Original Article

# Preferral Antibiotic Treatment Policy to be adopted in the 'Integrated Management of Childhood Illness Strategy in all the Developing Countries?

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*Abstract*

**Objectives:** To review the rationale and practice for the use of single dose antibiotics in 'children below five years' as pre-referral treatment in the emergency triage and treatment protocol of IMCI in the developing countries and also, to assess the available evidence on the suitability of adopting the use of pre-referral antibiotic treatment as a standard strategy of Emergency Triage and Treatment (ETAT) in "Integrated Management of Childhood Illnesses" (IMCI) for all developing countries.

**Methods:** Scientific, reliable information from the international articles (published and unpublished) were collected. A series of Medline search with key words were performed. Opinions of epidemiologists, public health officers and researchers University Alumni and senior health officials of some developing countries were included in this review.

**Results:** Indirect evidence regarding for or against adopting pre-referral antibiotic treatment were found in developing countries where IMCI was implemented. It was also noted that the efficiency ranking based on the health system performance correlated negatively with the per capita income (r=-0.7, p=<0.001) and the per capita health expenditure. (r=-0.6, p=0.001). The gap between mortality rates of the '<1' and '1 to 4' years age groups was narrower in countries such as Oman and Argentina compared to the other developing countries. While the doctor population ratio was higher in countries with better efficiency rankings, (r=-0.66, p=0.01).

**Conclusion:** The differences found within the developing world indicate that the use of pre-referral antibiotic is certainly open to modification depending on the resources and health system performance.

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## Introduction

Every year, around 10.5 million children in developing countries die before they reach their fifth birthday. Many of them perish during their first year of life.[1] Seven out of ten of these deaths are due to acute respiratory infections, diarrhea, measles, malaria or malnutrition, or a combination of these conditions.[2] Many sick children usually show signs and symptoms related to more than one infection. These overlaps mean that a single diagnosis may not be appropriate or possible, plus the treatment will be complicated because of the need to combine therapy for several ailments.[3]

The strategy of "Integrated Management of Childhood Illnesses" (IMCI) was formulated in 1991 to address this problem, and by December 2002, 109 countries had implemented this strategy.[4] It recommends proper selection of antibiotic and their use in therapeutic dosage during the early stages of infection. This is especially crucial to reduce mortality and irreversible disabilities in seriously ill children. The list of antibiotics that are recommended by the WHO includes *Ampicillin, Amoxicillin, Cefotaxime, Ceftriaxone, Cefalexin, Chloramphenicol, ciprofloxacin, Cotrimaxazole, Erythromycin, Gentamicin, Kenamycin, Nalidixic acid, Metronidazole, Penicillin* and *Tetracycline*.[5] Although a variety of antibiotics are used in informal practice, only Ceftriaxone and Chloramphenicol are included in the Emergency Triage and Treatment (ETAT) protocol as the parenteral pre-referral antibiotic treatment for seriously ill children.[2] In real settings, in most of the developing countries, seriously ill children often take a long time to reach a child health practitioner which necessitates the administration of one dose of antibiotic before the referral. However, the administration of pre-referral antibiotic and its blanket implementation is contentious particularly in the subgroup of developing countries, which are relatively better off.

This report presents a critical review of the literature to understand the rationale and practice of the use of single dose antibiotics in 'children below five years' as pre-referral treatment in the emergency triage and treatment protocol of IMCI in the developing countries, and also to assess the available evidence on the suitability of adopting the use of pre-referral antibiotic treatment as a standard strategy of ETAT in IMCI for all developing countries.

## Methods

This is a literature review type of study. It was conducted in 2004.

Scientific, reliable information from the international articles (published and unpublished) that primarily focused on the magnitude and the causes of childhood mortality and the child health care approaches in the past and at present as recommended by the World Health Organization, UNICEF and international pediatric societies were collected. The study focused on the feasibility of using the ETAT protocol in developing countries with a special reference to subgroups based on the mortality strata. A series of Medline search with key words "childhood mortality rates" were performed. Then the focus was switched to the abstract of the sorted articles and printed as hard copies of the articles on "IMCI", "ETAT", and antibiotics in childhood infection.

