Evidence-based Pediatrics and Child Health

Second edition

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Evidence-based Pediatrics and Child Health, Second edition CD Rom

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Foreword

Evidence-based medicine (EBM) is about solving clinical problems. In particular, EBM provides tools for using the original medical literature to determine the benefits and risks of alternative patient management strategies, and to weigh those benefits and risks in the context of an individual patient's experiences and values.

The term EBM first appeared in the medical literature in 1991; it has rapidly become something of a mantra. EBM is sometimes perceived as a blinkered adherence to randomized trials, or a healthcare managers’ tool for controlling and constraining recalcitrant physicians. In fact, EBM involves informed and effective use of all types of evidence, but particularly evidence from the medical literature, in patient care.

EBM’s evolution has included outward expansion: we now realize that optimal healthcare delivery must include evidence-based nursing, physiotherapy, occupational therapy, and podiatry – and specialization. We need evidence-based obstetrics, gynecology, internal medicine, and surgery – and indeed, urology, orthopedics, and neurosurgery. And of course, we need evidence-based pediatrics (EBP).

EBP involves use of a hierarchy of evidence, from meta-analyses of high quality randomized trials showing definitive results directly applicable to an individual patient, to relying on physiological rationale or previous experience with a small number of similar patients. The hallmark of the evidence-based practitioner is that, for particular clinical decisions, you know the strength of the evidence, and therefore the degree of uncertainty.

Unfortunately, practicing EBP is not easy. Practitioners must know how to frame a clinical quandary to facilitate use of the literature in its resolution. Evidence-based pediatricians must know how to search the literature efficiently to obtain the best available evidence bearing on their question, to evaluate the strength of the methods of the studies that they find, extract the clinical message, apply it back to the patient, and store it for retrieval when faced with similar patients in the future.

Traditionally, neither medical schools nor postgraduate programs have taught these skills. While this situation is changing, the biggest influence on how trainees will practice is their clinical role models, few of whom are currently accomplished EBP practitioners. The situation is even more challenging for those looking to acquire the requisite skills after completing their clinical training.

This text primarily addresses the needs of this last group, practising pediatricians. The text represents a landmark in a number of ways. It is among the first EBM text directed specifically at pediatricians. The book represents an effort to comprehensively address the EBM-related learning needs of this clinical community.

The book is also original in its structure. The text begins with chapters that introduce the tools for evaluating the original pediatric literature. The bulk of the text, however, provides examples of how to use the skills of the evidence-based pediatrician to address clinical problems in everyday practice. These chapters do not provide the answer to a clinical question. In fact, they point out that the answer today may not be the answer tomorrow, as new evidence emerges. What they do provide is an approach that clinicians can use to address questions that they currently face, and will face in the future.

The clinician may find the prospect of practising EBP daunting. Where, you may wonder, are you to find the time to identify, let alone evaluate, the studies relevant to the myriad clinical problems that you face on a daily basis? There are a number of answers to this question. One is the suggestion that there are a relatively small number of issues, perhaps one to two hundred in any individual’s practice, that are important and arise frequently enough, and for which there is high quality evidence, to warrant working familiarity with the data.

Whether or not this perspective is valid – and its validity may depend on the eye of the beholder – another answer comes from the increasing bank of preprocessed EBM resources. One can consider a classification of these resources that comes with the mnemonic 4S:

- the individual study
- the systematic review of all the available studies on a given problem
- a synopsis of both individual studies and summaries, and
- systems of information.

