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Highlights

- The World Health Organization recommend a balanced national strategy for antimicrobial resistance (AMR) control.
- Most awards were mainly focused on understanding the overall AMR status in South Korea.
- More balanced funding and co-operation with private and global sectors is needed.

Are we investing wisely? A systematic analysis of nationally funded antimicrobial resistance projects in Republic of Korea, 2003–2013

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ABSTRACT

From 2003–2013, South Korea has conducted the National Antimicrobial Resistance Safety Control Program (NARSCP). The purpose of the current study was to systematically review national antimicrobial resistance (AMR) research trends and to provide guidance on future allocation of research funding to enable a comprehensive approach in AMR control. This study collected project reports related to AMR published by the Ministry of Food and Drug Safety, the Ministry of Health and Welfare and the Korea Centers for Disease Control and Prevention between 2003 and 2013. These reports were analysed by topics based on the AMR action plan of the World Health Organization (WHO), period of study, categories along the research pipeline and types of receiving institution. A total of 198 project reports were included, with total funding of US$18.3 million. Mean funding per award was US$92 750, with a median of US$71 714. Among the WHO-suggested criteria, the basic microbial research and surveillance sector accounts for 143 (72.2%) of all awards. Yearly project funding increased from US$961 476 in 2003 to US$1 553 294 in 2013. Operational research was 61.5% and product development was 0.7% of the basic microbial research and surveillance sector. By institution, academia received 145 awards (73.2%). During progress of the NARSCP, total research funding increased significantly, but most awards were focused on understanding the overall picture of the nationwide AMR status. More balanced funding is needed, and encouraging active participation of private and international sectors is also required in reducing AMR.

1. Introduction

Antimicrobial agents play a crucial role in the treatment of infectious diseases. However, excessive and inappropriate use of antimicrobial agents has caused global increases in antimicrobial resistance (AMR) [1–3]. The emergence of resistant bacteria has resulted in treatment failures, increased mortality and significant healthcare costs [4,5]. The prevalence of resistance across a range of bacteria is high in Asia and specifically in South Korea [6]. According to an economic evaluation of AMR associated with meticillin-resistant *Staphylococcus aureus* (MRSA), implemented by the Korea Institute for Health and Social Affairs in 2006, the duration of hospital stay and the medical costs associated with AMR increased 1.8-fold and 1.25-fold, respectively [7]. The USA estimates the annual economic cost of AMR to be US$60 billion [8]. The World Health Organization (WHO) has repeatedly stated concerns about the increasing current and future threat posed by AMR and has strongly recommended strategic national and international approaches for AMR management [9,10].

In 2014, through the 67th World Health Assembly, the WHO emphasised the importance of the specific global action plans for AMR and presented a guideline of AMR control [11,12]. The USA and UK have already established strategies for AMR as well as initiatives on nationwide management [13–15].

AMR is increasing in South Korea. Since 2007, from the initiation of national surveillance programmes related to AMR, the prevalence of oxacillin-resistant *S. aureus* is consistently around 60%. Imipenem-resistant *Acinetobacter baumannii* increased from 20% to 62%, and imipenem-resistant *Pseudomonas aeruginosa* also increased from 26% to 42% [16]. Furthermore, South Korea continuously receives significant numbers of medical tourists from neighbouring countries, including China, where emerging issues related to AMR continue to cause serious concerns [17,18]. There is also noted widespread AMR across other Asian countries [19]. South Korea is a member of the G20 countries and has the 13th largest economy in the world [20]. In 2013, Korean research and development expenditure was 4.1% of the country's overall gross domestic product (GDP), second only to Israel and significantly higher than other developed countries such as the USA, UK, Germany and China [21]. Thus, how South Korea invests its research budgets is of great importance, not just for public health in South Korea but potentially for the global health community as well. It is imperative that distribution of limited resources uses strategic and smart approaches.

From 2003–2013, South Korea implemented a National Antimicrobial Resistance Safety Control Program (NARSCP), which was led by the Ministry of Food and Drug Safety (MFDS), the Ministry of Health and Welfare (MoHW) and the Korea Centers for Disease Control (KCDC) [22]. The first NARSCP, conducted from 2003–2007, was organised by the MFDS. During the second NARSCP, conducted from 2008–2013, the human health sector was organised by the MoHW and KCDC, and the veterinary health sector was organised by the MFDS [23].