The articles without abstracts in English and articles of 'no relevance' to the topic were omitted. Hyperlinks were used to gather the related articles. EMBASE data search was used. The European Scientific literature covered chemotherapeutic, anti-microbial activities, public health, health policy and management, pharmacology, pharmaceutics and clinical services. Search engines such as Yahoo and Google were utilized for literature on childhood mortality in developing countries, the ETAT Protocol of IMCI for the antibiotics for treating childhood infections and published and unpublished studies on pre-referral antibiotic treatment of severely ill children.

The official websites of the World Health Organization, Centre for Disease Control and Prevention, American Society for Microbiology, United Nation's Children Fund and 'Asian – Pacific Research Foundation for Infectious Diseases/ Asian network for the Surveillance of resistant Pathogens' were also visited. For the electronic search, used keywords such as IMCI, Serious childhood illnesses, Antibiotics, Ceftriaxone, Chloramphenicol, Child health care, Primary health care, and ETAT were used to generate the information. Libraries at Duieth, Cardiff University (Wales), Sultan Qaboos University and Royal Hospital and the World Health Organization Library (Oman) were also visited. Articles in English or having English abstract but published in other languages between year 1980 and 2003 were short-listed.

The selected articles comprised clinical intervention, public health invention, longitudinal types (Cohort and case control) and review articles. The articles comprising of case series of less than ten subjects, ecological studies and qualitative studies were excluded. The search was limited to the period between 1980 and 2004.

The articles were reviewed in full to determine their study methods, validity of results, ethical norms followed for conducting the research, outcome variables and important conclusions or messages deduced from the study with a particular reference to improving child healthcare in developing countries. Different color marker pens were used to highlight different topics under procedures, sample size, outcome variables and conclusions. The resource administrators of different organizations were contacted. They were the IMCI program manager and senior pediatricians in the Ministry of Health, Oman. Informal discussions with the epidemiologists, public health officers and researchers at UNICEF, WHO EMRO, University Alumni and senior health officials of some developing countries; such as Oman, Egypt, Saudi Arabia and India, helped to further strengthen the study methods. The flow chart explains clearly the steps adopted for the literature review (Fig. 1). For clarity and avoiding misclassification, it was important to refer to the WHO/UNICEF recommended standardized definitions of important parameters (Table 1).

