antibiotics were implemented and evaluated. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.



**Figure 3.** Countries where interventions to decrease inappropriate demand for antibiotics were implemented and evaluated. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

### **Heterogeneity in outcomes and outcome measures**

While individual studies in our review showed that national programmes had a positive impact on antibiotic use, it was

challenging to evaluate the impact across time and geography owing to the heterogeneity in outcome measures used to quantify the impact of the programmes. Differences in programme

**Table 3.** Study characteristics

Authors	Country	Title	Intervention	Study design	Year	Outcome measure	Risk of bias	Outcome
1 Krcmery and Gould (1999) <sup>8</sup>	Slovakia	Antibiotic policies in Central/Eastern Europe (CEE) after 1990	Institution of regulation (antibiotic committees)	Time series analysis	1994–7	Antibiotic consumption (number of antibiotic packages/year)	Moderate	Overall decrease of antibiotic consumption: ~11 000 packages/year in 1994 to ~9000 packages/year in 1997
2 Altunsoy et al. (2011) <sup>10</sup>	Turkey	The impact of a nationwide antibiotic restriction programme on antibiotic usage and resistance against nosocomial pathogens in Turkey	Institution of regulation (antibiotic committees)	Pre–post study	2001–5	Antibiotic consumption (g) Sales volume and value Resistance rates	Moderate	11.3% decrease in antibiotic consumption (g) and cost <ul style="list-style-type: none"> <li>• 60 074 g in 2001/2 to 38 129 g in 2003/4</li> <li>• 47 million USD in 2001/2 to 42 million USD in 2003/4</li> </ul> Negative correlation between ceftriaxone consumption (–36.8%) and the prevalence of ceftriaxone-resistant <i>Escherichia coli</i> and <i>Klebsiella</i> spp. ( $p=0.395$ , $P=0.332$ and $p=0.627$ , $P=0.037$ ); all non-significant Decreased use of carbapenems was correlated with decreased carbapenems-resistant <i>Pseudomonas</i> spp. and <i>Acinetobacter</i> spp ( $p=0.155$ , $P=0.712$ ; $p=0.180$ , $P=0.668$ ) Methicillin resistance rates of <i>S. aureus</i> decreased from 44% to 41% 44 500 fewer prescriptions in 2009 compared with 2008 <ul style="list-style-type: none"> <li>• Penicillin combinations (co-amoxiclav): 14.7% decrease in items per 1000 population/day</li> <li>• Fluoroquinolones: 7.1% decrease in items per 1000 population/day; <math>\leq 5\%</math> seasonal variation in fluoroquinolone use</li> <li>• Cephalosporins: 21.2% decrease in items per 1000 population/day</li> </ul> Increased number of NHS boards achieving $\geq 95\%$ compliance with the empirical prescribing policy (range: 65%–89%) Percentage of drug sales for antimicrobials decreased from 23.8% (2009) to 19.4% (2011) Sales volume for second- (24.51% to 9.46%) and third-line (21.54% to 4.78%) antibiotics decreased from 2010 to 2011, while sales volume for first-line antibiotics increased from 2010 to 2011 (7.96% to 13.94%) Percentage of drug sales for antimicrobials decreased from 25% (2011) to 17% (2012) Percentage of antimicrobial prescriptions decreased in both inpatient settings (68% versus 58%) and outpatient settings (25% versus 15%)
3 Nathwani et al. (2011) <sup>9</sup>	Scotland, UK	Scottish Antimicrobial Prescribing Group (SAPG): development and impact of the Scottish National Antimicrobial Stewardship Programme	Institution of regulation (antibiotic committees)	Time series analysis	2005–9	Antibiotic consumption (items per 1000 population/day) Compliance with national antibiotic prescribing indicators	Moderate	44 500 fewer prescriptions in 2009 compared with 2008 <ul style="list-style-type: none"> <li>• Penicillin combinations (co-amoxiclav): 14.7% decrease in items per 1000 population/day</li> <li>• Fluoroquinolones: 7.1% decrease in items per 1000 population/day; <math>\leq 5\%</math> seasonal variation in fluoroquinolone use</li> <li>• Cephalosporins: 21.2% decrease in items per 1000 population/day</li> </ul> Increased number of NHS boards achieving $\geq 95\%$ compliance with the empirical prescribing policy (range: 65%–89%) Percentage of drug sales for antimicrobials decreased from 23.8% (2009) to 19.4% (2011) Sales volume for second- (24.51% to 9.46%) and third-line (21.54% to 4.78%) antibiotics decreased from 2010 to 2011, while sales volume for first-line antibiotics increased from 2010 to 2011 (7.96% to 13.94%) Percentage of drug sales for antimicrobials decreased from 25% (2011) to 17% (2012) Percentage of antimicrobial prescriptions decreased in both inpatient settings (68% versus 58%) and outpatient settings (25% versus 15%)
4 Tao et al. (2013) <sup>11</sup>	China	Analysis of the current situation of antibiotics use in China: a hospital-based perspective	Institution of regulation (antibiotic committees)	Time series analysis	2008–11	Percentage of overall drug sales Sales volume and value	Moderate	Percentage of drug sales for antimicrobials decreased from 23.8% (2009) to 19.4% (2011) Sales volume for second- (24.51% to 9.46%) and third-line (21.54% to 4.78%) antibiotics decreased from 2010 to 2011, while sales volume for first-line antibiotics increased from 2010 to 2011 (7.96% to 13.94%) Percentage of drug sales for antimicrobials decreased from 25% (2011) to 17% (2012) Percentage of antimicrobial prescriptions decreased in both inpatient settings (68% versus 58%) and outpatient settings (25% versus 15%)
5 Xiao et al. (2013) <sup>12</sup>	China	Changes in Chinese policies to promote the rational use of antibiotics	Institution of regulation (antibiotic committees)	Time series analysis	2009–12	Antibiotic consumption (percentage of antimicrobial prescriptions) Percentage of overall drug sales	Moderate	Percentage of drug sales for antimicrobials decreased from 25% (2011) to 17% (2012) Percentage of antimicrobial prescriptions decreased in both inpatient settings (68% versus 58%) and outpatient settings (25% versus 15%)