Secondary journals such as Evidence-Based Mental Health, Evidence-Based Nursing, and ACP Journal Club which does the job for internal medicine – survey a large number of journals relevant to their area and choose studies that meet both relevance and validity screening criteria. Similarly, the Journal of Pediatrics summarizes selected published studies on a bimonthly basis. These journals present the results of these studies in structured abstracts or synopses that provide clinicians with the key information they need to judge their applicability to their own practices. Fame and fortune await the enterprising group who applies this methodology to produce evidence-based pediatrics.
If there is any chance it may be available, clinicians whose priority is efficient evidence-based practice seek a high quality systematic review rather than the primary studies addressing their clinical question. For issues of therapy, published systematic reviews, including those in the Cochrane Collaboration database, provide a rapidly growing repository of clinically useful summaries. Finally, clinicians often seek answers to questions about a whole process of care rather than a focused clinical question. Increasingly, clinicians asking these sort of questions can look to high quality evidence-based practice guidelines or clinical pathways to provide, in effect, a series of synopses that summarize available evidence. The best systems use computer technology to match the patient or problem characteristics with an evidence-based knowledge repository and provide patient-specific recommendations. At the same time, we must remember that recommendations can only be made for “average” patients, and the circumstances and values of the patient and family before us may differ. One way of dealing with this might be to bring the tools of decision analysis to the bedside.

Whatever the future holds for the increasing efficiency of evidence-based practice, the current text provides an introduction to a system of clinical problem-solving that is becoming a prerequisite for modern pediatric practice.

Gordon Guyatt
Richard Dawkins coined the term “meme” in his 1976 book *The Selfish Gene*. In his foreword to *The Meme Machine*, he describes a meme as “an entity that might play a role in the transmission of words, ideas, faiths, mannerisms, and fashions.” A meme may represent “a set of religious beliefs, a regional accent, a new word, a mannerism, a fashion or an idea.” The term, now included in the *Oxford English Dictionary*, is defined as “an element of culture that may be considered to be passed by a non-genetic means.” Like genes, memes can be transmitted vertically within a population, for example the passing of religious beliefs or mannerisms from parent to child, but memes also travel horizontally, like viruses in an epidemic. One example is the rapid spread of new terms such as “Y2K” over the internet. Another is the spread of a schoolyard craze – whether hula hoops, pogo sticks or yo-yos – through a generation of children the world over. A prerequisite for the transmission of a meme, whatever its nature, is the willingness of the human recipient to accept and imitate it. Committing a meme to paper (whether it be grandma’s chocolate brownie recipe or the rules of a new playground game), greatly enhances the likelihood that a meme will be transmitted and the accuracy with which this is achieved.

In the context of the above definition, evidence-based medicine (EBM) could be considered a meme. It is an element of medical culture that has been passed by non-genetic means, including imitation, to clinicians around the world. The term evidence-based medicine, coined in 1991 by Sackett and colleagues at McMaster University, is defined as “the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients.” The concept of EBM fell on the fertile ground of a generation of clinicians who were overwhelmed by the exponential growth of the medical literature and needed a means of locating, making sense of, and applying relevant information to their patients. Although some clinicians appeared to shun EBM, the concept spread like an epidemic through other groups of the medical profession – both vertically, from clinician to junior doctor or student (and sometimes in the reverse direction) and horizontally, amongst peers. The principles of EBM have been committed to paper and Sackett’s book, *How to Practice and Teach EBM* has found its way into thousands of white coat pockets. Increasingly, clinicians have access to electronic medical databases, while specialized journals that present evidence-based summaries of the literature have flourished. In many universities EBM is now incorporated into undergraduate and graduate medical curricula and postgraduate courses on how to practice and teach EBM abound.