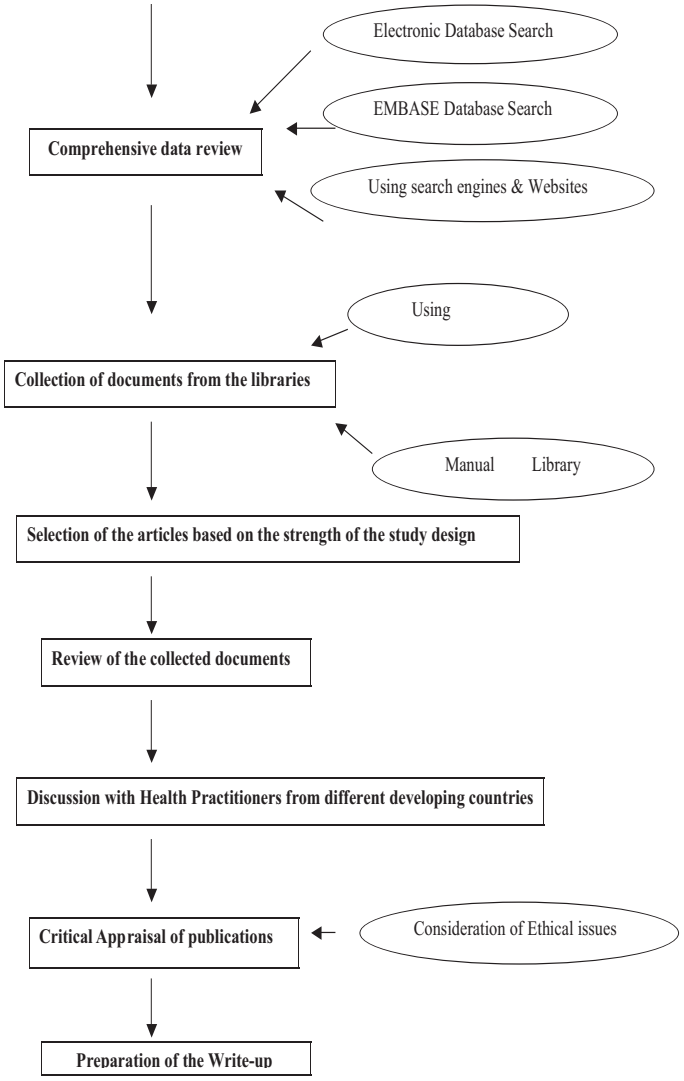


**Figure 1:** Flow chart showing summary of the Methodology adopted for this review.

**Table 1:** Definitions Used for the Literature Review of the Study

| | |
|---|---|
| 1 | **Developing countries**: as grouped by WHO based on various social, developmental and economic considerations. |
| 2 | **Seriously ill child**: child presenting with lethargy or inability to feed or convulsions. |
| 3 | **Meningitis**: Infection of outer layers of the brain. |
| 4 | **Severe diarrhea**: frequency of motion with severe dehydration. |
| 5 | **Serious respiratory tract infection**: child presenting with severe chest in drawing or abnormally sleepy or with convulsions; with fast breathing (60/ Minute or more). |
| 6 | **HIV in child**: child infected with HIV virus proven by laboratory investigation. |
| 7 | **Moderate and severe malnutrition**: more then -2 or -3 SD from the standard weight for age respectively. |

## Results

The literature review did not yield studies or reviews, which provided direct evidence for or against adopting pre-referral antibiotic treatment in all developing countries. However, indirect evidence regarding this issue were found in countries where IMCI was implemented.

The health indices of selected developing countries and their health system performance were correlated to the country ranking based on the childhood and adult mortality rates. We compared The per capita income, health related expenditures and country ranking were compared. (Table 2)

**Table 2:** Comparison of Per capita Income & Health Expenditures along with the Ranking of Countries Based on Health System Efficiency in Selected Countries.

| Group | Countries | GNI per capita | Per capita health expenditure | Proportion of GDP for health expenditure | Ranking |
|---|---|---|---|---|---|
| A | UK | 25,250 | 1,774 | 7.3 | 18 |
| | USA | 35,060 | 4,499 | 13 | 37 |
| | France | 22,010 | 2,335 | 9.5 | 1 |
| | Canada | 22,300 | 2,534 | 9.1 | 30 |
| | Germany | 22,670 | 2,759 | 10.6 | 25 |
| B | Turkey | 2,500 | 323 | 5 | 70 |
| | China | 940 | 205 | 5.3 | 144 |
| | Oman | 7,720 | 448 | 2.8 | 8 |
| | Vietnam | 430 | 124 | 5.2 | 160 |
| | Argentina | 4,060 | 1,091 | 8.6 | 75 |
| C | Russian federation | 2,140 | 405 | 5.3 | 130 |
| | Hungary | 5,280 | 846 | 6.8 | 66 |
| | Ukraine | 770 | 152 | 4.1 | 79 |
| | Belarus | 1,360 | 430 | 5.7 | 72 |
| D | India | 480 | 71 | 4.9 | 112 |
| | Egypt | 1,470 | 138 | 3.8 | 63 |
| | Sudan | 350 | 51 | 4.7 | 134 |
| | Peru | 2,050 | 238 | 4.8 | 129 |
| E | Ethiopia | 100 | 17 | 4.6 | 180 |
| | Zambia | 330 | 49 | 5.6 | 182 |
| | Zimbabwe | 470 | 171 | 7.3 | 155 |
| | South Africa | 2,600 | 663 | 88. | 175 |