There have been previous studies investigating research investments for AMR in the UK and across Europe [24,25]. This is the first study to describe the research investments related to AMR from the Korean funders (MFDS, MoHW and KCDC), which implemented NARSCP from 2003–2013 inclusive. We describe trends in total investment and across different types of research and also suggest future national and international research priorities.

2. Materials and methods

2.1. Data sources

This study collected award information through: (i) searching AMR-related research reports with keywords (antibiotics, antimicrobials, resistance, nosocomial infection and infection control) in the database of Policy Research Information Service & Management (http://www.prism.go.kr), the MFDS research management system (http://rnd.mfds.go.kr), electronic libraries of the National Center for Medical Information and Knowledge (http://library.nih.go.kr) and the National Assembly Library (http://nanet.go.kr); (ii) requesting award data from the policy-related divisions of the research aid institutions; and (iii) requesting award data directly from Korean research institutions. All award amounts were adjusted for inflation and are reported in 2013 US$. This study excluded AMR relating to viruses and parasites. Furthermore, tuberculosis was also excluded because this is covered by the Korean National Tuberculosis Control Program (ongoing since 1965 and data were not immediately available for analysis here), and thus NARSCP did not include projects directly related tuberculosis [26]. This study also excluded awards for research meeting support such as AMR-related academic symposiums.

2.2. Categorisation of awards

Categorisation was carried out by three authors (SHR, JCH and EHC) by reading the title and abstract of each award. Research awards were allocated to any of five categories used by the WHO's AMR action plan (awareness improvement, basic microbial research and surveillance, infection control, optimal use of antibiotics, and economic evaluation). In addition, awards were also categorised according to their type of science along the research pipeline. Categories were replicated from those used by the Research Investments in Global Health study [pre-clinical, clinical (phase 1, 2 or 3), product development, and implementation and operational research (including infection disease surveillance and epidemiology)] [27]. Statistical analysis was conducted using PASW Statistics for Windows v.18.0 (SPSS Inc., Chicago, IL).

3. Result

During the study period (2003–2013), the MFDS, MoHW and KCDC supported a total of 198 research projects, with a total investment of $18.3 million. Mean funding per award was $92 750 (standard deviation $72 126), with a median of $71 714 (interquartile range $44 377–119 750). Considering the awards according to the five categories suggested by the WHO's AMR action plan, 143 (72.2%) were categorised as basic microbial research and surveillance, with a total investment of $14.1 million

(76.8% of all investment) (Table 1). There was only one study in 2006, receiving $64 002 (0.3% of all investment), that focused on economic evaluation of AMR.

Temporal trends showed that total annual investment and individual award size broadly increased over the study period, from $961 476 (10 projects, mean award $96 147) in 2003 to $1 553 294 (14 projects, mean award $110 949) in 2013 (Fig. 1A). The proportion of research awarded by categories from WHO showed that most projects were focused on basic microbial research and surveillance (Fig. 1B).

Among the total 143 projects in the basic microbial research and surveillance category, pre-clinical research recorded 54 awards (37.8%) with total funding of $4 116 027 ($60 560 mean award), product development research recorded 1 award with total funding of $53 888, and operational research recorded 88 awards (61.5%) with total funding of $9 939 360 ($92 807 mean award). The distribution of the research pipeline was remained similar over the study period (Fig. 2). Within the operational research category, there were 10 projects related to awareness improvement (of which 2 had a physician-related focus and 8 focused on awareness in the community), 33 for infection control, 11 for optimal use of antibiotics (of which 8 had a focus on physicians in hospitals and 3 focused on antibiotic use in the community) and 1 for economic evaluation.

By receiving research institution, academia (such as universities and academic societies) received 145 awards (73.2%) with total funding of $12 546 019 (68.3% of all investment) and public institutions such as national agencies received 44 awards

(22.2%) with total funding of $4 861 917 (26.5%). Private institution and private research facilities received 9 awards (4.5%) with total funding of $956 601 (5.2%).

There were 178 studies (89.9%) receiving $16 916 285 (92.1% of all investment) that did not focus on a specific pathogen but more broadly carried out research on general issues relating to AMR. Of the remainder, 11 awards focused on *Staphylococcus*, 7 on *Treponema* and just 1 each for *Escherichia coli* and *Streptococcus*. There was no clear association between the trend of annual investment and the resistance trends of major pathogens (Fig. 3). There were no included research projects that could be categorised as global health.

