INTRODUCTION
Chapter 1

Introduction

Some portion of this chapter appeared in the article;

1.1 Evidence Based Practice

The healthcare system until early 1980’s was dominated by eminence based practice, where clinical decisions mainly relied on the expertise of clinicians.\(^1\) This approach underwent a major criticism as the decisions based only on expert opinions could be biased, subjective or obsolete and therefore it experienced a steady transition towards evidence based practice. In evidence based practice, the expert opinion is supplemented by information from best available research and client’s (patient) needs/preferences for making “informed” clinical decisions.\(^2\) Integration of information from three varied sources ensures optimum utilization of health resources and promotes consistent healthcare practices. Evidence based practice
involves five principal steps, popularly referred to as 5 A’s; Ask, Access, Appraise, Apply and Audit. The process begins by asking a relevant question after detailed assessment of the patient which identifies the key problem, treatment strategies, alternative treatments and desired outcomes. An extensive literature search is carried out to procure the best available research publications to find an appropriate answer to the framed question. In the next step, the evidence gathered from published literature is assessed for its worthiness by undertaking the critical appraisal in terms of (1) Validity - evaluating the methodological rigour of the studies (2) Impact - evaluating the clinical importance of the evidence (3) Applicability - evaluating the extent to which the evidence can be put to use in specific context. The critically appraised evidence is later integrated with practitioner’s expertise and patient expectations and applied to practice. Last step involves self evaluation of the entire process to identify the shortcomings and opportunities for improvement. Evidence based practice has extended its branches in recent years to other disciplines like education, marketing, engineering, public policies and many others.

Figure 1.1: Evidence Based Practice
1.2 Systematic Reviews

Acquisition of best up-to-date external evidence is the most challenging aspect of evidence based practice owing to the myriad number of research articles in the ever expanding medical science, published in numerous research journals/electronic databases. Reading through such a huge volume of literature and keeping oneself updated to the latest innovations would be an unattainable task for any busy practitioner. In addition, quality concerns of publications, contradicting results and language barriers (publications in foreign languages) complicate the process. Systematic reviews procure all the available published studies pertaining to a specific question, cull out the methodologically flawed or irrelevant ones among them, critically appraise the retained publications and condense their results to offer a comprehensive evidence.3

Figure 1.2: Steps involved in a systematic review

First step of a systematic review process is formulating an appropriate research question which is focussed, unique and answerable. Research question of a systematic review is based on four key components namely Population, Intervention, Comparison and Outcome, which is popularly referred to as “PICO” format. This
step is followed by development of protocol, where all proceedings of the review are explicitly described. Systematic review protocol encloses details of authors, background of the review, objectives, inclusion-exclusion criteria, search methods, data collection, analysis, acknowledgements, contributions of authors, funding sources, potential conflict of interest and references. Locating and selecting potentially relevant studies is the most crucial, skill oriented and arduous exercise of a systematic review. It demands for an elaborate, exhaustive and well-structured search strategy for searching electronic databases, hand searching of printed journals and also searching of foreign language articles, unpublished or grey literature to capture all available literature concerned to the research question. The identified articles undergo three stages of screening - title screening, abstract screening and full text screening and finally only the articles which meet the inclusion criteria find inclusion into the review. With the help of a valid data extraction form, details regarding objectives, methodology and results (summary estimates of pre specified outcomes) of the included articles are extracted. Further, the articles are subjected to quality check by a procedure known as “risk of bias assessment”. Risk of bias is defined as “any systematic error that results from the way the study was designed and executed”. These systematic errors adversely affect the internal validity of findings of studies. There are many tools available for risk of bias assessment, the popular one being the Cochrane risk of bias assessment tool for randomized controlled trials. It evaluates the risk of bias in terms of six important criteria; Random sequence generation (selection bias), Allocation concealment (selection bias), Blinding of participants and personnel (performance bias), Blinding of outcome assessment (detection bias), Incomplete outcome data (attrition bias) and Selective reporting (reporting bias). Risk of bias is assessed for each study separately and bias pertaining to each of the criteria is classified into three grades namely high risk, unclear risk and low risk. The decision regarding the overall risk
of bias of all studies is taken by constructing risk of bias graph and risk of bias summary (tells the percentage of overall high risk, unclear risk and low risk with respect to each criterion). There are many other tools available for risk of bias assessment specific to different study designs. Risk of bias assessment is followed by a procedure known as meta-analysis in which the estimates of many studies pertaining to an outcome are combined together to obtain a single estimate called pooled estimate or overall estimate. Review is documented in a manner as stated in the protocol. Deviations from the protocol (if any), strengths, limitations, existing biases, and recommendations for further research are clearly stated. Final review is published in a suitable journal and it is updated periodically with new searches to incorporate newly published studies.\textsuperscript{3,4,5}