(Data source: WHO-Country profiles, WHO World health report 2000)

The differences in per capita income and per capita health expenditure within country groupings were evident. It was noted that the efficiency ranking based on the health system performance correlated negatively with the per capita income (r=-0.7, p=<0.001) and the per capita health expenditure, (r=-0.6, p=0.001).
In contrast, the performance ranking had no significant correlation with the proportion of GDP for health expenditure in these groups of countries (r=0.2, p=0.2), as shown in Table 3.

**Table 3:** Comparison of Child Mortality and DTP3 Coverage (2002- WHO-UNICEF data) with Efficiency Ranking of Selected Countries

| Group | Countries | <1 year mortality | Under five mortality | DTP3 coverage 2002 (%) | Ranking |
|---|---|---|---|---|---|
| A | UK | 7 | 6 | 91 | 18 |
| | USA | 7 | 8 | 94 | 37 |
| | France | 5 | 6 | 98 | 1 |
| | Canada | 5 | 6 | 97 | 30 |
| | Germany | 5 | 6 | 97 | 25 |
| B | Turkey | 40 | 51 | 78 | 70 |
| | China | 37 | 44 | 79 | 144 |
| | Oman | 20 | 23 | 99 | 8 |
| | Vietnam | 34 | 47 | 75 | 160 |
| | Argentina | 20 | 23 | 88 | 75 |
| C | Russian federation | 16 | 21 | 96 | 130 |
| | Hungary | 9 | 11 | 99 | 66 |
| | Ukraine | 14 | 18 | 99 | 79 |
| | Belarus | 11 | 15 | 99 | 72 |
| D | India | 65 | 86 | 70 | 112 |
| | Egypt | 41 | 49 | 97 | 63 |
| | Sudan | 78 | 128 | 40 | 134 |
| | Peru | 34 | 54 | 89 | 129 |
| E | Ethiopia | 101 | 175 | 56 | 180 |
| | Zambia | 106 | 185 | 78 | 182 |
| | Zimbabwe | 59 | 112 | 58 | 155 |
| | South Africa | 48 | 76 | 82 | 175 |

(Data Source: WHO-UNICEF 2002 profile of countries in child health & World Health report 2000)

The ranking with the DTP immunization coverage and mortality statistics of children aged less than one year and those aged less than five years were compared. The gap between mortality rates of the two age groups was narrower in countries such as Oman and Argentina compared to most of the other developing countries. The mortality rates were lower and coverage was more extensive among countries that had higher rankings. This was demonstrated by a significant correlation obtained between mortality rates (r=0.7, p=<0.001 for less than one year mortality and (r=0.76, p=<0.001for under five mortality), DTP immunization coverage (r=-0.66, p=0.001) and performance ranking.

A comparison of human resources in healthcare using the doctor-population ratio in different countries according to its performance rankings was carried out, (Table 4). A higher ratio was found in countries with better efficiency rankings, (r=-0.66, p=0.01).

**Table 4:** Comparison of Human Resources in Health Care with the Ranking based on Health System Efficiency of Selected Countries.