Continued

Table 3. Continued

Authors	Country	Title	Intervention	Study design	Year	Outcome measure	Risk of bias	Outcome
6 Malmvall et al. (2007) <sup>17</sup>	Sweden	Reduction of antibiotics sales and sustained low incidence of bacterial resistance: report on a brood approach during 10 years to implement evidence-based indications for antibiotic prescribing in Jönköping County, Sweden	Institution of regulation (antibiotic committees)	Time series analysis	1993–2005	Antibiotic consumption (DDD per 1000 inhabitants/day in primary care) Resistance rates	Moderate	31% decrease in overall antibiotic consumption: 15.9 DDD in 1993 to 11.0 DDD in 2005 <ul style="list-style-type: none"> <li>Decrease most evident in children 5 to 14 years (number of antibiotic prescriptions decreased 52% (from 23 352 to 11 127)</li> </ul> No increase in the prevalence of resistant pneumococci or <i>Haemophilus influenzae</i> in the county
7 Zhang et al. (2017) <sup>13</sup>	Tianjin, China	Effectiveness of antibiotic use management in Tianjin (2011–2013): a quasi-experimental study	Institution of regulation (antibiotic committees)	Quasi-experimental study	2011–13	Antibiotic consumption (percentage of antibiotic use in inpatients; DDD per 100 patient days)	Moderate	Decrease in percentage of antibiotic use by inpatients (%): 60.38% in 2011 to 46.88% in 2013, $P < 0.000$ Decrease in DDD/100 patient days: 51.60 DDD in 2011 to 35.37 DDD in 2013, $P < 0.000$ Decrease in DDD per 1000 inhabitants/day: 16.3 DDD in 1993 to 13.0 DDD in 1997 <ul style="list-style-type: none"> <li>Reduction was most pronounced for children (0–6 years old): 15.7 DDD in 1993 to 9.7 DDD in 1997 per 1000 children/day</li> </ul>
8 Mölstad et al. (1999) <sup>14</sup>	Sweden	Major change in the use of antibiotics following a national programme: Swedish Strategic Programme for the Rational Use of Antimicrobial Agents and Surveillance of Resistance (STRAMA)	Institution of regulation (antibiotic committees)	Time series analysis	1980–97	Antibiotic consumption (DDD per 1000 inhabitants/day)	Moderate	Decrease in DDD per 1000 inhabitants/day: 15.7 DDD in 1995 to 12.6 DDD in 2004 Decrease in number of prescriptions per 1000 inhabitants per year: 536 prescriptions in 1995 to 410 prescriptions in 2004 <ul style="list-style-type: none"> <li>Reduction most prominent for children aged 5–14 years and macrolides</li> </ul> National frequency of penicillin-resistant <i>S. pneumoniae</i> increased from 4% to 6% despite decrease in antibiotic use among children Resistance in <i>S. pneumoniae</i> also increased to erythromycin, tetracyclines and co-trimoxazole between 1994 and 2004 Rate of ampicillin-resistant <i>E. coli</i> in urinary cultures increased from 17% to 24%, trimethoprim-resistant <i>E. coli</i> increased from 8% to 15% from 1997–2004 Decrease in DDD per 100 patient days: 39.37 DDD in 2011 to 26.54 DDD in 2012, $P < 0.001$ Decrease in percentage of antibiotic use in outpatient cases: 24.12% in 2011 to 18.71% in 2012, $P = 0.109$ Decrease in percentage of antibiotic use in inpatient cases: 64.85% in 2011 to 60.10% in 2012, $P = 0.006$
9 Mölstad et al. (2008) <sup>15</sup>	Sweden	Sustained reduction of antibiotic use and low bacterial resistance: 10-year follow-up of the Swedish STRAMA programme	Institution of regulation (antibiotic committees)	Time series analysis	1987–2004	Antibiotic consumption (DDD per 1000 inhabitants/day; number of prescriptions per 1000 inhabitants per year) Resistance rates	Moderate	Decrease in DDD per 1000 inhabitants/day: 15.7 DDD in 1995 to 12.6 DDD in 2004 Decrease in number of prescriptions per 1000 inhabitants per year: 536 prescriptions in 1995 to 410 prescriptions in 2004 <ul style="list-style-type: none"> <li>Reduction most prominent for children aged 5–14 years and macrolides</li> </ul> National frequency of penicillin-resistant <i>S. pneumoniae</i> increased from 4% to 6% despite decrease in antibiotic use among children Resistance in <i>S. pneumoniae</i> also increased to erythromycin, tetracyclines and co-trimoxazole between 1994 and 2004 Rate of ampicillin-resistant <i>E. coli</i> in urinary cultures increased from 17% to 24%, trimethoprim-resistant <i>E. coli</i> increased from 8% to 15% from 1997–2004 Decrease in DDD per 100 patient days: 39.37 DDD in 2011 to 26.54 DDD in 2012, $P < 0.001$ Decrease in percentage of antibiotic use in outpatient cases: 24.12% in 2011 to 18.71% in 2012, $P = 0.109$ Decrease in percentage of antibiotic use in inpatient cases: 64.85% in 2011 to 60.10% in 2012, $P = 0.006$
10 Zou et al. (2014) <sup>16</sup>	China	Is nationwide special campaign on antibiotic stewardship programme effective on ameliorating irrational antibiotic use in China? Study on the antibiotic use of specialized hospitals in China in 2011–2012	Institution of regulation (antibiotic committees)	Pre-post study	2011–12	Antibiotic consumption (DDD per 100 inpatient days; percentage of antibiotic use in outpatient and inpatient cases)	High	Decrease in DDD per 100 patient days: 39.37 DDD in 2011 to 26.54 DDD in 2012, $P < 0.001$ Decrease in percentage of antibiotic use in outpatient cases: 24.12% in 2011 to 18.71% in 2012, $P = 0.109$ Decrease in percentage of antibiotic use in inpatient cases: 64.85% in 2011 to 60.10% in 2012, $P = 0.006$