EBM is the subject of a series of specialty texts published by BMJ Books and including *Evidence Based Cardiology*, *Evidence Based Gastroenterology and Hepatology*, and *Evidence Based Pediatric Oncology*. We are pleased to present the second edition of *Evidence-Based Pediatrics and Child Health*. The first edition was well reviewed, well received by its readers and underwent several reprints. One reviewer described the book as “a practical tutorial in the process and practice of evidence-based medicine,” saying that “if any book is to persuade paediatricians to practice evidence-based paediatrics, this is it.” More importantly, our colleagues assert that the book is used by clinicians to inform clinical practice and also provides a source of teaching material on “how to do EBM.” The first book spawned two series on evidence-based pediatrics, in the *BMJ* and the *Western Journal of Medicine*, and its format has been adapted for use in a current series on evidence-based pediatrics in the *Archives of Diseases in Childhood*. The first edition, the second edition of *Evidence-Based Pediatrics and Child Health* is intended as a “primer” in EBM rather than a “master class”. Its target audience is pediatricians, family physicians, and other healthcare workers who deal with children. It is not a book aimed at a readership with a PhD in epidemiology and therefore avoids the use of complex statistics and obscure terminology. Neither is it a standard pediatric text. It makes no attempt to be comprehensive and neither purports to cover all conditions presenting to pediatricians, nor all possible aspects of a single disease. Rather, it aims to introduce the principles of EBM and to illustrate, with the use of “real” and exclusively pediatric cases, how to incorporate these principles into daily clinical practice. This book is purposely written in an informal, conversational tone. This is intended to convey the idea that the knowledge imparted to the reader comes from a clinical colleague who is aware that, in order to make it reasonable for a busy clinician to practise EBM, the process must be realistic, time-efficient, and have practical relevance. Although this is a multi-author book, we have tried to ensure some consistency of style and theme throughout. While the information in some chapters represents a thorough systematic review of the literature, other chapters illustrate...
the “quick and dirty” approach that we are all forced to use in our busy clinical practices. We thank all authors for their valuable contributions and Mary Banks, our editor, for her unfailing support.

Format and contents

The format of this book is similar to that of the first edition. Section I provides readers with the conceptual background and skills they need to practise each component step of EBM, namely identifying the need for information, asking clinical questions, and finding, evaluating, and applying the evidence. Each chapter starts with a clinical scenario, introduces the concepts involved in critical appraisal of, for example, a paper on therapy, and then demonstrates the process using publications from the literature. In keeping with the structure of the JAMA series “Users’ Guides to the Literature” we adhere to the sequence of assessing first the study’s validity, then its results, and then its application to the child in question. The converse method, to start by assessing applicability to the patient and going on to assess validity only if applicability is shown, has its proponents. We are yet to be convinced that the former method is problematic.

Section I also contains some chapters addressing topics that are often omitted from EBM texts. These include the assessment of quality of life, the use of scales to rank the strength of evidence, issues of clinical measurement and disagreement, and the evidence-base for various methods of continuing education. There is evidence that physician performance is enhanced for those who learn to use EBM and apply it to their clinical practice. Also, evaluation of medical students taught EBM skills shows that this approach improves their ability to evaluate the clinical literature, and enhances lifelong learning skills.

Section II covers some routine interventions for the care and prevention of disease in children (including well child examination, immunization, and injury prevention) and Section III covers a range of common and/or important illnesses (including diabetes, asthma, and gastroenteritis) that present to pediatricians. Each is written by practising clinicians and commences with a “real world” scenario. The reader is led through the process of EBP – asking questions about the case, searching and evaluating the evidence and summarizing the answers found before applying the relevant information back to the original “case”. We should stress that in resolving clinical questions the available evidence is not the only consideration. Patient and family preferences, risk aversion, cost and cultural issues, and quality of life must be considered. Different clinicians, with their own patients, in different settings, may come to conclusions that are different from those reached by the authors. We emphasize the Bayesian approach to evidence: the evidence is like a diagnostic test in that it adds information to prior knowledge and sways clinicians a predictable and measurable distance. Thus, clinicians with access to the same information may end up in a different place because their starting point was different. The important thing is to be able to make explicit the influence of the evidence (which is empiric and quantifiable) and the patients’ or clinicians’ prior beliefs and values (which are highly individual) on the question at hand.

The rationale behind the book’s case-based format is that it is easier for readers to learn how EBP can be used in their practices if they are provided with comprehensive clinical examples. The reader should not be disappointed that the whole of pediatrics is not covered, that the information provided on each topic is not comprehensive, and that the answer to a clinical question is rarely a clear “yes” or “no”. This is a book about “process.” It does not try to provide all the answers, but does demonstrate how the questions posed by the chapter authors can be addressed. It also illustrates the concept that, when making any decision based on evidence, you must weigh the potential benefits against the potential harms. Thus, the book provides a framework for readers to use when managing their own patients. For easy reference and to enable repetition or expansion, summary search strategies that identify the database and search terms are “boxed”. Inevitably, the search for evidence to answer a clinical question often identifies areas in which there is a lack of good evidence. This has led authors to suggest topics for future research, which appear at the end of each chapter.

