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Meta-analysis on Antibiotic Resistance and Its Irrational Use in India: Need of Antibiotic Stewardship Program Implementation

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Abstract

Antibiotic resistance is a major health issue in developing countries. This issue is increasing exponentially due to increased consumption, easy availability of medicine and higher incidence of inappropriate use. Moreover, India stands as one among the highest infectious disease burdened country in the world. This study aims to conduct a statistical analysis to find the association between antibiotic resistance and its irrational use in India. Thereby, emphasizing the need for the antibiotic stewardship program implementation in India. The inclusion criteria applied by the researchers for the literature search process include that the study should be scientific peer-reviewed articles which are published from 2011 to 2023 in the English language. The database source used by the researchers for the scientific literature search includes PubMed, Elsevier Science Direct, and Google Scholar. Among the 10 studies used in the meta-analysis, a total sample size of 146,536 was considered for the assessment of bacterial resistance and irrational antibiotic use in India. The researchers conducted the statistical analysis by using RewMan software of version 5.4.1. The forest plot, funnel plot, and PRISMA 2009 recommendations flow diagram are used to illustrate the statistical data. This investigation shows the statistical relationship between the two variables. Hence the irrational use can be tackled by the implementation of the antibacterial stewardship programs in every hospital at the national level.

Keywords: Antibacterial resistance, meta-analysis, antibiotics, stewardship program, antibiotic resistance in India

INTRODUCTION

Antibacterial resistance is one of the most challenging health issues faced by every country across the world. The improper use of antibiotics speeds up the process of resistance [1]. Antibacterial resistance is a crucial health problem particularly in developing countries, where increased consumption and easy availability of medicines leads to the high incidence of inappropriate antibiotic use and greater levels of resistance compared to developed countries. The increase in the infectious disease burden in India, makes it stand as one among the highest in the world [2]. As per the recent study estimates, the crude death rate is about 416.75 deaths per 100,000 persons due to infectious causes in India [3]. Treatment failure arises from the incorrect use of existing antibiotics due to a lack of development of newer generation medicines.

As a result, newly emerging infectious diseases are becoming an increasing threat that increases

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morbidity and premature mortality [4]. Infection with antibiotic-resistant bacteria may cause severe illness, an increased risk of complications, and an increased rate of hospital admission [5]. Due to a high rate of infectious diseases and inadequate healthcare infrastructure in India, antibiotics are used more often than necessary in place of other preventative measures and vaccine coverage. For this reason, India is quite concerned about the high level of antibiotic resistance [6].

According to a study by World Health Organization (WHO), more than half of the patients incorrectly administer their medications and more than 50% of the drugs are prescribed, dispensed and sold inappropriately. The irrational use of medicines is carried out in the form of overuse, underuse, and misuse of prescription or over-the-counter drugs [7]. The importance of using antibiotics sensibly to prevent antibiotic resistance in India has been brought to light by recent studies [2]. Thus, one of the logical ways to curtail antimicrobial resistance is to decrease inappropriate or irrational prescribing of antibiotics [3]. Antibiotic resistance leads to an increased amount of healthcare costs [5]. However, the healthcare cost for patients with resistant infections is higher than the cost for non-resistant infections. The non-resistant infections will prolong the duration of infection, longest hospital stays, increased mortality and additional diagnostic tests [1].

Antibiotic stewardship programs often target such irrational utilization of antibiotics [3]. Antibiotic stewardship program is a multidisciplinary approach with effective interventions and strategies to improve appropriate antibiotic usage. It aims to avoid inappropriate use of antibiotics, optimize the selection of antibiotic dose, route, and duration of treatment for best therapy outcomes, along with minimizing harmful adverse effects, excessive costs, and the emergence of resistance [8]. Nevertheless, the national-level antimicrobial stewardship plan is not implemented in India [9]. Meta-analysis is the statistical way of combining the results from two or more separate studies with potential advantages of improvement in precision and the ability to answer questions not presented by individual studies [10].

This study aims to conduct a statistical analysis to find the association between antibiotic resistance and its irrational use in India. Thereby, emphasizing the need for the antibiotic stewardship program implementation in India.