11	Allouch <i>et al.</i> (2016) <sup>7</sup>	Lebanon	Antibiotic use, cost, and consumption in tertiary hospitals in Lebanon: a comparative study before and after an implementation of antibiotic-restriction program (ARP)	Institution of regulation (clinical guidelines)	Retrospective cohort study	March–June 2013	Antibiotic consumption (proportion of subjects' antibiotic consumption pre and post implementation of antibiotic-restriction programme) Hospital antibiotic expenditure	Moderate	Decreases in proportional consumption of third-generation cephalosporins (19% to 12%, $P<0.001$ ), increase in the consumption of penicillin derivatives (24% to 28%, $P<0.001$ ). Decrease in rate of restricted antibiotic use: 37.1% versus 26.1%, $P<0.0001$ 22.3% decrease in the expenditure on all antibiotics ( $P<0.001$ ). 90% of hospitals had key structural resources and tools in place for effective antibiotic management and infection control 35% relative reduction from 2004 to 2008 in the incidence of nosocomial acquisition of MRSA among patients admitted to acute care hospitals 36% decrease in number of reimbursed packages per 1000 inhabitants per day Increased compliance with hand hygiene: 49% to 69% in 2005; 53% to 69% in 2007 Decrease in resistance rates from 2000 to 2007 ● Penicillin resistance in <i>S. pneumoniae</i> decreased from ~16% to ~10% ● Tetracycline resistance in <i>S. pneumoniae</i> decreased from 32% to 22% ● Erythromycin resistance in <i>S. pneumoniae</i> decreased from 37% to 25% ● Macrolide resistance in <i>Streptococcus pyogenes</i> decreased from 17% in 2001 to 2% in 2007
12	Goosens <i>et al.</i> (2008) <sup>19</sup>	Belgium	Achievements of the Belgian Antibiotic Policy coordination committee (BAPCOC)	Institution of regulation (clinical guidelines); public education campaigns	Time series analysis	1999–present	Antibiotic consumption (number of reimbursed packages per 1000 inhabitants per day) Hospitals with key structural resources and tools in place for effective antibiotic management and infection control Incidence of nosocomial acquisition of MRSA among patients admitted to acute care hospitals Resistance rate Compliance with hand hygiene	High	90% of hospitals had key structural resources and tools in place for effective antibiotic management and infection control 35% relative reduction from 2004 to 2008 in the incidence of nosocomial acquisition of MRSA among patients admitted to acute care hospitals 36% decrease in number of reimbursed packages per 1000 inhabitants per day Increased compliance with hand hygiene: 49% to 69% in 2005; 53% to 69% in 2007 Decrease in resistance rates from 2000 to 2007 ● Penicillin resistance in <i>S. pneumoniae</i> decreased from ~16% to ~10% ● Tetracycline resistance in <i>S. pneumoniae</i> decreased from 32% to 22% ● Erythromycin resistance in <i>S. pneumoniae</i> decreased from 37% to 25% ● Macrolide resistance in <i>Streptococcus pyogenes</i> decreased from 17% in 2001 to 2% in 2007
13	Tambić-Andrišević (2009) <sup>20</sup>	Croatia	Antibiotic resistance control in Croatia	Prescribing restrictions	Time series analysis	2003–8	Antibiotic consumption (DDD per 1000 inhabitants/day)	High	Decrease in DDD per 1000 inhabitants/day (outpatient): 23.6 DDD in 2003 to 22.6 DDD in 2008 Decrease in DDD per 1000 inhabitants/day (inpatient): 2.5 DDD in 2002 to 1.5 DDD in 2008 Decrease in oral antimicrobial prescriptions per 1000 inhabitants: 25.3% decrease in prescriptions, driven by decreases in $\beta$ -lactams, sulphonamides and tetracyclines Decrease in DDD per 1000 inhabitants: 4.620 DDD per 1000 inhabitants in 1995 to 4.122 DDD in 1996 Decrease in tetracycline use: 578 DDD in 1995 to 391 DDD in 1996 Decrease in percentage of antimicrobial use: 4.5% reduction in the use of antimicrobials in the primary healthcare sector in 1998 to 1999
14	Conly (2012) <sup>18</sup>	Canada	Antimicrobial resistance programs in Canada 1995–2010: a critical evaluation	Prescribing restrictions; public education campaigns	Time series analysis	1995–2010	Antibiotic consumption (oral antimicrobial prescriptions per 1000 inhabitants)	High	Decrease in DDD per 1000 inhabitants/day (inpatient): 2.5 DDD in 2002 to 1.5 DDD in 2008 Decrease in oral antimicrobial prescriptions per 1000 inhabitants: 25.3% decrease in prescriptions, driven by decreases in $\beta$ -lactams, sulphonamides and tetracyclines Decrease in DDD per 1000 inhabitants: 4.620 DDD per 1000 inhabitants in 1995 to 4.122 DDD in 1996 Decrease in tetracycline use: 578 DDD in 1995 to 391 DDD in 1996 Decrease in percentage of antimicrobial use: 4.5% reduction in the use of antimicrobials in the primary healthcare sector in 1998 to 1999
15	Sørensen and Monnet (2000) <sup>21</sup>	Denmark	Control of antibiotic use in the community: the Danish experience	Prescribing restrictions	Time series analysis	1995–6	Antibiotic consumption (DDD per 1000 inhabitants; percentage of antimicrobial use)	High	Decrease in DDD per 1000 inhabitants/day (inpatient): 2.5 DDD in 2002 to 1.5 DDD in 2008 Decrease in oral antimicrobial prescriptions per 1000 inhabitants: 25.3% decrease in prescriptions, driven by decreases in $\beta$ -lactams, sulphonamides and tetracyclines Decrease in DDD per 1000 inhabitants: 4.620 DDD per 1000 inhabitants in 1995 to 4.122 DDD in 1996 Decrease in tetracycline use: 578 DDD in 1995 to 391 DDD in 1996 Decrease in percentage of antimicrobial use: 4.5% reduction in the use of antimicrobials in the primary healthcare sector in 1998 to 1999