4. Discussion

The emphasis on AMR management has been increasing, as shown by the publication of the WHO AMR action plan. The WHO has placed an emphasis on collaborative and government-led efforts on AMR issues. South Korea had conducted NARSCP under the supervision of government agencies including the MFDS, MoHW and KCDC. The current study analysed the AMR research projects funded by NARSCP from 2003–2013, categorising the awards by study type, type of science along the research pipeline, and trends in investment over time. This is the first study that has reviewed AMR research trends based on categorisations of the WHO's AMR action plans.

Although annual funding has broadly increased over the study period, there is noted volatility in total investment per annum. For example, the main reason for a decrease in research investment in 2008 was because of the termination of the first NARSCP by the MFDS in 2007. Likewise, the second funding decline in 2013 was mainly due to termination of the second NARSCP. These findings highlight the dependence on projects schedules and unstable support of national AMR programmes. Compared with the levels of funding applied to basic microbial research and surveillance (76.8% of the total investment), research projects in the categories of awareness improvement (3.2%) and optimal use of antibiotics (5.5%) were relatively small and presumably insufficient. Despite the importance of carrying out economic evaluations of AMR management, only one project received investment in this area. Moreover, operational research covered the majority of investment, whilst there was very little investment for clinical trials and product development research.

The prevalence of resistance is worryingly high and is still increasing across much of Asia and in South Korea for pathogens of global importance such as MRSA, vancomycin-resistant enterococci, imipenem-resistant *A. baumannii* and imipenem-resistant *P. aeruginosa*. Within South Korea, prescription of broad-spectrum antibiotics is increasing and may be influencing the changing epidemiology of AMR [28]. Therefore, there is a strong argument for increasing investment in pathogen-specific research alongside the portfolio of general AMR projects, as well as research on smarter policies relating to antibiotic stewardship. The clear lack of cross-border research indicates little focus from government sources on South Korea's position and contribution to the global health community and related AMR issues. There is no obvious indication that institutions are widely collaborating with international groups and this would be a clear and important area with potential for expansion (particularly with countries where there are significant business, trade or tourist interests and thus greatest potential for contributing to evolution of resistance trends). There is also an argument that it is an ethical imperative that South Korea, as a high-income country, should further contribute to global efforts to address AMR.

A limitation of this study is that it only considered the research projects conducted by the NARSCP-associated government agencies, which account for 12.1% of the total South Korea national fiscal budget and only considered the funding body's internal reporting systems [29]. Owing to resource constraints, we could not properly consider the impact or outputs of the research projects included here. The lack of private sector investment information is a main data gap of this study, and resource constraints meant we could not obtain and analyse data from the Korean Institute of Tuberculosis. We did not consider AMR related to virology, parasitology and tuberculosis. We also did not include research relating to development of new products that could impact on AMR trends, such as vaccines.

As the WHO has announced their AMR action plans, the importance of AMR management is receiving global attention. The WHO Global Observatory on Health R&D is also wishing to establish a global strategy to inform thinking about resource allocation for research, and this will require national and international data sets of R&D analyses across all areas of health [30]. Through the NARSCP portfolio, total investment in AMR research has steadily increased over time, as has the median award per project and the number of projects annually. None the less, there was no significant effort to reduce the increasing trends or high prevalence of resistance for several pathogens. Funding sources are unstable and there is a lack of emphasis on pathogen-specific research. International collaborations and research related to prescription of antibiotics and health economics are some of the areas that need to be improved. Following termination in 2013 of the second NARSCP, South Korea appears to be in need of further leadership with regard to government research in the area of AMR to more fully contribute to national and international priorities. Analyses such as these can support AMR surveillance systems and contribute to improved efforts regarding resource allocation for research—we must invest wisely.

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References

[1] Boucher HW, Talbot GH, Bradely JS, Edwards JE, Gilbert D, Rice LB, et al. Bad bugs, no drugs: no ESKAPE! An update from the Infectious Disease Society of America. Clin Infect Dis 2009;48:1–12.

[2] Schwartz B, Bell DM, Hughes JM. Preventing the emergence of antimicrobial resistance. A call for action by clinicians, public health officials and patients. JAMA 1997;278:944–5.

[3] Theuretzbacher U. Global antibacterial resistance: the never-ending story. J Glob Antimicrob Resist 2013;1:63–9.