METHODOLOGY

Primary Eligibility Criteria

The inclusion criteria applied by the researchers for the literature search process include that the study should be scientific peer-reviewed articles which are published from 2011 to 2023 in the English language. The study period is restricted because as the year passes, rapidly progressing changes were encountered in the prescribing pattern, consumption, and resistance rate of antibiotics. However, considering recent studies will offer newer perspectives and refined methodologies that are evident for robust results through meta-analysis. The epidemiological studies conducted in India should be included.

Strategies involved in literature search

Database source utilized by the researchers for the scientific literature search includes PubMed, Elsevier Science Direct, and Google Scholar. After that, the studies that were gathered through a literature search are vetted using inclusion and exclusion criteria. The search strategy includes the terms such as “Resistance developed to antibiotics use in India”, “antibiotic resistance in India”, “bacterial resistance to antibiotics in India”, “prevalence of antibacterial resistance in India”, “irrational use of antibiotics in India”, “improper use of antibiotics in India”, “misuse of antibiotics in India”, “inappropriate use of antibiotics in India”.

Inclusion And Exclusion Criteria

This study includes epidemiological studies such as cross-sectional studies, cohort studies, and prospective and retrospective studies. This study is conducted on bacterial resistance to antibiotics and the irrational use of antibiotics in India. The studies on the effect of bacterial resistance that occurred

only in humans were included. The studies conducted only in India were considered. The study outcome must represent bacterial resistance to antibiotics and the irrational use of antibiotics in India. The exclusion criteria involve the studies that are published as only abstracts and literature reviews that do not have enough data; case studies that have lower sample size, studies not conducted in India, study on animals and studies having improper statistics.

DATA ABSTRACTION

The Microsoft excel is used for abstracting the data. The articles are thoroughly examined and the data were independently extracted for analysis. The extracted data are represented in Table 1 by categorizing them as name of first author, publication year, study method, sample size, gender, age, year in which the study conducted, and study outcome variable.

Statistical analysis

The statistical analysis was conducted by Rew Man software version 5.4.1. The random effect was used during analysis to limit the heterogeneity of studies included. Thus, the meta-analysis of epidemiological studies was done by using the inverse variance random effects model by calculating the odds ratio of individual studies included.

Table 1. List of study characteristics used in the meta-analysis [3, 6, 7, 11–16, 17].

Sl. No.	Authors	Published year	Study Design	Sample Size	Age	Gender	Study Period	Outcome variable
1	Ahmed *et al*. [7]	2016	Cross-Sectional	303	Under 5 years	Males: 176, Females: 127	2012–13	Irrational use of antibiotics
2	Kaur *et al*. [3]	2018	Observational	517	45 years (SD=18 years)	Males: 180, Females: 120	2016–17	Irrational use of antibiotics
3	George *et al*. [15]	2015		204	43.84 y ears	Males: 78, Females: 118	-	Irrational use of antibiotics
4	Moolchandani *et al*. [14]	2017	Cross sectional	3090	16–64 years	Males: 792, Females: 452	2015–16	Bacterial resistance rate
5	Jajoo *et al.* [11]	2018	Cohort study	2588	Neonate s	Males: 1717, Females: 926	2011–15	Bacterial resistance rate
6	Dash *et al*. [12]	2013		1670	18–85 years	Males: 664, Females: 1006	2010–12	Bacterial resistance rate
7	Mehrishi *et al*. [13]	2019	Retrospective	1878	-	Males: 498, Females: 1380	2014–15	Bacterial resistance rate
8	Shivani Gupta et al., [17]	2014		830	14–72 years	Males: 135, Females: 157	2010–11	Bacterial resistance rate
9	Gandra *et al*. [6]	2016	Retrospective	135268	1-65 years	Males: 83,055, Females: 50904	2008–14	Bacterial resistance rate
10	Mohammed *et al*. [16]	2020		188	Median (IQR) age of 53.5 (30.75) years	Males: 119, Females: 69	-	Irrational use of antibiotics

The tools used in the study to evaluate the statistical heterogeneity were Tau^2 and I^2. Tau^2 is the tool in Rew Man software that represents the estimate of between-study variance and I^2 is an index to analyze dispersion of effect sizes in meta-analysis. An I^2 value of more than 75% will be considered as high and more than 50% as substantial heterogeneity. The pooled estimates were provided along with a 95% confidence interval. A p-value of <0.05 is considered statistically significant and the publication bias is tested by using a funnel plot.