Continued



Table 3. Continued

Authors	Country	Title	Intervention	Study design	Year	Outcome measure	Risk of bias	Outcome
16 Fürst et al. (2015) <sup>22</sup>	Slovenia	The influence of a sustained multifaceted approach to improve antibiotic prescribing in Slovenia during the past decade: findings and implications	Prescribing restrictions; public education campaigns	Time series analysis	1995–2012	Antibiotic consumption (DDD per 1000 inhabitants/day); prescriptions per 1000 inhabitants; Resistance rates	Moderate	Decrease in prescriptions per 1000 inhabitants: 791.29 prescriptions in 1999 to 525.97 prescriptions in 2012 Decrease in DDD per 1000 inhabitants/day 20:38 DDD in 1999 to 14.01 DDD in 2012 ( $P<0.0001$ ); driven by significant decreases in tetracyclines; phenoxymethylpenicillin, cephalosporins and macrolides <i>S. pneumoniae</i> resistance to penicillin decreased from 14.5% to 10%. <i>S. pneumoniae</i> resistance to macrolides increased from 5.4% to 21% Decrease in DDD per 1000 inhabitants/day (1997 to 2008) <ul style="list-style-type: none"> <li>• Amoxicillin: 4.12 to 3.69</li> <li>• Tetracycline: 1.79 to 2.06</li> <li>• Macrolides: 1.12 to 0.49</li> <li>• Nitroimidazole: 0.22 to 0.15</li> <li>• Fluoroquinolone: 0.12 to 0.35</li> </ul> Primary <i>H. pylori</i> levofloxacin resistance rose from 4.9% in 2000–7 to 8.3% in 2008–10 and to 13.4% in 2011–12, $P=0.001$ Decrease in percentage of antibiotic prescription: lower by 12% in 2004 compared with 2000 Decrease in DDD per 1000 inhabitants/day: 14.57 DDD in 2004 to 2.80 DDD in 2000 <ul style="list-style-type: none"> <li>• Highest: increase in prescribing was established for macrolides (1.05 versus 1.64 DDD); penicillins were also prescribed more frequently (6.41 versus 6.56 DDD), but other subgroups were prescribed less frequently (cephalosporins and quinolones)</li> </ul> Quinolone resistance rates in disease-causing isolates of <i>E. coli</i> increased from 0.4% in 1992 to 4.9% in 2006. Since 2006, surveillance of isolates from community-acquired infections showed a decrease in resistance rates to 4.1% in 2008. Changes in number of antibiotic prescriptions per week <ul style="list-style-type: none"> <li>• Fluoroquinolones: 1905 fewer prescriptions per week, <math>P&lt;0.0001</math> between 2000 and 2001; driven by decrease in ciprofloxacin prescription (2084 fewer prescriptions per week, <math>P&lt;0.0001</math>)</li> <li>• Nitrofurantoin: 200 more prescriptions per week, <math>P&lt;0.0001</math></li> <li>• Trimethoprim/sulfamethoxazole: 532 more prescriptions per week, <math>P&lt;0.0001</math></li> </ul>
17 Liou et al. (2015) <sup>23</sup>	Taiwan, China	The primary resistance of <i>Helicobacter pylori</i> in Taiwan after the national policy to restrict antibiotic consumption and its relation to virulence factors—a nationwide study	Prescribing restrictions	Time series analysis	1997–2008	Antibiotic consumption (DDD per 1000 inhabitants/day); Resistance rates	Low	
18 Duborjica-Kovačević (2006) <sup>24</sup>	Montenegro	Antibiotic prescribing policy of the Republic Health Insurance Fund of Montenegro in the period 2000–2004: effects of drug utilization reform strategy	Prescribing restrictions	Pre–post study	2000–4	Antibiotic consumption (DDD per 1000 inhabitants/day); percentage of antibiotic prescriptions	High	
19 Cheng et al. (2012) <sup>25</sup>	Australia	Control of fluoroquinolone resistance through successful regulation	Prescribing restrictions	Time series analysis	1992–2010	Resistance rates	High	
20 Marshall et al. (2006) <sup>26</sup>	Canada	Impact of administrative restrictions on antibiotic use and expenditure in Ontario: time series analysis	Prescribing restrictions	Time series analysis	1999–2002	Antibiotic consumption (number of prescriptions per week)	Low	