[4] Song JH. Current status and future strategies of antimicrobial resistance in Korea. Korean J Intern Med 2009;77:143–51.

[5] Gandra S, Barter DM, Laxminarayan R. Economic burden of antibiotic resistance: how much do we really know? Clin Microbiol Infect 2014;20:973–80.

[6] Kang CI, Song JH. Antimicrobial resistance in Asia: current epidemiology and clinical implications. Infect Chemother 2013;45:22–31.

[7] Park EJ. *Impact of antimicrobial resistance on economic outcome*. Sejong City, South Korea: Korea Institute for Health and Social Affairs; 2006.

[8] US Centers for Disease Control and Prevention (CDC). *Antibiotic resistance threats in the United States, 2013.* Atlanta, GA: CDC; 2013. http://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf [accessed 1 February 2016].

[9] World Health Organization. *Antimicrobial resistance: global report on surveillance 2014*. Geneva, Switzerland: WHO; 2014.

[10] World Health Organization. *Antimicrobial resistance, Resolution.* 2011. Regional Committee for the Western Pacific, 62 Session.

[11] World Health Organization. *Antimicrobial resistance.* 67th World Health Assembly Agenda Item 16.5. 2014.

[12] World Health Organization. *Draft global action plan on antimicrobial resistance*. 2014. http://apps.who.int/gb/ebwha/pdf_files/EB136/B136_20-en.pdf [accessed 1 February 2016].

[13] UK Department of Health. *UK five year antimicrobial resistance strategy 2013 to 2018*. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/244058/20130902_UK_5_year_AMR_strategy.pdf [accessed 1 February 2016].

[14] The White House. *National strategy for combating antibiotic-resistant bacteria*. 2014. http://www.cdc.gov/drugresistance/pdf/carb_national_strategy.pdf [accessed 1 February 2016].

[15] European Centre for Disease Control and Prevention/European Medicines Agency. *The bacterial challenge: time to react*. http://ecdc.europa.eu/en/publications/Publications/0909_TER_The_Bacterial_Challenge_Time_to_React.pdf [accessed 1 February 2016].

[16] Kim HS, Kim JI, Chan C, et al. Monitoring of antimicrobial resistance on non-tertiary hospitals in Korea, 2007–2013. Public Health Weekly Report

2015;8:1092–5. http://www.cdc.go.kr/CDC/cms/cmsFileDownload.jsp?fid=31&cid=66231&fieldName=attach1&index=1 [accessed 21 March 2016].

[17] South Korean medical tourism increasing. Int Med Travel J 2014. http://www.imtj.com/news/south-korean-medical-tourism-increasing/ [accessed 1 February 2016].

[18] Xiao Y, Li L. The actions of China in containing antimicrobial resistance. AMR Control 2015. http://www.globalhealthdynamics.co.uk/wp-content/uploads/2015/05/07_Xiao-Li.pdf [accessed 1 February 2016].

[19] Lai CC, Lee KW, Xiao YH, Ahmad N, Veeraraghavan B, Thamlikitkul V, et al. High burden of antimicrobial drug resistance in Asia. J Glob Antimicrob Resist 2014;2:141–7.

[20] The World Bank. *GDP 2014*. http://data.worldbank.org/indicator/NY.GDP.MKTP.CD?order=wbapi_data_value_2014+wbapi_data_value+wbapi_data_value-last&sort=desc [accessed 1 February 2016].

[21] The World Bank. *Research and development expenditure 2014*. http://data.worldbank.org/indicator/GB.XPD.RSDV.GD.ZS?order=wbapi_data_value_2013+wbapi_data_value&sort=desc [accessed 1 February 2016].

[22] Korea Food and Drug Administration. *National Antimicrobial Resistant Safety Control Project Report*. 2003.

[23] Lee KW. *Study of antimicrobial resistance management system*. Korea Food and Drug Administration; 2011

[24] Head MG, Joseph R, Fitchett JR, Cook MK, Wurie FB, Atun, R, et al. Systematic analysis of funding awarded for antimicrobial resistance research to institutions in the UK, 1997–2010. J Antimicrob Chemother 2014;69:548–54.

[25] Kelly R, Zoubiane G, Walsh D, Ward R, Goossen H. Public funding for research on antibacterial resistance in the JPIAMR countries, the European Commission, and related European Union agencies: a systematic observational analysis. Lancet Infect Dis 2016;16:431–40.