All chapters that were included in the 1st edition have been updated and the 2nd edition has been expanded considerably. In Section I a new Chapter 1 provides an overview of EBM and includes discussion of some topical issues in EBM – publication bias, analysis bias, and conflict of interest. The addition of chapters on communicating evidence to patients, qualitative research, complementary and alternative medicine, and informatics is timely. Increasingly, parents come to consultations “armed” with a recent Cochrane review or other information about their child’s condition downloaded from the web. We must embrace the arrival of IT and take every opportunity to help carers interpret the literature and to involve them in informed decision-making about their child’s care. Four new chapters on neonatology for the generalist have been added to Section III. The neonatal topics now covered – neonatal abstinence syndrome, pain control in the newborn, neonatal encephalopathy, outcome of prematurity and apnea – reflect societal change, the changing nature of our practices, and the rapid recent expansion in published data in neonatology.

So is EBM a passing “fad” or is it here to stay? If, as Gordon Guyatt says in his Foreword to this book, “evidence-based medicine is about solving clinical problems,” then clearly EBM is “a prerequisite for modern pediatric practice”. More than ever, there is a legal imperative for clinicians to
keep up to date so as not to risk providing suboptimal care – or ending up in the courts! In pediatrics, a delay in the use of beneficial treatments, such as antenatal steroids in preterm labor to prevent neonatal respiratory distress and avoidance of prone sleeping to minimize the risk of SIDS, has previously resulted from our failure to act on the available evidence. However, we should be heartened by one recent study showing that the primary intervention was supported by evidence from at least one randomized trial or convincing non-experimental evidence in 75% of pediatric admissions.

EBM is part of the e-revolution currently occurring in our health systems. The integration of evidence into our practices is made infinitely easier by access to electronic databases of the medical literature and to summarized sources of evidence. However keeping up to date is a daunting task. Over 2 million scientific papers are published each year and keeping abreast of pediatrics alone would require reading more than five journal articles every day of the year. Most busy clinicians admit they have little time to read and many seek information from local “experts”. To add to our woes, conventional continuing medical education programs do little to improve patient care. Thus, throughout the book, the emphasis is on illustrating “shortcuts” for the busy clinician, whether to ensure good capture of the relevant literature or to evaluate its quality. For example, the reader is encouraged to use high quality “secondary” or “synthesized” evidence such as systematic reviews, when available, rather than to scour MedLine for the answer to a question of therapy. These evidence sources not only minimize the time required for searching, but provide the clinician with “predigested” information located, critically appraised, and summarized by skilled colleagues.

We hope that this book will help clinicians to more easily find and understand information relevant to patient care. EBM is not about saving money and it is not just about randomized trials. Both good clinical skills and good evidence are essential for the practice of EBM. We acknowledge that EBM does have limitations – not least of which is lack of evidence applicable to pediatrics and child health. As pediatricians, our challenge is to increase the number of clinical studies and systematic reviews addressing diseases of childhood. Similarly, it is important that we put pressure on editors of other sources of synthesized evidence, such as ACP Journal Club, Evidence Based Medicine, and Clinical Evidence, to include more topics on pediatric and child health. As researchers, we should identify knowledge gaps and encourage the conduct of quality clinical trials of therapies for use in children.

EBM may never convince its critics, but is certainly preferable to the alternatives – including “eminence-“, “vehemence-“, and “confidence-“ based medicine as proposed by Isaacs and Fitzgerald. The future for EBP will be bright if we can both capitalize on our clinical expertise and ensure that we harvest, critically evaluate, and judiciously use the available evidence to improve patient care. We hope that this book will provide an impetus for busy clinicians to practise EBP and some practical tips to facilitate this task and ensure better outcomes for our patients.

References

Glossary of terms

Algorithm An explicit description of the ordered sequence of steps to be followed in patient care under specified circumstances.