### 1.3 Meta-analysis

Meta-analysis is the statistical aspect of the systematic review. The word “Meta” denotes something that is more comprehensive. Karl Pearson in 1904 first attempted meta-analysis by pooling the data on typhoid inoculation to compare the mortality and infection among soldiers who had volunteered for inoculation against those who had not volunteered.\textsuperscript{6} Gene V Glass in 1976 coined the term “Meta-analysis”, defining it as “the statistical analysis of a large collection of analysis results from individual studies for the purpose of integrating the findings”.\textsuperscript{7} Data for meta-analysis are the results or effect sizes or effect estimates along with their corresponding variances extracted from studies during data extraction process, which can be odds ratio, risk ratio for dichotomous outcomes or mean difference for continuous outcomes. The end-product of meta-analysis is an overall estimate or a pooled estimate which is obtained as the weighted average of effect estimates of individual studies.\textsuperscript{3,5,8} It is given by:
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\[ T = \frac{\sum_{i=1}^{n} W_i Y_i}{\sum_{i=1}^{n} W_i}, \quad i = 1, 2, 3, \ldots, n \]  

(1.1)

Where, \( n \) is the number of studies, \( T \) is the pooled estimate, \( Y_i \) is the effect estimate of \( i^{th} \) study, \( W_i \) is the weight assigned to \( i^{th} \) study, which is given by \( W_i = 1/\sigma_i^2 \), \( \sigma_i^2 \) is the variance of effect estimate of \( i^{th} \) study. Variance of \( T \) is obtained as \( V(T) = 1/\sum_{i=1}^{n} W_i \) and \( \sqrt{V(T)} \) gives the standard error of \( T \).

1.3.1 Modelling approaches of meta-analysis

There are two different modeling approaches of meta-analysis namely fixed effect model and random effects model. Fixed effect model works on the assumption that there is one common unknown true effect and different studies estimate that effect with different precision (figure 1.3a). Consequently, the observed variation across the summary estimates of different studies is due to chance alone. In a fixed effect model, weights are assigned inversely to the within study variability i.e., \( W_i = 1/\sigma_i^2 \), therefore it accounts for only variability within studies. Whereas, random effects model accounts for variability both within studies and also between the studies by assuming that each study estimates its own unknown true effect (figure 1.3b). In random effects model, \( W_i = 1/(\sigma_i^2 + \hat{\tau}^2) \), where \( W_i \) is the weight given to \( i^{th} \) study, \( \sigma_i^2 \) is the within study variability, \( \hat{\tau}^2 \) is estimate of between studies variability.\(^5\)\(^8\)

\[ \hat{\tau}^2 = \frac{\sum_{i=1}^{n} Q - (n - 1)}{\sum_{i=1}^{n} W_i - (\sum_{i=1}^{n} W_i^2)/(\sum_{i=1}^{n} W_i)}, \quad \hat{\tau}^2 = 0 \text{ if } Q < (n - 1) \]  

(1.2)

Where, \( Q \) is the Cochran’s \( Q \) statistic or Chi-squared statistic (equation 1.3). Fixed effect model allocates the weightage to a study in direct proportion to its
sample size, whereas the random effects model distributes the weights more evenly by allocating a relatively smaller weightage for larger sized studies and relatively higher weightage for smaller sized studies than fixed effect model. Consequently, the confidence intervals (CI) in case of random effects model will be wider than that of fixed effect model. Therefore, the random effects model is said to be more conservative than fixed effect model.