RESULTS

The researchers considered 10 studies out of 4728 studies that were identified in the literature search. The analysis considered 146,536 patients with antibiotic resistance and the individuals encountered irrational antibiotic use that is responsible for antibacterial resistance. The comprehensive selection criteria were depicted in the PRISMA flow diagram (Figure 1).

Among the 10 studies included that are extracted and presented, 6 studies were based on bacterial resistance to the antibiotics [6, 8, 11–14], and four studies report the irrational use of antibiotics [3, 7, 15, 16]. The class of antibiotics that are commonly misused and became resistant is represented in the bar graph in Figure 2 and the studies including various species of resistant bacteria are presented in the bar graph in Figure 3. The statistical analysis is represented through a forest plot in Figure 4 and a funnel plot in Figure 5. The forest plot (Figure 4) is the graph used to show an association between studies. The individual study is represented by the square, which indicates the effect size and the weightage of the study centered at the point with a horizontal line indicating the effect size at the confidence interval in the graph. The black diamond estimates the overall effect size with horizontal lines on both sides of the overall confidence interval. The asymmetrical funnel plot suggests the existence of publication bias.

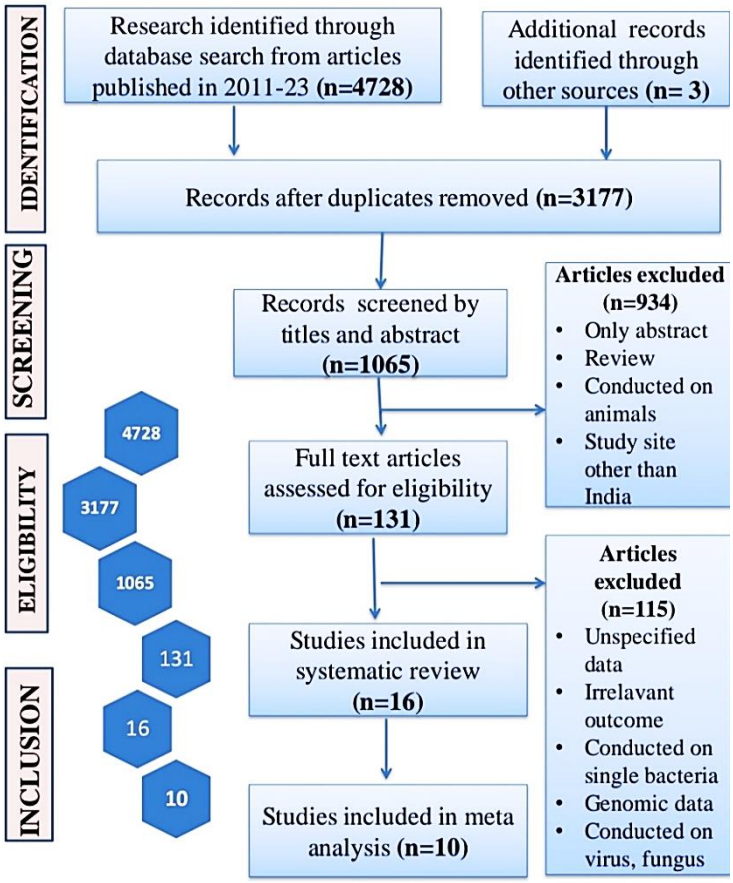

Figure 1. The PRISMA flow diagram for meta-analysis.