[26] Kim JH, Yim JJ. Achievements in and challenges of tuberculosis control in South Korea. Emerg Infect Dis 2015;21:1913–20.

[27] Head MG, Fitcher JR, Cooke MK, Wurie FB, Hayward AC, Atun R. UK investments in global infectious disease research 1997–2010: a case study. Lancet Infect Dis 2013;13:55–64.

[28] Yoon YK, Park GC, An H, Chun BC, Sohn JW, Kim MJ. Trends of antibiotic consumption in Korea according to national reimbursement data (2008–2012). Medicine (Baltimore) 2015:94:e2100.

[29] Ministry of Strategy and Finance. *Open fiscal data 2013*. http://www.openfiscaldata.go.kr/portal/theme/themeProfile3.do [accessed 1 February 2016].

[30] Kieny MP, Viergever RF, Adam T, Boerma T, Røttingen JA, et al. Global platform to inform investments for health R&D. Lancet 2016;387:1157.

Fig. 1. (A) Cumulative distribution of investment by the category of antimicrobial resistance (AMR) action plan and the period and (B) proportional breakdown of the category of AMR action plan within the period.

Fig. 2. Total annual investment on antimicrobial resistance research by the research pipeline.

Fig. 3. Annual investment for antimicrobial resistance research alongside resistance trends of selected pathogens of importance in South Korea.

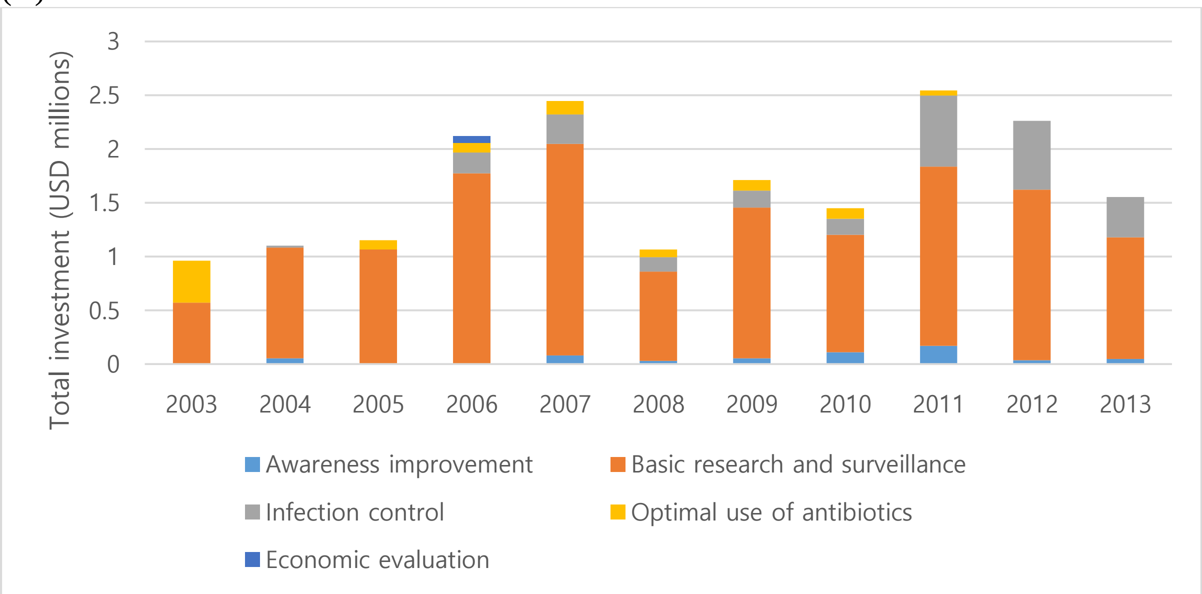
Table 1

Investment in antimicrobial resistance (AMR) by the number, total investment, and mean and median awards by categories from the World Health Organization (WHO)