Absolute risk The probability (rate) of a specified outcome during a specified period in the control and experimental groups. Sometimes referred to as the control event rate (CER) and experimental event rate (EER) respectively. In contrast to common usage, the word “risk” may refer to adverse events (such as seizure or the need for ventilation), or desirable events (such as prevention of complications or cure).

Absolute risk difference The absolute arithmetic difference in the event rate (risk of an outcome) in the treatment (experimental) and control groups in a randomized trial. The absolute risk difference may be an: Absolute risk reduction (the bad outcome is less frequent in the treatment than control group); an Absolute risk increase (the bad outcome is more frequent in the treatment than control group); an Absolute benefit reduction (the good outcome is less frequent in the therapy group).

Allocation concealment A method used to ensure that the result of randomization (allocation to groups) in a trial is concealed from the individual responsible for actually allocating the patient. Concealment can be achieved by separating the randomization and recruitment process. For example randomization might be determined by a centralized agent (for example, pharmacy); by use of an on-site computer with restricted access; by use of identical, coded containers; or using sequentially numbered opaque and sealed envelopes. “Concealment” is different from “blinding”.

Association A statistical relationship between two variables or events, which does not imply a causal relationship.

Baseline risk The risk (probability) that a child within a specified population will have a particular condition or disease at the present time or the risk (probability) that the child will develop a particular outcome in the future.

Best Evidence An electronic database of over 1000 abstracted articles that have been published in the journals Evidence Based Medicine and ACP Journal Club. All articles have been deemed methodologically sound and are accompanied by a commentary written by a content expert and outlining its importance and usefulness to clinical practice (www.bestevidence.org).

Bias (systematic) Any trend in the collection, analysis, interpretation, publication, or review of data that can lead to conclusions that are systematically different from the truth.

Blinding (masking): Blinding is any method used to deny investigators, patients and assessors information about allocation of patients to treatment groups. Knowledge of allocation might influence measurements, observations, or management and thereby introduce bias into a clinical trial. The terms double-blinded or triple-blinded are best avoided and it is preferable to state precisely who (assessor, investigator or patient) was blinded to group allocation.

Boolean logical operator A group of search terms (for example, “AND”, “OR”, and “NOT”) available in MedLine (and other searchable databases), which help in refining the search strategy. For example the request “gastroenteritis AND loperamide” will give the articles common to both sets. The search “gastroenteritis OR loperamide” will give both sets of articles, while use of the term “NOT” will help exclude irrelevant articles.

Case–control study An observational study in which a group of children with an outcome of interest (for example, leukemia) and a group of children who have not experienced the same outcome are compared to see how exposure to suspected risk factors (for example, viral agents, radiation) differs between the two groups. This type of study provides a relatively quick and easy way to measure risk factors and is most useful for the study of rare diseases. However bias and confounding may influence the results and it is difficult to infer causation from this type of study.

Case report (series) Uncontrolled observational studies consisting of a report on one (or a series of) patients with an intervention and/or outcome of interest.

CINAHL (Cumulative Index of Nursing and Allied Health) An electronic database of nursing and allied health sciences literature, including health education, occupational and physiotherapy, social services at www.cinahl.com (1983—).

Clinical Evidence A publication containing summaries of evidence on questions of therapy, prepared by clinicians and epidemiologists using standardized methodology. Published by BMJ Books and updated approximately every 6 months. Predominantly relates to adult medicine but contains a section on Child Health (www.clinicalevidence.com).
Clinical practice guideline  A statement designed to assist decision-making about health care for specific clinical circumstances. Although some guidelines are based on a systematic review of the literature, others are not evidence-based. In the absence of published evidence, recommendations may be based on “consensus expert opinion”.

Clinically significant  A finding that is clinically important. Here, “significant” means “important” (rather than statistically significant). Where the word “significant” or “significance” is used without qualification in this text, it is being used in its statistical sense.

Cochrane Library  A regularly updated, electronic database containing several literature databases including the Cochrane Database of Systematic Reviews (CDSR), the Database of Abstracts of Reviews of Effects (DARE), Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Methodology Reviews, and the Cochrane Methodology Register (CMR). Also contains information about the Cochrane Collaboration. It is available on CD-ROM or on the Internet with free access for all in some countries (www.cochranelibrary.com).