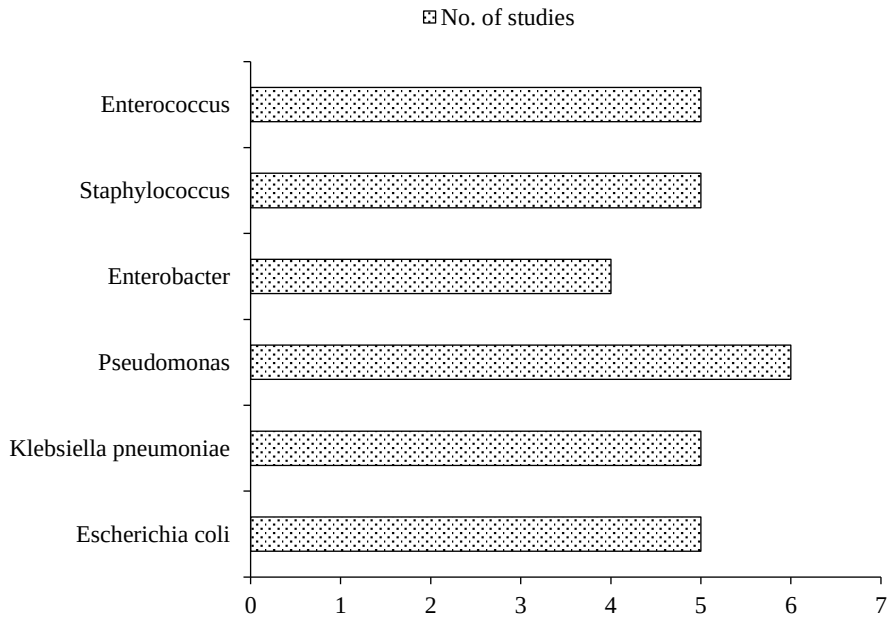

Figure 2. Several studies that include various species of resistant bacteria were presented through a bar graph.

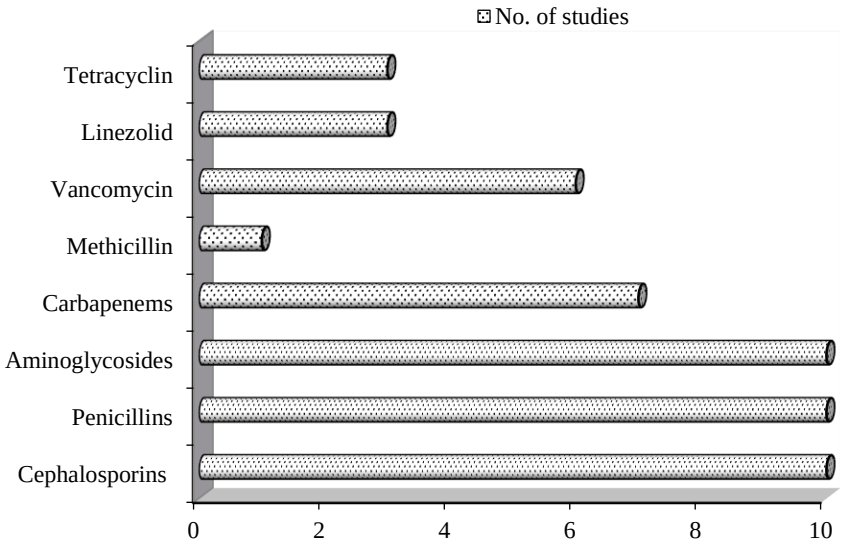

Figure 3. The number of classes of drugs that are commonly misused and that became resistant.

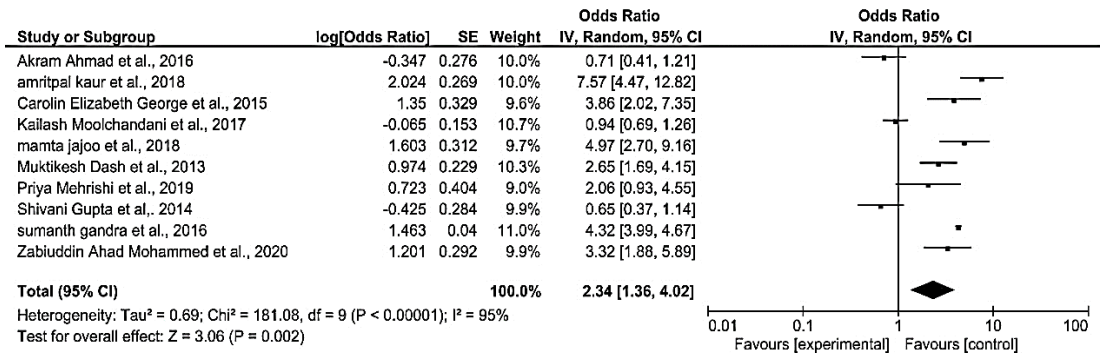

Figure 4. Forest plot of studies included in meta-analysis by using Rew Man.