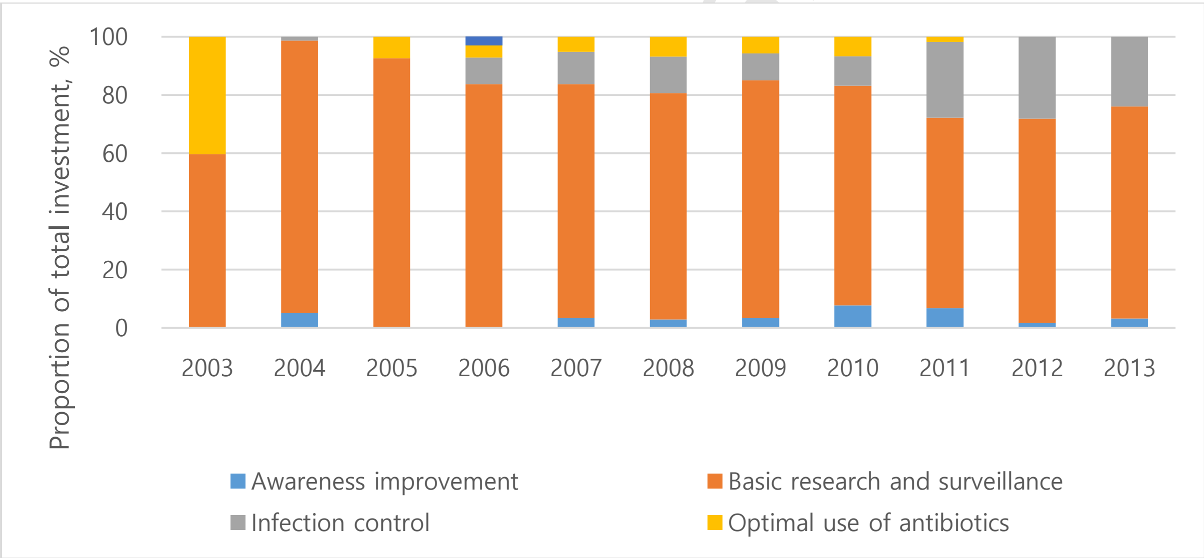
Type	No. of awards	Proportion (%)	Total investment (US$)	Proportion (%)	Mean award (S.D.)	Median award (IQR)
Awareness improvement	10	5.1	592 208	3.2	5 922 075 (46 421)	42 620 (30 102–60 726)
Basic microbial research and surveillance	143	72.2	14 109 276	76.8	98 666 (66 791)	78 270 (52 991–127 152)
Infection control	33	16.7	2 592 845	14.1	78 571 (87 011)	38 146 (28 999–98 054)
Optimal use of antibiotics	11	5.6	1 006 208	5.5	91 473 (102 937)	62 368 (36 389–89 104)
Economic evaluation	1	0.5	64 003	0.4	64 003	64 003
Total	198	100	18 364 539	100	92 750 (72 126)	71 714 (44 377–119 750)

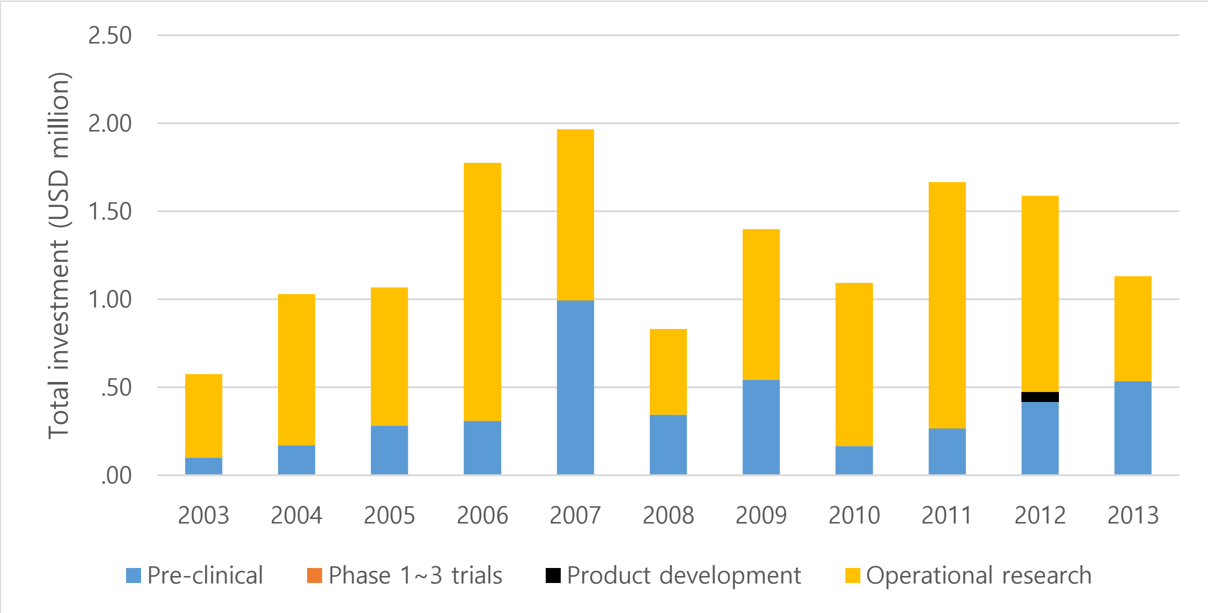
S.D., standard deviation; IQR, interquartile range.

