Promotion of antimicrobial stewardship following the issuance of the antimicrobial resistance national action plan in Japan: a systematic review of 2016 to 2020

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REVISED ABSTRACT

Background
Antimicrobial resistance (AMR) is a global threat with the potential to cause a significant healthcare burden. In 2016, the Japanese government issued the national action plan (NAP) for AMR. Since the issuance of this plan, several studies on antimicrobial stewardship programs (ASP) have been published in Japan. We therefore performed the present systematic review of these studies to elucidate the current state of ASP and the impact of the NAP on promotion of ASP.

Methods
Medline (PubMed) and EMBASE were searched for studies published between January 2016 and the end of September 2021. ROBINS-I was used to assess the risk of bias in interventional studies, and the Newcastle-Ottawa Scale was used to assess the quality of cohort, case-control, and cross-sectional studies.

Results
Eighty studies, including 30 (37.5 %) interventional studies, 15 (18.8 %) database-oriented studies, and nine (11.3 %) analytical studies (one case-control study, six cohort studies, and two cross-sectional studies), were included. All the interventional studies were before-after trials, and interrupted time series analysis was commonly used to assess changes in antimicrobial consumption per intervention. Five database-related studies demonstrated decreasing antimicrobial consumption after issuance of the NAP.

Conclusion
Several ASP studies were published after the issuance of the NAP, suggesting that the latter promoted research into ASP. A few, database-related studies showed a positive impact of the NAP on antimicrobial consumption. However, more high-quality studies, especially interventional studies using appropriate methodology and standardized data collection, continue to be necessary.
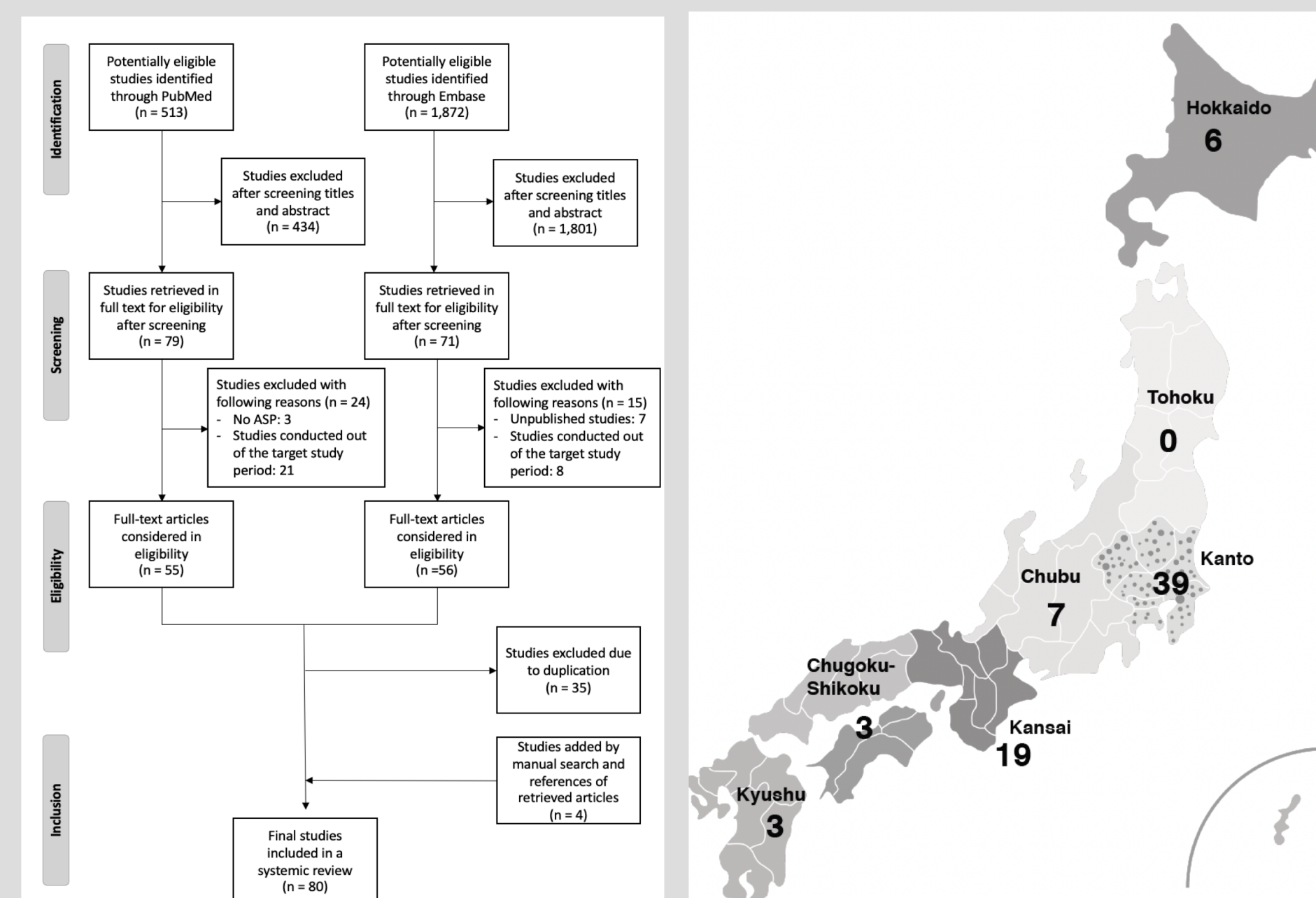
INTRODUCTION