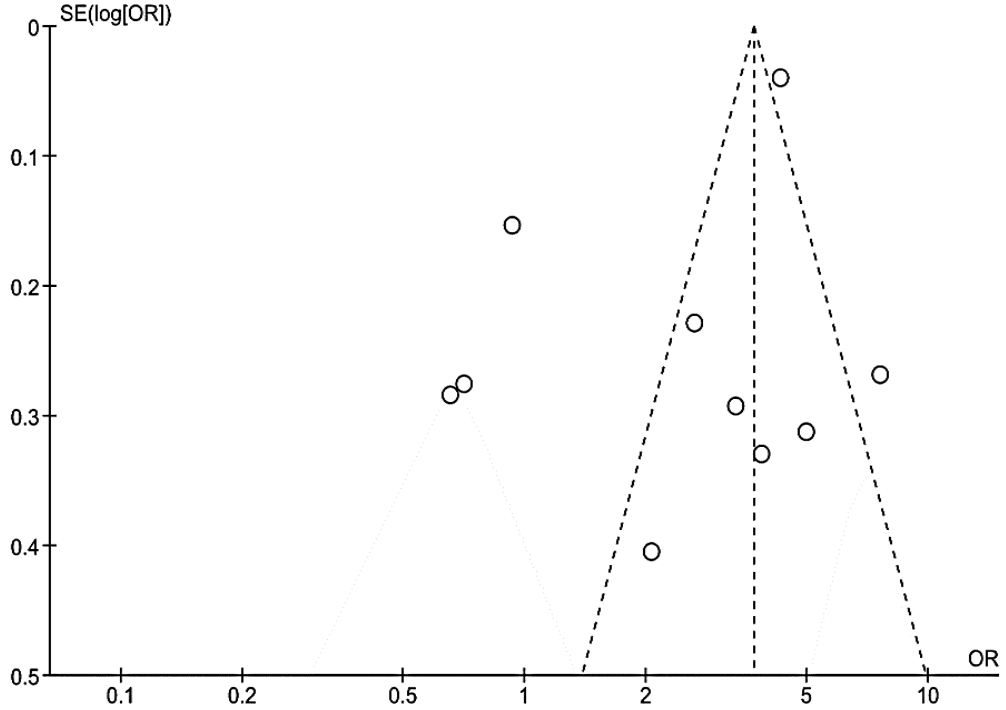

Figure 5. Funnel plot in meta-analysis.

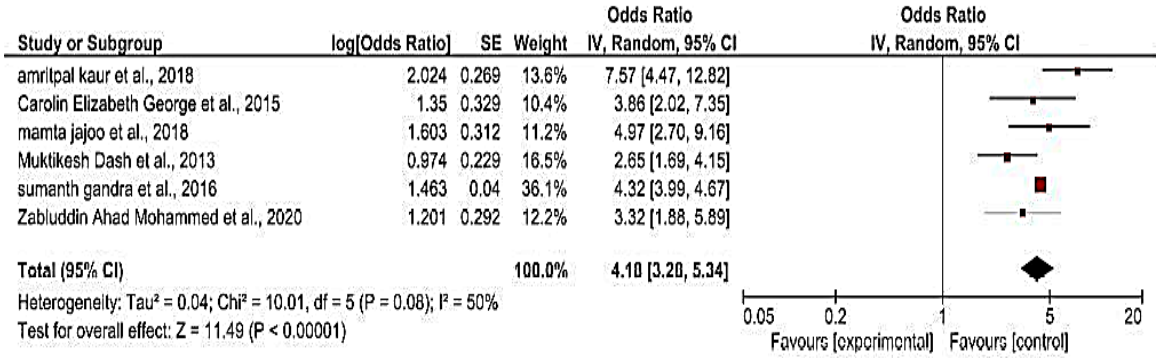

Figure 6. Forest plot showing association after exploring the heterogeneity.

The heterogeneity takes place due to the sampling variations among the effect sizes of collected studies in meta-analysis. The strategies used to limit heterogeneity includes conducting random effect and subgroup analysis and also by excluding studies from the analysis. Upon consideration of random effect meta-analysis, the heterogeneity measures I^2=95%, Tau^2=0.69, and Chi^2=181.08. The subgroup analysis cannot be considered as there are no significant changes with that analysis. Hence the researchers considered 6 studies by excluding four studies due to variation in the outcome. Then the study showed 50% heterogeneity that can be acceptable and presents the association between bacterial resistance to antibiotics and the irrational use of antibiotics with an overall effect size of 4.18 (at 95% CI 3.28, 5.34) (Figure 6).