| Group | Countries | Doctor: Population ratio (per one lakh population per year) | Reference Year | Ranking |
|---|---|---|---|---|
| A | UK | 164 | 1993 | 18 |
| | USA | 279 | 1995 | 37 |
| | France | 303 | 1997 | 1 |
| | Canada | 229.1 | 1995 | 30 |
| | Germany | 350 | 1998 | 25 |
| B | Turkey | 121 | 1998 | 70 |
| | China | 161.7 | 1998 | 144 |
| | Oman | 133 | 1998 | 8 |
| | Vietnam | 48 | 1998 | 160 |
| | Argentina | 268.4 | 1992 | 75 |
| C | Russian federation | 421 | 1998 | 130 |
| | Hungary | 357 | 1998 | 66 |
| | Ukraine | 299 | 1998 | 79 |
| | Belarus | 443 | 1998 | 72 |
| D | India | 48 | 1992 | 112 |
| | Egypt | 202 | 1996 | 63 |
| | Sudan | 9 | 1996 | 134 |
| | Peru | 93.2 | 1997 | 129 |
| E | Ethiopia | - | - | 180 |
| | Zambia | 6.9 | 1995 | 182 |
| | Zimbabwe | 13.9 | 1995 | 155 |
| | South Africa | 56.3 | 1996 | 175 |

Data source- WHO estimates of health personnel.

## Discussion

The WHO classified its 191 member states based on the mortality data of children 'under five years' of age and male adults in the age group 'between 15 and 59 years.' The 1999 data on mortality was utilized to further categorize the member countries into five mortality strata.[5] Group 'A' represents the developed countries and groups 'B', 'C', 'D' and 'E' represents developing countries. In this classification, a differentiation was made within the developing countries. Those with high resources and well-developed health infrastructure e.g. Oman, Saudi Arabia, UAE etc. could be grouped into one class of developing countries (Group B) while those with relatively poor resources and less developed health services such as Yemen, Somalia etc. were classified into another (Group C). Although WHO cautions that this classification is not official, it can still be used since the present group of developing countries is too vast as it includes a diverse group of countries with diverse resources. The WHO has successfully applied these strata for estimating the global burden of disease study and used the same for comparisons among member countries. The strata are based on the childhood and the adult mortality.

Various factors are responsible for childhood mortality. Implementation of certain planned interventions in different setups has resulted in a decline in childhood mortality rates. Many community-based surveys conducted by international organizations indicate that improved nutritional status, better environmental conditions, availability of medical care to the mothers before and after delivery, and management of children

with infections are some of the factors responsible for the decline in the mortality rates. However, this decline is not universal. In many developing and under-developed countries, there is a lack of an organized approach, resource constraints and work overload, leading to compromises in the quality of healthcare.

In the developing countries, the rate of decline in childhood mortality was 2.5% per year from 1960 to 1990 whereas it was 1.1% per year from 1990 to 2001. Although this deceleration may be expected in areas with low rates of mortality, unfortunately it was also seen in high-rate regions.[6] Such stagnation in the decline of childhood mortality was also observed in large countries such as India.[7] It should be noted that these gains in mortality are not evenly distributed amongst nations. There are various factors for the differences. The most important is the burden of malnutrition existing in some countries. A child often has more than one infection in the context of malnutrition, which has a synergistic effect on mortality. Measles is often complicated by pneumonia or diarrhoea in a malnourished child. Children who are mildly undernourished have a two-fold higher risk of death than those who are better nourished. The risk increases upto 5 and 8 fold for a moderate and severely malnourished child respectively.

Another factor is the lack of hygienic and safe environments in most of the developing countries, while some have made rapid improvements in such matters. Ingestion of unsafe water, the inadequate availability of water for hygienic practices, and a lack of access to sanitation contribute to around 1.5 million child deaths and around 88% of deaths from diarrhea.[6] Social factors influence the hygiene, health seeking behavior and compliance to healthy practices e.g. Breast feeding practices vary in different countries.

To reduce childhood mortality, WHO under the "Health for All by the year 2000" initiative recommended a multi-sectored approach. The direct interventions focused on children 'under 5 years'. These interventions include vaccination against common childhood illnesses. Unfortunately, in many countries of Africa and Central Asia, all infants do not receive the benefit of immunization while in some areas coverage is limited.[8] In these countries, morbidity from diarrhea, acute respiratory infections, growth retardation and stunting (PEM) are still major public health problems.