(A)

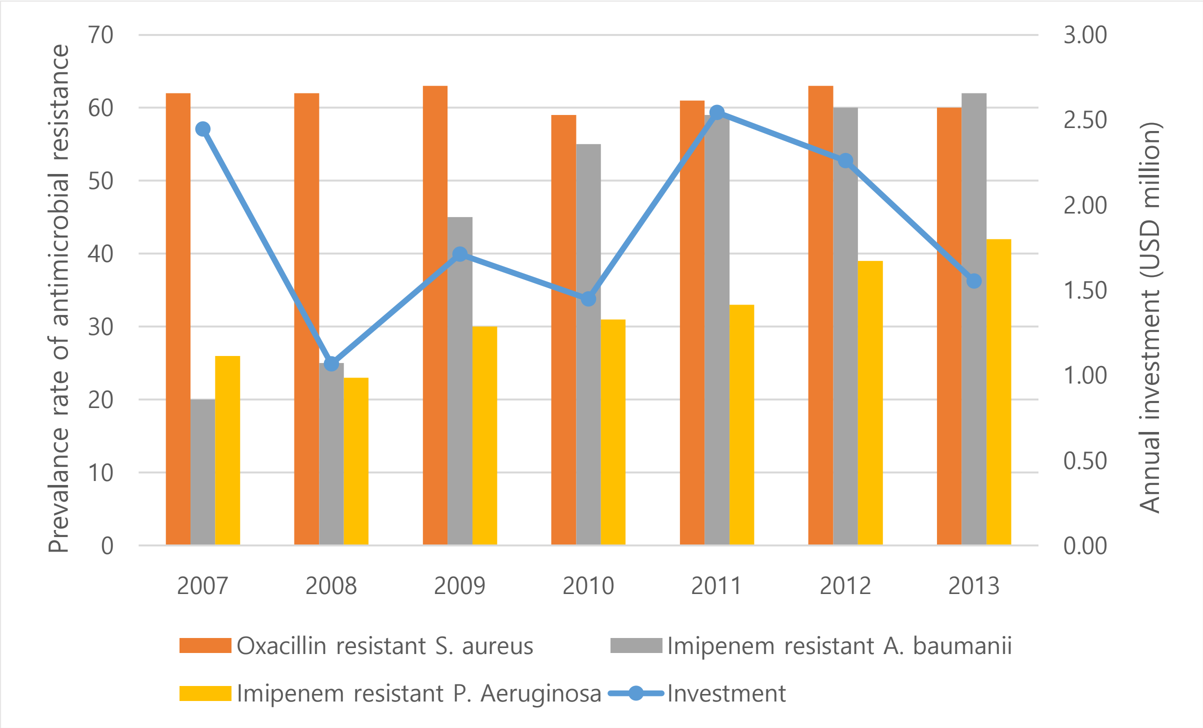

Total investment (USD millions)
3
2.5
2
1.5
1
0.5
0
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
Awareness improvement
Basic research and surveillance
Infection control
Optimal use of antibiotics
Economic evaluation

(B)


Proportion of total investment, %
100
80
60
40
20
0
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
Awareness improvement
Basic research and surveillance
Infection control
Optimal use of antibiotics



Total investment (USD million)
2.50
2.00
1.50
1.00
.50
.00
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
Pre-clinical
Phase 1~3 trials
Product development
Operational research


Prevalance rate of antimicrobial resistance
70
60
50
40
30
20
10
0
3.00
2.50
2.00
1.50
1.00
0.50
0.00
Annual investment (USD million)
2007
2008
2009
2010
2011
2012
2013
Oxacillin resistant S. aureus
Imipenem resistant A. baumanii
Imipenem resistant P. Aeruginosa
Investment