- Antimicrobial resistance (AMR) is a global threat with the potential to cause a significant healthcare burden. A landmark AMR report underscored the need for a global response to counter the emergence of antimicrobial-\resistant organisms, which can substantially increase mortality.
- The Ministry of Health, Labour and Welfare (MHLW) of Japan issued a national action plan (NAP) for AMR in 2016.[5] The key priorities endorsed by the NAP included public awareness and education, surveillance and monitoring, infection prevention and control, appropriate use of antimicrobials, research and development, and international cooperation.
- We therefore performed a systematic review of ASP-related studies conducted in Japan to elucidate the impact of the NAP on current antimicrobial stewardship program (ASP) activities in the country.

METHODS

- The present systematic review aimed primarily to review ASP studies conducted by Japanese institutions from the issuance of the NAP in 2016 through 2020.

- The studies included in the analysis were categorized as interventional (e.g., randomized controlled trials, quasi-experimental studies, and before-after trials), analytical (e.g., case-control studies, cohort studies, and cross-sectional studies), descriptive (e.g., cohort studies and cross-sectional studies), database-related, questionnaire-based, or other.

- The literature in two databases, including Medline (PubMed) and EMBASE, from January 2016 through September 2021 was searched using terms.

- The risk of bias in each interventional study was assessed by two authors using ROBINS-I, a tool for assessing the risk of bias in non-randomized studies. A study was considered to have a low risk of bias if its score in each domain was low. A high score in at least one domain was regarded as a critical risk. Two authors assessed the quality of observational studies using the Newcastle-Ottawa Scale (NOS) for cohort studies and case-control studies, which evaluates sample selection, comparability, and exposure.
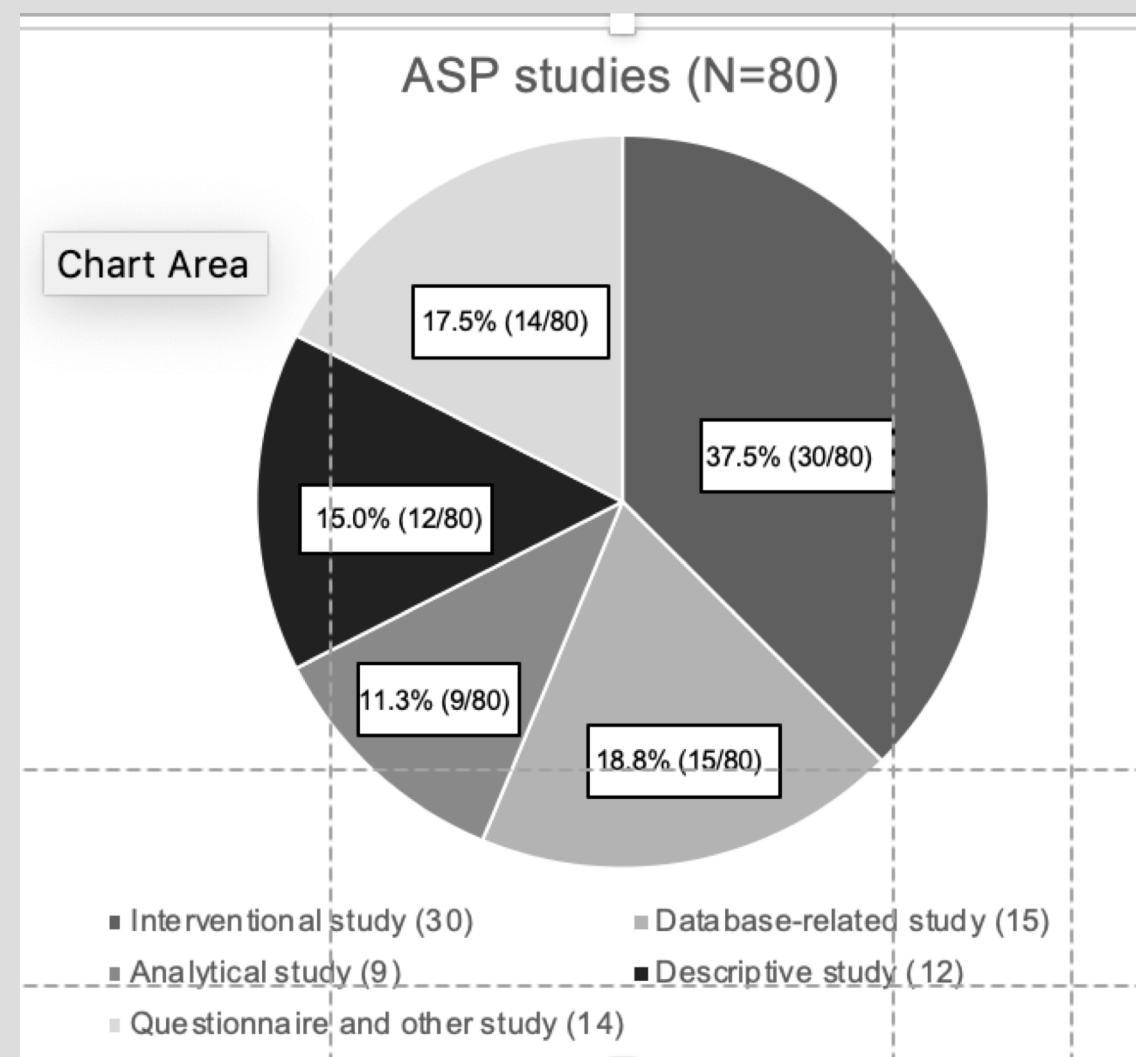
RESULTS