![Figure 1.3: Fixed and Random effects model - “Introduction to Meta-Analysis” by Borenstein et al](image)

### 1.3.2 Heterogeneity

Variability between the summary estimates of studies is termed as heterogeneity. Presence of heterogeneity can be detected by visual inspection of forest plot (figure 1.4) for the overlap of confidence intervals of estimates of individual studies. A poor overlap indicates the presence of high heterogeneity. It can also be statistically detected by Cochran’s Q statistic or Chi-squared statistic.

$$Q = \sum_{i=1}^{n} W_i (Y_i - T)^2 \sim \chi^2_{(n-1)df}$$  \hspace{1cm} (1.3)

A p-value < 0.1 indicates the presence of a statistically significant heterogeneity. There is also I\(^2\) statistic to quantify the heterogeneity as a proportion.
It is given by;

\[ I^2 = \frac{Q - (n - 1)}{Q} \times 100\% \]  \hspace{1cm} (1.4)

An \( I^2 \) of 0% - 30% represents a negligible heterogeneity, 31% - 50% represents moderate heterogeneity, 51% - 75% represents substantial heterogeneity and 76% -100% represents considerable heterogeneity. This is only a rough guide for interpreting heterogeneity and the cut-offs might vary under different situations.

### 1.3.3 Diagrammatic representation of meta-analysis

Meta-analysis is diagrammatically represented by “Forest Plot”. Forest plot of meta-analysis of four studies of the systematic review “Antibiotics for acute otitis media in children” for the outcome “pain after 24 hours” is depicted below.

![Forest Plot](image)

Figure 1.4: Forest Plot
1.4 Relevance of systematic reviews and meta-analysis in evidence generation

A systematic review process involves meticulous procedures to select, appraise and synthesize the results of individual studies giving a minimum scope for the bias to penetrate. Integration of results of several studies reduces uncertainty and helps to obtain a precise result with enhanced statistical power. Since all the procedures are clearly described apriori and results are statistically combined, the evidence is more reliable and robust. Systematic reviews settle the controversies created by conflicting results of different studies for a same research question and also highlight where there is a lack of evidence, which stimulates new research. Furthermore, they document where enough evidence already exists. Therefore funding organizations can stop funding for the research for which evidence already exists. Because of these reasons, the systematic reviews and meta-analysis occupy the peak of hierarchy of evidence pyramid.

![Evidence pyramid](image-url)
The meta-analysis technique has been subjected to profound methodological upgradations/innovations and has found its extension beyond medicine and health care to many other disciplines such as education, law, astronomy and zoology.\(^3\)

### 1.5 Important organizations involved in production of systematic reviews

Cochrane collaboration (www.cochrane.org) is the leading agency and an international non-profit organization with more than 50,000 specialists in health care involved in preparing, maintaining, updating systematic reviews of health care and making them readily available.\(^10\) It was founded in 1992 and named after the British Epidemiologist, Archie Cochrane. The Cochrane systematic reviews account for a very transparent appraisal with a strong methodological framework. The Cochrane collaboration includes 53 review groups for production of reviews within specific areas of healthcare. “Cochrane Handbook of Systematic Reviews of Interventions”\(^5\) provides all the details for the preparation of Cochrane systematic reviews. The collaboration also offers a freely downloadable and user friendly software called RevMan (Review manager) to facilitate preparation and maintenance of systematic reviews. Annual Cochrane colloquium is hosted by Cochrane collaboration every year in different parts of the world which is the gathering of members and stakeholders of Cochrane collaboration to discuss the recent innovations and ideas concerned to methodology of systematic reviews.

The Campbell collaboration\(^11\), Evidence for Policy and Practice Information and Co-ordinating (Eppi) Centre\(^12\), Centre for Reviews and Dissemination\(^13\)(CRD) and Public Health Evidence South Asia\(^14\) (PHESA) are some of the other organizations involved in production and dissemination of high quality systematic reviews in various disciplines of science.
1.6 Public health interventions

According to WHO, “public health interventions include organized measures to prevent disease, promote health, and prolong life among the population as a whole”.15 Their primary focus is to create cordial conditions where people can be healthy. There are marked differences between clinical interventions and public health interventions. Clinical interventions operate in a standardized setting, involving a closely monitored homogenous cohort of people as study population, well defined (straight forward) intervention, common mode of administration of intervention and uniformly measured outcomes.16 Controlled conditions ensure that the observed outcomes are mainly due to the effect of intervention. Public health interventions on the other hand operate in an uncontrolled environment, cater to a heterogeneous population, comprise of multiple components and are mostly driven by the contextual factors. Effectiveness of a public health intervention cannot be determined by means of a single outcome measure. This leads to the assessment of many outcomes.16,17 Because of these characteristics, the public health interventions are addressed as “complex interventions”.