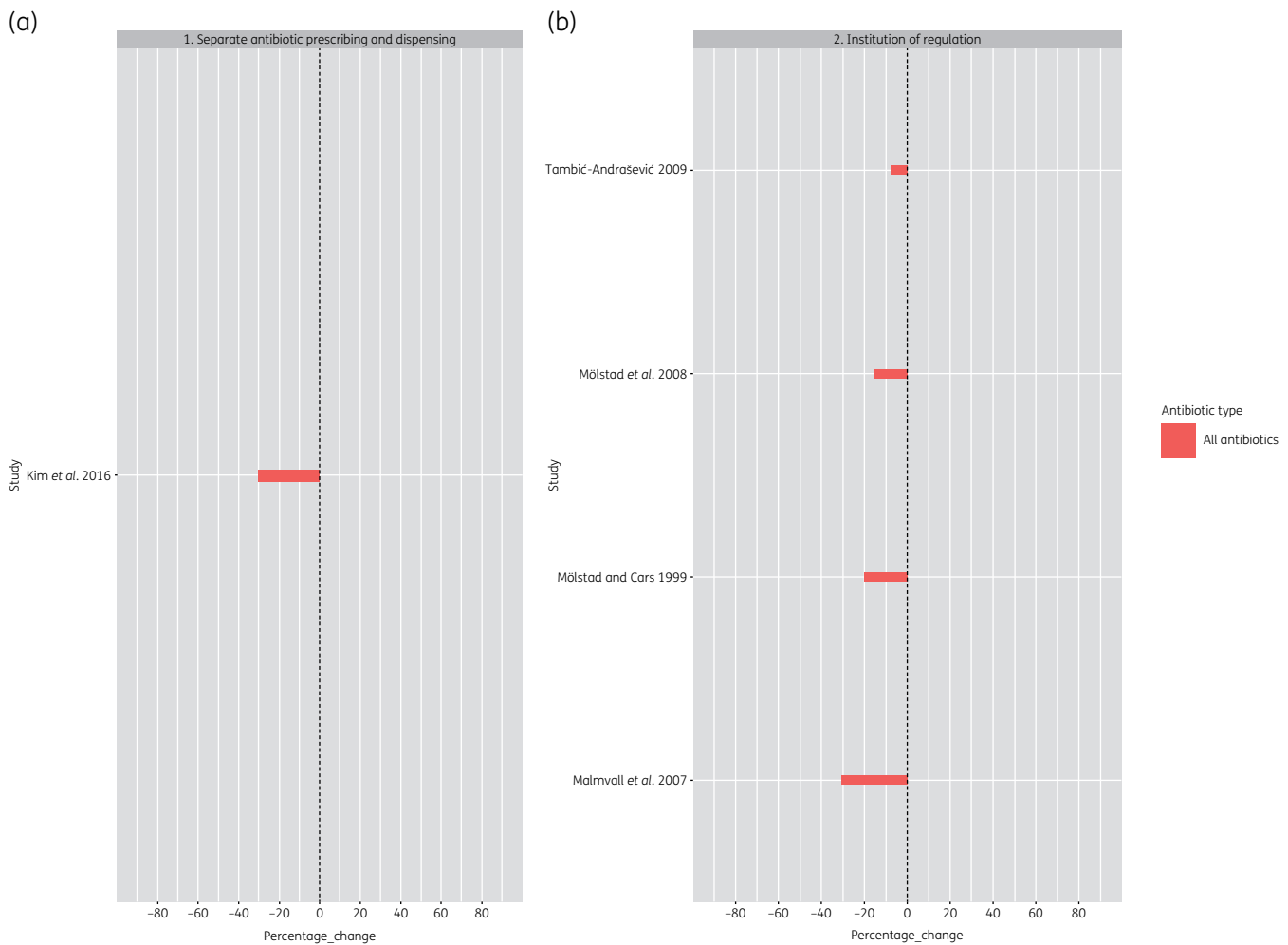
21	Klemann <i>et al.</i> (2016) <sup>27</sup>	Brazil	Socioeconomic determinants of antibiotic consumption in the state of São Paulo, Brazil: the effect of restricting over-the-counter sales	Prescribing restrictions	Time series analysis	2008–12	Antibiotic consumption (DDD per 1000 inhabitants/day)	Moderate	Decrease in DDD per 1000 inhabitants/day: 8.44 DDD in 2008 to 8.06 DDD in 2012
22	Rivas and Alonso (2011) <sup>28</sup>	Venezuela	Regulation of dispensing drugs and their effect on the consumption of antibiotics in Venezuela	Prescribing restrictions	Retrospective study	2005–8	Antibiotic consumption (DDD per 1000 inhabitants/day)	Moderate	Decrease in DDD per 1000 inhabitants/day (2005 to 2008) <ul style="list-style-type: none"> <li>• Diaminopyrimidines-sulfonamides: 1.11 to 1.01</li> <li>• Tetracyclines: 0.45 to 0.44</li> <li>• Aminoglycosides: 0.1357 to 0.1377</li> <li>• Rifampicin: 0.0111 to 0.012</li> <li>• Penicillins and first-generation cephalosporins: 6.37 to 8.09</li> <li>• Macrolides and lincosamides: 2.03 to 2.85</li> <li>• Fluoroquinolones: 1.68 to 2.58</li> <li>• Third-generation cephalosporins: 0.15 to 0.34</li> </ul> No significant difference between control and experimental cities: 7% increase in non-prescription probability in antibiotics immediately after the policy was in place, but the effect diminished over time
23	Chou <i>et al.</i> (2003) <sup>29</sup>	Taiwan	Impact of separating drug prescribing and dispensing on provider behaviour: Taiwan's experience	Separation of antibiotic prescribing from dispensing	Time series with control group	1996–9	Antibiotic prescription (probability of non-prescription) Average drug dispensing expenditure per visit	Low	Non-significant changes in average drug dispensing expenditure per visit Decrease in DDD per 1000 inhabitants/day: 28.8 DDD in 1998 to 22.8 DDD in 2008
24	Kim <i>et al.</i> (2016) <sup>30</sup>	South Korea	Antibiotic control policies in South Korea, 2000–2013	Separation of antibiotic prescribing from dispensing	Time series analysis	1998–2008	Antibiotic consumption (DDD per 1000 inhabitants/day)	High	Decrease in percentage of annual primary care prescriptions of antibiotics per physician (dividing the number of new filled prescriptions by the number of prescribers per year): <ul style="list-style-type: none"> <li>• 19.8% decrease in Minnesota</li> <li>• 20.4% decrease in Wisconsin</li> </ul> Decrease in the number of outpatient antibiotic prescriptions per 1000 inhabitants/day (2003 to 2007): <ul style="list-style-type: none"> <li>• Cephalosporins: 70 to 58</li> <li>• Macrolides: 134 to 110</li> <li>• Penicillins: 155 to 141</li> <li>• Fluoroquinolones: 101 to 101</li> <li>• Others: 66 to 61</li> <li>• Total: 526 to 471</li> </ul>
25	Belongia <i>et al.</i> (2005) <sup>31</sup>	Wisconsin and Minnesota, USA	Impact of statewide programme to promote appropriate antimicrobial drug use	Campaigns for healthcare professionals; public education campaigns	Pre-post study with control	1998–2003	Antibiotic prescription; annual primary care prescriptions of antibiotics per physician	Low	
26	Weiss <i>et al.</i> (2011) <sup>32</sup>	Quebec, Canada	Impact of a multipronged education strategy on antibiotic prescribing in Quebec, Canada	Campaigns for healthcare professionals; public education campaigns	Time series analysis	2003–7	Antibiotic consumption (number of outpatient antibiotic prescriptions per 1000 inhabitants/day)	Moderate	