This study aims to statistically summarize the bacterial resistance rate and irrational use of antibiotics that are considered the main cause of bacterial resistance in India. A meta-analysis is carried out in accordance with the PRISMA 2009 guidelines and statistical analysis is done via the RewMan version 5.4.1. The statistical results are represented by the PRISMA flow diagram 2009, forest plot and funnel plot. Thus, researchers concluded that bacterial resistance is booming in India due to its irrational use and thus irrational use of antibiotics should be tackled through the implementation of an antibacterial stewardship program.

DISCUSSION

The irrational use of antibiotics in various sectors has resulted in an increase in the extended antimicrobial resistance. Moreover, it has attained less attention in spite of its drastic impacts. The easy availability of antibiotics results in the irrational use of antibiotics contributing to antimicrobial resistance [18]. A total sample size of 146,536 was considered for the meta-analysis from the 10 selected studies. This study demonstrates the statistical association between two variables.

According to a study conducted by Sahoo *et al*., patient overload, unqualified practitioners and highly expensive antibiotics are major reasons for improper antibiotic prescribing. The interviewed physicians said that a doctor should treat approximately 50–90 patients per day in both rural and urban healthcare centers. Usually, the patient overloading will lead to improper diagnosis, inadequate treatment and improper use of antibiotics [19]. Furthermore, practice of self-medication, over-the-counter availability, use of broad-spectrum antibiotics, and neglecting the proper dosage shows the factors responsible for the increased misuse of antibiotics and exponentially increasing antimicrobial resistance [18]. A meta-analysis conducted by Bell *et al*., depicts that the initial analysis with 243 studies has shown positive association between bacterial resistance and antibiotic intake in community, which means that if consumption increases, the resistance also increases and vice versa [4]. These results were partially similar to our study, where there is an association between bacterial resistance and irrational use of antibiotics. These two studies depict a similar association between bacterial resistance and irrational use of antibiotics. Both studies, being meta-analyses conducted in India. Most of the study participants in a study conducted in India believed that the development of a local guideline is more beneficial and improves rational antibiotic use. In a study conducted to assess irrational and excessive antimicrobial exits in 10 developing countries, the study researchers of India advise that both patients and physicians have a critical role in rational antibiotic use. Awareness programs and counseling should be done to provide the necessary information to the patient from the high-risk groups. Therefore the provision of continuing education for the healthcare professional is essential for the successful implementation of stewardship program in a large extent [20]. One of the strategies to counter inappropriate antibiotic use in India would be to initiate antibiotic stewardship programs [8]. Optimization and reduction in the antibiotics use are possible through the implementation of the antimicrobial stewardship at the national level at every tertiary and secondary care hospitals. For the successful implementation of these programs in developing countries need the consideration of certain factors including enhancing political perseverance, organizational dedication, and implementation of the national stewardship guidelines [9].

The meta-analysis conducted has many strengths. This study has inclusion criteria in that it includes epidemiological studies with statistical analysis and excludes the studies, which showed irrelevant outcomes and inappropriate study outcomes. This analysis has overcome the heterogeneity via exclusion of certain studies and hence proved that there is an association between antibiotic resistance and its irrational use in India. Furthermore, this study has some limitations such as the study considered only bacteria but no other microbes like fungi, or viruses. In future studies, this study can be considered as a basis for assessing the reduction in irrational use of antibiotics upon implementation of an antimicrobial stewardship program.

CONCLUSION

This study shows that there is a huge number of antibiotic-misuse in India. The irrational use of antibiotics is responsible for the increasing antibacterial resistance in a developing country like India. This study revealed a statistically significant association between antibiotic resistance and its irrational use in India. There are limited publications from India on prevention of infection and control and it is even more limited for antibiotic stewardship. Henceforth, more and more studies should be conducted in this domain as the resistance is drastically increasing not only among the broad spectrum but also among the preserved antibiotics. Thus, the irrational use can be tackled by the implementation of the antibacterial stewardship programs in every hospital at the national level.

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Conflict of Interest

The authors declare that there is no conflict of interest.

Abbreviations

CI: Confidence Interval.

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