1.7 What is complexity? What makes public health interventions complex?

Complexity refers to “having many interconnected and varied parts and consequently hard to understand fully”.18 The focus of Public health interventions is mainly to promote health and prevent ill health among people of a community or a population rather than cure specific groups of ailing people who are in need of treatment. In addition to this, diversities in culture, customs, literacy and other factors lead to disparities in the uptake of intervention. Public health interventions
are need based, address a broader dimension of health and require community participation and co-ordination with many other sectors. Therefore, they comprise of a range of activities or components which interact in varying proportions. As a consequence, it would not be possible to define the most active component of the intervention and figure out which component or combinations of components are pivotal in achieving the outcome/s. Further, they face a stiff competition from co-interventions i.e., the people might receive the same or a similar intervention from other sources. Public health interventions exhibit a higher degree of acquaintance to the context in which they perform. Context constitutes the external influences such as social, economical, cultural, political factors etc. that may either behave as a barrier or facilitator for implementation of the intervention. There is a proximity between the context and population characteristics, as a result of which changes in context directly reflect on the responses of the people. It is one of the important factors which decide the composition and mode of delivery of intervention. Context varies with time and place and this makes it impossible to devise a standard public health intervention which works in the same way wherever and whenever applied. Therefore the most challenging aspect of designing a public health intervention is deciding the ideal combination of the components specific to a given context - ensuring that the components are compatible among themselves and/or do not counteract each other. Evaluation of the effectiveness of intervention imposes further challenge in terms of defining the outcome measures which are valid and reliable across such a wide and heterogeneous population in a dynamic context. Also, it will be not be feasible to have a primary outcome measure which measures the totality of effectiveness of entire intervention, which necessitates for the measurement of several outcomes at multiple levels to capture the unintended consequences. Apart from this, the observed outcomes are subjected to influence of other factors (co-interventions) in addition to the intervention. In a nutshell,
complexity in public health interventions is due to an interlink between population, intervention, context and the outcomes.

1.8 Evidence Based Public Health

Evidence based public health is “the conscientious, explicit and judicious use of current best evidence in making decisions about the care of communities and populations in the domain of health protection, disease prevention, health maintenance and improvement”. In the recent times, evidence based public health has garnered much attention owing to the high expectations from the public health programmes and bulk expenses involved in implementing them. Implementing a right intervention in the right context is of utmost importance and it requires considerable amount of good quality evidence. Randomized controlled trials (RCT) are regarded as the robust among all the study designs and are known to provide evidence which is of exceptional quality. They are considered as ‘gold-standard’ to evaluate the ‘efficacy’ of clinical interventions under ‘best controlled’ conditions. However, they seem to be ‘restrictive’ to determine the ‘effectiveness’ of public health interventions which perform in ‘real-world’ conditions with too many factors influencing the outcome/s. The term restrictive signifies that RCTs lack the flexibility to accommodate the inherent complexity in public health interventions. RCTs are relatively less predominant in public health than in other fields of health care due to the following reasons; requirement of high budget, long follow up periods (long duration between intervention administration and occurrence of outcome), requirement of services of personnel from many disciplines such as epidemiology, biostatistics, behavioural sciences, health economics, health care management etc., contamination problems due to movement of people between intervention and control areas, poor compliance/high dropout rate and difficulty in timely outcome
assessment. Therefore, cross-sectional studies, quasi experimental studies are frequent on public health interventions.\textsuperscript{23} In the light of these complications, the evidence based public health experiences challenges in terms of; (1) Determining the best package of intervention components for a particular context (2) Generalizability of findings - the results of RCTs (or of any study design) are restricted to a particular context (3) Questionable internal validity of studies owing to the failure to capture complexity.\textsuperscript{24}

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Key Points

» Evidence based practice is the integration of expert opinion, best available research evidence and client needs.

» Acquisition of best up-to-date external evidence is the most challenging aspect of evidence based practice owing to the myriad number of research articles in the ever expanding medical science published in numerous research journals/electronic databases.

» Systematic reviews with meta-analysis assimilate bulk of research findings and provide comprehensive evidence which is of superior quality.

» Meta-analysis is the statistical aspect of the systematic review. The end-product of meta-analysis is an overall estimate or a pooled estimate which is obtained as the weighted average of summary estimates of individual studies.

» Complexity in public health interventions is due to an interlink between population, intervention, context and the outcomes.

» Meta-analysis of interventions conducted at population level is considered to be a challenging exercise due to their inherent complexity.