Continued

Table 3. Continued

Authors	Country	Title	Intervention	Study design	Year	Outcome measure	Risk of bias	Outcome
27 Chahwakilian et al. (2011) <sup>33</sup>	France	Impact of the French campaign to reduce the inappropriate ambulatory antibiotic use on the prescription and consultation rates for respiratory tract infections	Campaigns for healthcare professionals; public education campaigns	Retrospective cohort study	2001–9	Antibiotic prescription (DDD per 1000 inhabitants/day; number of ambulatory antibiotic prescriptions per 1000 inhabitants/year; proportion of consultations resulting in antibiotic prescriptions)	Moderate	Decrease in DDD per 1000 inhabitants/day: 35.7 DDD in 2001 to 30.2 DDD in 2009 Decrease in the number of ambulatory antibiotic prescriptions per 1000 inhabitants/year • Pharmacy-based data: 1404 in 2001 to 1118 in 2009; 20.4% decrease • Physician-based data: 863 in 2001 to 577 in 2009; 33.1% decrease driven by decreased prescriptions for RTIs 23% decrease in the number of consultations for RTIs between 2001 and 2009 Decrease in the proportion of consultations resulting in antibiotic prescriptions: 58% in 2001 to 46% in 2009
28 Plachouras et al. (2014) <sup>34</sup>	Corinth, Greece	Promoting prudent use of antibiotics: the experience from a multifaceted regional campaign in Greece	Campaigns for healthcare professionals; public education campaigns	Pre–post study with control	January–February 2009	Antibiotic consumption (DDD per 1000 inhabitants/year; percentage of antibiotic use)	Moderate	Increase in DDD per 1000 inhabitants/year: 26 DDD (January–February 2009) to 32 DDD (March 2009) Changes in percentage of antibiotic use, $P=0.02$ : • Amoxicillin and penicillin: 34.3% increase • Macrolides: 21.9% decrease • Second-generation cephalosporins: 6.4% decrease • Fluoroquinolones: 21.9% decrease • Amoxicillin clavulanate: 9.4% decrease
29 Bernier et al. (2014) <sup>35</sup>	France	Outpatient antibiotic use in France between 2000 and 2010: after the nationwide campaign, it is time to focus on the elderly	Campaigns for healthcare professionals; public education campaigns	Time series analysis	2000–10	Antibiotic prescription (number of weekly antibiotic prescriptions per 1000 inhabitants)	Moderate	30% (95% CI –36.3 to –23.8) decrease in weekly antibiotic prescriptions during campaign period; no significant differences during non-campaign period 21% increase (95% CI 12.9%–29.6%) antibiotic consumption in seniors
30 Hemo et al. (2009) <sup>36</sup>	Israel	Can a nationwide media campaign affect antibiotic use?	Campaigns for healthcare professionals; public education campaigns	Pre–post study	2004–5; 2005–6	Antibiotic consumption (purchasing rates for upper respiratory infection, otitis media and pharyngitis)	Low	Decrease in antibiotic purchasing rates for: • Upper RTI (OR = 0.75; 95% CI 0.69–0.81) • Otitis media (OR = 0.65; 95% CI 0.59–0.72) • Pharyngitis (OR = 0.93; 95% CI 0.89–0.97)
31 Lambert et al. (2007) <sup>37</sup>	England	Can mass media campaigns change antimicrobial prescribing? A regional evaluation study	Public education campaigns	Pre–post study	2004, 2005	Antibiotic prescription; antibiotic prescriptions per 1000 STAR-FU (Specific Therapeutic group Age-Related Prescribing Units)	Moderate	21.7 fewer items prescribed per 1000 population ( $P<0.0005$ ); 5.8% absolute reduction in prescribing
32 Sabuncu et al. (2009) <sup>38</sup>	France	Significant reduction of antibiotic use in the community after a nationwide campaign in France, 2002–2007	Public education campaigns	Time series analysis	2002–7	Antibiotic prescription; number of antibiotic prescriptions per 100 inhabitants	Low	26.5% (95% CI –33.5 to –19.6) decrease in the number of antibiotic prescriptions per 100 inhabitants: • Mean number of all antibiotic prescriptions for all classes decreased (penicillins, cephalosporins, macrolides, cyclines, etc.) except for quinolones • Greatest decline –35.8% (95% CI –48.3% to –23.2%) observed in young children aged 6–15 years.