Cochrane Collaboration  This international network (named after the epidemiologist Archie Cochrane) has a unique role in evaluating and collating health care interventions with the ultimate aim of helping people make well informed health-care decisions. The collaboration prepares, disseminates, and updates systematic reviews of the literature (for example, RCTs for interventions). This process involves searching the medical literature, classifying articles according to study type, and abstracting, analyzing and summarizing information in a standardized way.

Cochrane Central Register of Controlled Trials (CENTRAL)  A database within the Cochrane Library containing all randomized controlled trials identified by the members of the Cochrane Collaboration and which may be relevant for inclusion in Cochrane Reviews. Over 370,000 trials were listed in Issue 4, 2003.

Cochrane Database of Systematic Reviews (CDSR)  A database within the Cochrane Library, updated quarterly, of all systematic reviews completed by members of the Cochrane Collaboration using strict methodological criteria. It contains both completed reviews and reviews in progress (Protocols). Over 3000 reviews were listed in Issue 4, 2003.

Cochrane Methodology Register (CMR)  A database of abstracts of books and articles related to methodological issues relevant to summarizing evidence about health care in systematic review.

Cochrane review  see systematic review.

Cohort study  A study that follows a group of people over time and compares outcomes in people exposed to a particular factor or intervention (for example, a vaccine or a medicine) and in people not exposed (or exposed to different levels or doses). This type of observational study is useful to determine whether a specific exposure is the cause of a specified outcome (often adverse). A prospective or concurrent cohort follows participants forward in time and is more reliable than a retrospective cohort study, which look back in time to ascertain whether or not participants with a particular outcome were exposed to the agent in question. Cohorts including of a single group of patients are used to evaluate prognosis. Cohort studies may also called longitudinal, prospective, incidence or follow up studies.

Co-intervention  An intervention given apart from the intervention under study. When evaluating randomized controlled trials, it is important to determine whether co-interventions were applied equally to treatment and control groups.

Completer analysis  Analysis of data only from children who remained at the end of the study. This contrasts to intention-to-treat analysis, which uses data from all children who were enrolled in a study regardless of whether they remained at the end of the study (see below).

Confidence interval (CI)  Gives an indication of the precision of an estimate for example, of treatment effect. The 95% CI is most often reported and indicates the range of results that would be obtained 95% of the time if a study with the same size and design were repeated. This is similar to saying that the true value of an estimate (never exactly known) has a 95% chance of falling within the confidence interval.

Confounder (confounding variable)  A variable (or factor) that distorts the true relationship between the study variable of interest and the outcome of interest, because it is also related to that outcome. The process of randomization should ensure equal distribution of confounders amongst study groups and hence minimize distortion of results by confounders.

Consolidated Standards of Reporting of Trials (CONSORT)  Evidence based and regularly updated guidelines published by a group of editors of biomedical journals, scientists, epidemiologists and statisticians, to standardize the format for reporting of randomized controlled trials.

Controls  In a randomized controlled trial with two or more interventions, controls are children in the comparison (rather than the treatment or intervention) group who are allocated to receive either a placebo, no treatment, or the current best treatment. In a case–control study the control (a member of the comparison group) is someone who does not have the outcome or disease of interest.
Cost-benefit analysis An economic assessment to determine whether the cost of an intervention is worth the benefit by measuring both cost and benefit in the same (usually monetary) units.

Cost-effectiveness analysis An economic analysis in which the effects of treatment (for example, vaccination) are converted into health terms so that the costs of treatment can be described in terms of some additional health gain (for example, prevention of rotavirus infection).

Critically appraised topic (CAT) A short summary of evidence from a one or more publications that address a specific clinical question. This allows people to share the results of critical appraisals. CATs are not systematic literature reviews (examples can be found at www.ped.med.umich.edu/ebm/cat.htm).

Cross sectional study An observational study design that involves surveying a population for an exposure, an outcome, or both at one point in time or over a specified time period. These studies are relatively easy to perform but can only establish association (not causation) and are susceptible to bias (for example, recall bias) and confounding.