Developing countries are not only a heterogeneous group in terms of mortality, but also in many other health indices. Over the past 50 years, the average life expectancy at birth has increased globally by almost 20 years from 46.5 years in 1950-55 to 65.2 in 2002.[9] The wide gap in life expectancy, which was seen between the developed and developing countries in the 1950's has now shifted to between the developing countries with high mortality and low mortality. The increase in life expectancy was largely attributed to better access to housing, sanitation and education, a trend to smaller families, growing incomes and public health measures.[9] Public health measures, particularly the national programs or other program strategies recommended by the WHO have played a major role in achieving optimal health in the developing countries.

However, it is generally believed that the success of these programs are to a large extent influenced by the country's priorities regarding the health services and local factors especially community participation. In addition, the differences in the quality and quantity of health system may also influence these indices. The economic indicators and health indices and the relation between them were explored in order to identify the differences. For example, Oman is a country placed under 'low child and low adult mortality group,' but its gross national per capita income is US $ 7,720. Whereas China and Vietnam, even though they are in the same group, their per capita income is US $940 and US $430 respectively. On the other hand, it was apparent that South Africa, with a gross national per capita income of US $2,600, had high child and very high adult mortality rates. In the same group (high child and adult mortality rates), Ethiopia has a per-capita income of only US $100. This seems to suggest that the mortality patterns are not entirely related to national income, and a higher per capita income does not indicate better health for the people.

The economic transition that is occurring around the world has created challenges and also opportunities in the health sector. The pace of the economic transition varies from one developing country to another. This process has resulted in policies towards less spending in social service sectors or reduced subsidy in core social service sectors such as health and education. In this scenario, the per capita health expenditure can be considered as a measure of the commitment of the governments towards better health of the people. Again there were wide differences within the developing world, as well as between developing and developed countries.

In the developing world, per capita health expenditure ranged from US $1,091 in Argentina to as low as US $17 in Ethiopia. Do these differences in health expenditures affect the performance of health systems or on the health indices? The World Health Report for 2003 stated that the most impressive declines in child mortality have occurred in developed countries, and in low mortality developing countries whose improved economic situation may have resulted in possible increase in health expenditures. The health indices, especially the mortality rates and immunization coverage are improving at a faster pace in better off countries with a fast developing economy compared to poorer countries. However, the success stories in many poor countries among the developing world like China and Oman demonstrate clearly that much progress

can be made with limited resources.[9] The successes with limited resources are definitely having a bearing while specific strategies are planned in IMCI.

The differences in achievements are not only apparent between countries but also between populations within the countries. It was interesting to note that the gains that were achieved in most of the developing countries have been for the 'better off' segments of the population compared to the poorer segments within the country. There is considerable variability in child mortality across different income groups within countries. Data collected by 106 demographic and health surveys in more than 60 countries showed that children from poor households had a significantly higher risk of dying before the age of 5 years than children from richer households.[9] Studies on the inequalities in healthcare were reviewed to identify reasons for these differences. Makinen et al. in their study on inequalities in healthcare use and expenditures, they used data from eight developing countries and countries in transition and they found that access to healthcare was unequally distributed to the advantage of the richer in nearly all the countries.[10] It seems that healthcare access is a critical factor for consideration in the implementation of the strategy of pre-referral antibiotic treatment in ETAT.

Human resources for healthcare are central to managing and delivering health services. Despite the undoubted importance of human resources to the functions of health systems, consistent and updated data regarding this aspect was not available. The inconsistency with regards to the availability of Physicians in the Primary health set-up was a major factor in deciding the quality of care.[11] In the group of developing countries, at one end of the spectrum, some of the countries in the Middle East such as Oman provide specialist level care in the Primary care. The same is provided by General Practitioners in India and at the other end of the spectrum, health workers in some African countries are responsible for primary healthcare. In comparison, the differences in human resources for healthcare and the doctor population ratio were taken as the indicator. It was found that a higher doctor population ratio was associated with top efficiency ranking of the countries. Thus availability of human resources and their distributions across three levels of healthcare system is one important factor, which could influence the decision for the use of a pre-referral antibiotic treatment.