33	Parsons et al. (2004) <sup>40</sup>	England	Did local enhancement of a national campaign to reduce high antibiotic prescribing affect public attitudes and prescribing rates?	Public education campaigns	Time series analysis	1995/6–99/2000	Antibiotic prescription; number of antibiotic prescriptions per 1000 patients dispensed between 1995/6 and 1999/2000 Proportion of participants who believed that children should be prescribed antibiotics for a fever	Moderate	Decrease in number of antibiotic prescriptions per 1000 patients: 686 1995/6 to 431 in 1999/2000; not significant Decrease in the proportion of responders who believed that children should be prescribed antibiotics for a fever: 56% in 1995/6 to 49% in 1999/2000
34	Wutzke et al. (2006) <sup>39</sup>	Australia	Evaluation of a national programme to reduce inappropriate use of antibiotics for upper respiratory tract infections: effects on consumer awareness, beliefs, attitudes and behaviour in Australia	Public education campaigns	Time series analysis	2001–4 (June to August)	Antibiotic prescription (total antibiotic prescriptions dispensed in the community; total antibiotic prescriptions dispensed for upper respiratory tract infections)	Moderate	Decrease in total antibiotic prescriptions in the community: 23.08 million antibiotic prescriptions in 1998/9 to 21.44 million in 2001/2 Decrease in total antibiotic prescriptions for upper respiratory tract infections: 216 000 fewer prescriptions for upper respiratory tract infections from 2001 to 2003



**Figure 4.** Percentage change in DDD per 1000 inhabitants per day post intervention. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

outcomes between settings could stem from differences in study designs, data collection methods and the diverse number of outcome indicators used. The WHO recommends use of DDD to assess and compare trends in drug consumption between population groups.<sup>41</sup> However, only 10 studies used this outcome measure (Figure 4).

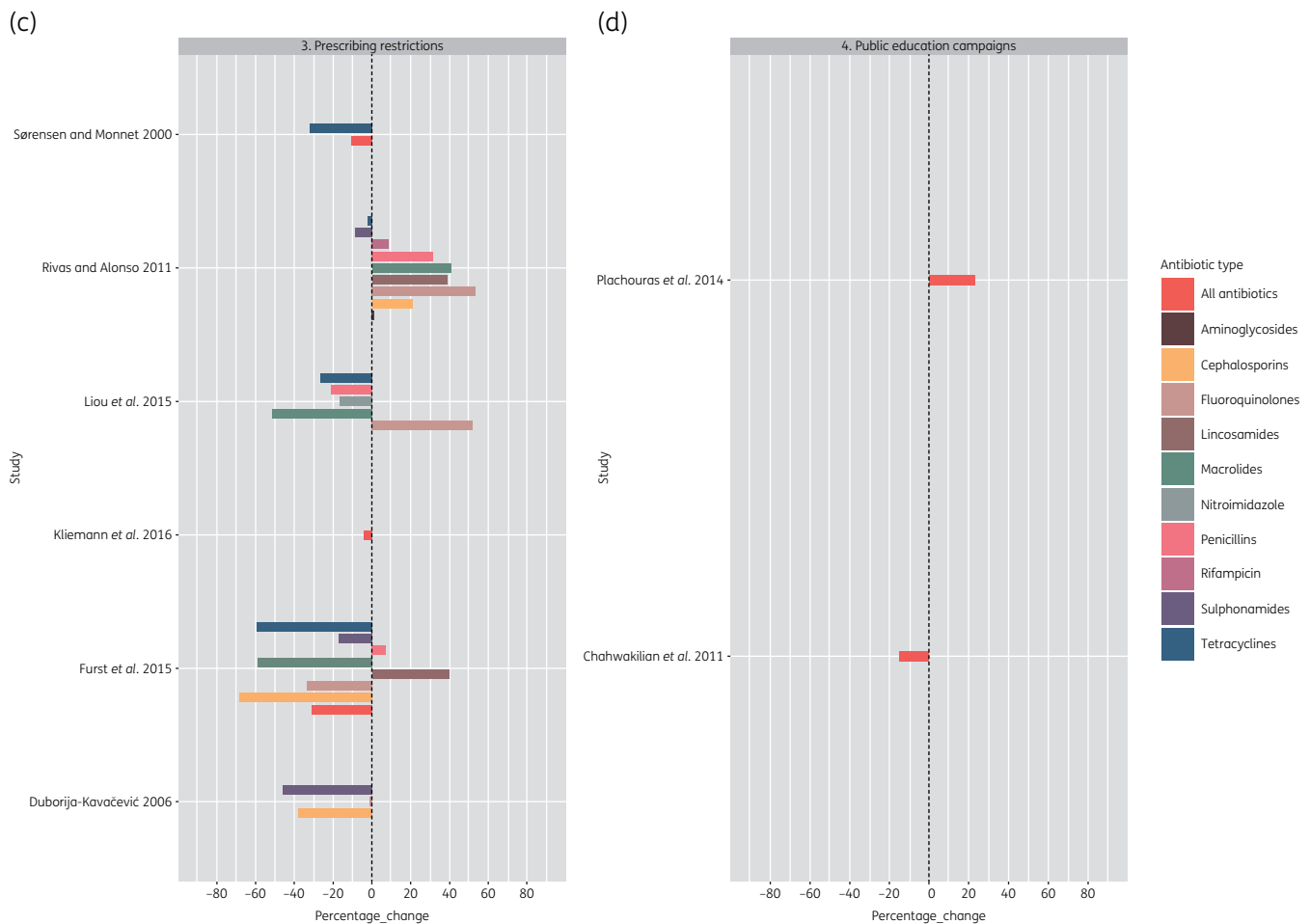
## Discussion

In our systematic review of responsible use initiatives that have been implemented at the national and/or subnational level to address antibiotic resistance, we identified 34 articles that detailed interventions carried out in 21 high- and upper-middle-income countries. These interventions addressed both access to and demand for antibiotics, with the most common outcome measure of impact being changes in antibiotic consumption. Heterogeneity of study designs, populations, analytical strategies and effect measures meant it was not possible to conduct a meta-analysis. However, overall evidence suggested that interventions were effective in reducing antibiotic consumption in different countries to varying degrees.