Evidence-based child health A useful evidence-based health care resource at www.ich.bpmf.ac.uk/ebm/ebm.htm

Ecological study An observational study that compare summary data for example, disease prevalence between populations at a particular point in time. Bias and confounding cannot be controlled.

Effect size “Effect size” is a measure of effect used for continuous data when different scales are used to measure an outcome (for example, mood). In statistical terms, it is defined as the difference in means between the intervention and control groups divided by the SD of the control (or both) group(s). For continuous outcomes (such as pain scores or height) effect size may be expressed as the standardized mean difference or weighted mean difference. However, the term “effect size” is also used generically to describe the magnitude of the estimate of therapeutic effect for dichotomous outcomes. In this situation the size of an effect can be expressed as a relative risk or an odds ratio.

Effectiveness A measure of the benefit from an intervention for a given health problem under usual practice conditions, i.e., a “real world” clinical setting. This measure takes into consideration compliance and acceptance by the patient as well as the efficacy of an intervention. It is useful for assessing the relative risks-benefits of a treatment.

Efficacy A measure of the benefit from an intervention for a given health problem under ideal practice conditions, i.e., in a randomized controlled trial with full patient compliance.

The size of the effect may be greater than in the real world situation.

EMBASE The electronic bibliographic database of Excerpta Medica – the European equivalent of MedLine – with a focus on drugs and pharmacology. Covers over 3000 journals from over 100 countries (1974–).

Event The occurrence of a dichotomous outcome that is being sought in a study (such as seizure, death, or an improvement in group score).

Event rate The proportion of patients in each treatment group in whom an event occurs. May be expressed as control event rate (CER) or experimental event rate (EER).

Evidence-based health care The application of the principles of evidence based medicine is extended to all health-care related activities, including clinical care, purchasing, and management.

Evidence-based medicine (EBM) The conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients (after Sackett). The practice of EBM involves integrating clinical expertise (information from history taking, examination) with the best available research evidence and including patients (with their individual preferences and values) in decision making about their health care.

Exclusion criteria Pre-specified criteria that exclude patients from enrolment in a clinical study (even if they meet inclusion criteria).

Follow up Observation of individuals or groups for health-related outcomes over a period of time. In a randomized trial loss of substantial numbers of patients to follow up may bias study results.

Forest plot A diagram representing the results of individual trials included in a meta-analysis and a summary statistic.

Funnel plot A method of plotting the sample size against the effect size of results of individual trials included in a meta-analysis and a summary statistic. Used in meta-analysis, to investigate whether or not publication bias is likely to have occurred.

Grateful Med Software available through the National Library of Medicine to help non-experts search MedLine. The search can be conducted using author name, title of article, or subject.

Hazard ratio (HR) This is broadly equivalent to relative risk, but is used when the risk is not constant with respect to time. If however, the assumption is made that the risks remain in proportion between population groups in a study then, although the absolute risks (hazards) may alter as time passes, the hazard ratio between groups remains constant. The term
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is typically used in the context of survival over time and is then broadly equivalent to the relative risk of death. If the HR is 0.5 then the risk of dying in one group is half the risk of dying in the other group.

**Heterogeneity** In the context of meta-analysis, heterogeneity means dissimilarity between studies. It can be due to differences in reported effects (statistical heterogeneity), in patients, treatments or outcomes (clinical heterogeneity), or in study design (methodological heterogeneity). Heterogeneity may render pooling of data for meta-analysis unreliable or inappropriate. Statistical tests can be used to determine whether the degree of heterogeneity is greater than would be expected by chance.

**Homogeneity** In the context of meta-analysis, homogeneity means similarity between studies (opposite of heterogeneity).

**Inception cohort** A group of patients recruited as close as possible to the onset of the target disorder for example, when they developed clinical symptoms. This is the best type of cohort to examine short and long term prognosis (future outcome) of an individual with a particular disease.

**Incidence** The number of new cases of a condition occurring in a specified population over a specified period of time.