PRISMA flow diagram for the systematic review and the number of publications by geography

RESULTS

Proportion of ASP studies in systematic review

ASP studies (N=80)

- 37.5% (30/80)
- 18.8% (15/80)
- 11.3% (9/80)
- 15.0% (12/80)
- 17.5% (14/80)

- Interventional study (30)
- Analytical study (9)
- Questionnaire and other study (14)
- Database-related study (15)
- Descriptive study (12)

Database-oriented study assessing the efficacy of national action plan

Author (year)	Type of study	Intervention or exposure	Main outcome of interest	Changes or findings
Muraki et al. (2020)	Database-related	National ASP reimbursement	Proportion of antimicrobial prescriptions	In ASP fee implementation phase, the number of prescriptions decreased. - 0-4 y/o (31.4% → 26.9% [-4.5%]) - 5-9 y/o (37.7% → 31.4% [-6.3%]) - 10-14 y/o (45.0% → 40% [-5%])
Kusama et al. (2021)	Database-related (ITSA)	National action plan (NAP) in 2016	Proportion of antimicrobial prescription	In 2020 versus 2013, AMU reduction was 15.0% for total antimicrobials. - 26.3% for cephalosporins - 23.5% for fluoroquinolones - 24.6% for macrolides
Ji et al. (2021)	Database-related (ITSA)	NAP	Antimicrobial consumption	Change in prescribing rate Intercept in April 2016, β2 (P=0.44) Slope change in prescription rate after April 2016 (P <0.01) The antibiotic prescription rate declined from 49.9% in 2008 to 39.0% in 2018, and the rate of decrease accelerated after NAP implementation.
Okubo et al. (2021)	Database-related (ITSA)	NAP	Antimicrobial consumption	NAP implementation changed the annual absolute reduction in the antibiotic prescription rate from − 16.0 DOTs/1,000 visitors (95% CI:− 16.4–15.6) to − 239.3 per 1,000 visitors (95%CI:− 240.0–238.6).
Sato et al. (2021)	Database-related	NAP	Antimicrobial consumption	There was no significant change in the trend of antibiotic use between the pre-and post-NAP periods (trend difference, −0.01% per week; 95% CI: −0.10% to 0.07%). Similarly, for patients with gastroenteritis, there was no significant change in the trend of antibiotic use between the pre-and post-NAP period (trend difference, −0.02% per week; 95% CI, −0.04% to 0.01%).

RESULTS

- Single-center studies accounted for approximately half (41/80) the studies. Forty-four (55.0%) studies were published by a university or university hospital, and 28 (35.0%) were published by a public hospital.

- All 30 interventional ASP studies were before-after trials chiefly conducted at a public or university hospital. Interrupted time series analysis (ITSA) comparing the proportion or rate of primary outcomes between pre-intervention and intervention periods was used in 13 studies (43.3%).

- The number of publications differed by region, suggesting that ASP activities can vary geographically. Moreover, significant variations in the quality of the studies included in the present systematic review complicated assessment of the overall efficacy of ASP activities.

- Most of the interventional studies (27; 90%) were considered to have a moderate risk of bias, and three studies (10.0%) were regarded as having a critical risk of bias according to ROBINS-I. Most of the analytical studies appeared to be of adequate quality with the NOS score ranging from three to nine.

CONCLUSIONS

- The present systematic review revealed that more ASP studies were published after the issuance of the plan.

- Some interventional studies demonstrated the success of their intervention, and several database-related studies demonstrated a positive impact of the NAP on antimicrobial consumption.

- However, it is difficult to conclude that changes in antimicrobial practices or use were achieved by the issuance of the plan or the national ASP guidelines.

- More high-quality studies, especially interventional studies using an appropriate methodology and standardized data collection, are needed to address the issues surrounding antimicrobial resistance.