However, summarizing evidence of the impact of national interventions from our review was challenging, because studies used a wide range of evaluation and outcome measures, such as compliance rates, resistance rates, general knowledge and perceptions surrounding antibiotic use and antibiotic resistance, and population levels of antibiotic consumption. The heterogeneous outcome measures used to evaluate the effectiveness of the intervention made comparison of results challenging and could pose potential difficulties in decision making or implementation of interventions.

While antibiotic consumption was the most common type of outcome reported, it was also measured in a number of different ways, including prescription rates, sales value or volume, number of prescriptions and DDD. Due to variability in specific outcome measures used, only 10 comparable studies evaluating the impact of national programmes on DDD were available. Standardized outcomes and outcome assessment tools would greatly enhance capacity to monitor global progress in addressing AMR, and allow better assessments of intervention effectiveness in different settings.

Additionally, although establishing a direct link between antibiotic consumption and resistance rates is a crucial aspect of



**Figure 4.** Continued.

evaluating national initiatives, we found only five studies in our review linking population-level antibiotic consumption to resistance levels, and these reported mixed results; in some studies, decreased antibiotic consumption did not lead to lowered resistance rates. Establishing an association between antibiotic consumption and resistance rates could help to determine the extent to which reducing antibiotic consumption is an effective intervention, as well as to assess how this compares with other types of interventions, such as improving vaccination coverage and reducing animal antibiotic use. However, the evidence on this remains limited.

There were other challenges in evaluating the success of national- or subnational-level AMR interventions. First, most of the studies included in our review were before–after evaluations. As such, secular changes independent of the intervention might have affected outcomes, such as changes in vaccination policies, or improvements in medical education. Second, reductions in overall population-level antibiotic consumption may not be synonymous with reductions in inappropriate antibiotic use. It was not possible from these data to determine how much inappropriate use was reduced by specific interventions. Further, comparison across countries was challenging as studies were done over different timescales and at different timepoints. Lastly, as most of the

evaluations included in our review were not long term, it was difficult to assess whether reduction in antibiotic consumption from the intervention was sustained over time, whether it led to other adverse outcomes (e.g. increased prescribing of third-line antibiotics) or whether antibiotic consumption bounced back after a certain time period.

### Strengths and limitations

In interpreting evidence from these national interventions, several limitations should be borne in mind. We were unable to exclude publication bias or reporting bias, which might have impacted the validity and generalization of our conclusions. Very few studies included in our review showed limited or no impact post intervention; the majority of them were examples of interventions that had a positive impact. We were also unable to identify evaluations of national programmes that were not published. Additionally, all the published studies evaluating national implementation of AMR interventions came from high- and upper-middle-income countries, despite the fact that increases in antibiotic consumption are largely driven by increased demand in LMICs.<sup>2</sup> Previous evidence has shown that LMICs have different priorities and contextual issues, such as health system processes, patient demand, varying

cultures of care, availability of universal access to quality antimicrobials, laboratory infrastructure and surveillance systems.<sup>42,43</sup> In these settings, multipronged interventions combining different restrictive and enabling strategies are more likely to be effective.<sup>44</sup>

Although we were unable to review unpublished evidence, we sought to minimize potential biases due to language and geography as much as possible, by not applying any language restrictions in our review, and searching smaller, more regionally focused databases (e.g. WPRIM) to capture regional or geographically focused research that may not have been indexed in larger, standard academic databases. Similar to a preceding study,<sup>44</sup> this review sought to bring together evidence on the types of government policy interventions and options in addressing AMR. One notable strength of this review is the focus on the population impact of evaluated national interventions to address AMR. This has important policy implications, because although the efficacy of many interventions to address AMR may have been determined in idealized trial conditions in specific settings, it is difficult to generalize their impact, even if they can be scaled up nationally. Published evaluations of national interventions using standardized methods should form a key component of national action plans to address AMR, so that information on what types of interventions work in different settings can be readily shared and adapted by other countries.

## Conclusions

Based on the available evidence from primarily high-income countries, our systematic review highlights that strategies to reduce inappropriate demand and access to antibiotics appear to have a quantifiable impact primarily on antibiotic consumption, but more evidence is needed on the long-term impacts of these interventions, such as increases in the consumption of antibiotic subtypes, impacts on prevalence of antibiotic-resistant organisms, as well as the health and economic burden of these infections. It is also challenging to generalize interventions such as restricting access to non-prescription antibiotics to other settings where there may not currently be an adequate number of qualified prescribers in primary care, and where there may be adverse consequences in terms of restricting access to necessary antibiotics. More evidence is needed on the types of interventions that are relevant and effective in these settings. In addition, harmonizing the use of standardized outcome measures in the evaluation of national programmes addressing AMR is crucial to enable comparisons of interventions that are carried out in different settings, longer term and across different populations.

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## Transparency declarations

None to declare.

## Author contributions

All authors attest that they meet the ICMJE criteria for authorship. J. M. L. and C. C. T. conceived the idea for the manuscript and drafted the paper. All authors contributed to critically revise the manuscript and approved the final article.

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