Availability of sufficient infrastructure and its accessibility, drug policies and the availability of drugs are all important issues to be considered when it comes to implementation, as well as evaluation, of specific health strategies such as pre-referral antibiotic treatment. Although this aspect has been taken into consideration in the planning of the IMCI generic guidelines, no studies were found evaluating the impact after implementation of IMCI. Availability of facilities for emergency care is also a matter of importance. Improving such facilities, especially for severely ill children, has received substantial attention and resources in developed countries.[12] In contrast, a World Health Organization study surveying hospital care in seven developing countries showed numerous, significant deficiencies in triage and emergency care. These deficiencies were; non-availability of standardized assessment and treatment guidelines, understaffing (particularly at night), poorly trained staff, and little appreciation of the need for urgent treatment, inadequate facility organization for triage, and inadequate drugs and supplies.[13]

All of the above mentioned, plus deficiencies in the referral process, leading to an incomplete referral cycle result in severely ill children experiencing delays in the implementation of life saving emergency treatment. These deficiencies are not uniformly applicable to all the developing countries. From studies relating to referral system efficiency, some of the criteria for optimal functioning were identified. They are; the extent of bypassing phenomenon, quality of care, and availability of specialized care in first level referral facility, referral recording process, feedback process and facility for emergency transportation.[14] Such studies from Pakistan, Zambia, Mexico and Namibia have indicated deficiencies in the pyramidal referral system.[14,15,16,17] With respect to some of the better off developing countries such as Oman, the indicators of health system performance suggest that these criteria are more favorably satisfied.[18] Thus sufficient infrastructures and the existence of an efficient referral system could be possible factors that negate implementing a pre-referral antibiotic policy.

The presence of microbiological laboratory facilities would be one of the necessary inputs for not providing pre-referral antibiotic treatment. Unfortunately, this was lacking in most of the developing countries. Lack of diagnostic facilities in the referral hospitals of first and second levels is a problem in many developing countries and has major implications for implementation of treatments considered as the standard protocol in the industrialized countries.

The differences that were found within the developing world indicate that the use of pre-referral antibiotic is a strategy, which is certainly open to modification depending on the resources and health system performance. The favorable doctor population ratio, availability of health infrastructure, better accessibility of health facilities and efficient referral processes are all factors that could substantially influence the decision for not recommending the use of pre-referral antibiotic treatment in ETAT of IMCI protocol.

A literature review type of study has inherent limitations, as the authors are not directly involved in testing the hypothesis. They rely on the previous author's study methodology and objectives. In

this review, many studies contained epidemiological flaws. Some had small sample sizes, with no justification of sample selection and size, while in other studies, a credible randomization process was lacking and conclusions were drawn without proper justification.

If the investigator had the opportunity to conduct the study with specific objectives, the study design would be more fitting to the need. Hence accuracy and reliability of information that can be obtained from such indirect sources and studies performed by others with flaws in methodology would be viewed with some caution. Moreover, influence of publication bias affecting this review cannot be ruled out. In developing countries, many studies do not reach international journals and this make some important studies inaccessible. Also, the influence of competing interests particularly in pharmacological intervention studies and other factors that might be an integral part of the outcome following the intervention such as demographic factors and severity of the condition is unlikely to be mentioned in some of the published studies.

## Conclusion

The available evidence based information strongly suggests that pre-referral antibiotic treatment policy should be adopted in the 'Integrated Management of Childhood Illness' strategy in developing countries belonging to groups C, D and E. But the developing countries of group B should adopt policies based on the available resources and need in their respective countries. In addition, large countries should further review situations in smaller health provinces to implement pre-referral antibiotic treatment policy.

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