**Intention-to-treat analysis** Data from all children who were originally enrolled into a randomized controlled trial are analyzed, regardless of whether they remained until the end of the trial, withdrew from the trial, or swapped treatment groups. Intention-to-treat analysis (as opposed to completer analysis) is preferred in RCTs because it mirrors the changes to treatment and non-compliance that may occur in clinical practice. It also minimizes the risk of attrition bias that can influence results if participants are excluded from data analysis.

**Kappa statistic** A measure of agreement between observers that is beyond the agreement expected based on chance alone. A value of kappa > 0.8 is excellent and kappa < 0.4 is poor agreement.

**Likelihood ratio (LR)** The LR is the ratio of likelihoods for a given test result. The LR for a test indicates the likelihood that a given test result would be expected to occur in a patient with the target disease, compared to the likelihood of that same result in a patient without that disease, i.e., a LR is the ratio of the proportions of patients with and without disease who have a given test result. LR can help evaluate the usefulness or performance of a diagnostic test and compare it to other tests. The LR of a test with binary results can be calculated from sensitivity and specificity. LR = sensitivity/(1–specificity) for a positive test and LR = (1–sensitivity)/specificity for a negative test. The LR can be used in conjunction with the pretest probability to estimate post-test probability (the chance that a child with a particular diagnostic test result will have a particular diagnosis).

**Likelihood ratio nomogram** A nomogram that simplifies determination of post-test probability from pretest probability and likelihood ratio, eliminating the need for calculations. (Adapted from Fagan, *N Engl J Med* 1975;293:257.)

**MedLine** A huge database of medical articles, compiled by the United States National Library of Medicine. It indexes millions of articles from over 4000 journals published in over 70 countries and covering clinical medicine, biological sciences, health education, social and information sciences and health-related technology. MedLine is available in printed form (*Index Medicus*), on the Internet or on CD-ROM. Software to access MedLine includes PubMed and OVID (Ovid Technologies).

**MeSH headings (Medical Subject Headings)** The headings (terms) used by the United States National Library of Medicine to index publications in MedLine. In the MeSH system, broad subject headings branch into a series of progressively narrower headings.

**Meta-analysis** A statistical technique that uses quantitative methods to summarize in a single estimate the results of several studies included in a systematic review. When using this technique, studies are weighted depending on the variance of the results, the size of the study and the event rate in the study.

**Morbidity rate** Rate of illness but not death in a specific population.

**Mortality rate** Rate of death in a specific population.

**N-of-1 randomized trials** A trial in which the benefit and risks of a treatment are evaluated in an individual patient (a randomized trial in one individual). In such trials, the patient undergoes pairs of treatment periods organized so that one period involves the use of experimental treatment and the other involves the use of an alternate of placebo therapy. The treatments are given in a random order and the patient and the clinician are blinded to the treatment received during each period. The clinician and patient document specific outcomes during the trial. Usually the pair of treatments is given three times in order to convince the participant and clinician that a treatment is either effective, ineffective, or harmful.

**Negative predictive value (NPV)** The chance of not having a disease given a negative test result.

**Number needed to treat (NNT)** One measure of treatment effectiveness. NNT is the number of children that you would need to treat with a specific intervention for a given period of time to prevent one additional adverse outcome or achieve one additional beneficial outcome. NNT can be calculated as 1/absolute risk reduction.
Number needed to harm (NNH) One measure of harm from treatment. NNH is the number of people you would need to treat with a specific intervention for a given period of time to cause one additional adverse outcome. NNH can be calculated as \(1/\text{absolute risk increase}\).

Odds The odds of an outcome is the ratio of the number of people with the outcome to the number of people without the outcome.

Odds ratio (OR) OR is one measure of treatment effectiveness. It is the ratio of the odds of an outcome in the experimental or treatment group to the odds of that outcome in the control group. The closer the OR is to one, the smaller the difference in effect between the experimental intervention and the control intervention. If the OR = 1 (or the CI of the OR cross 1) then there is no difference in outcome rate in the treatment and control groups. If the OR is > (or <) 1, then the effects of the treatment are more (or less) than those of the control treatment. Note that the effects being measured may be adverse (for example, death or disability) or beneficial (for example, cure or survival). The OR is analogous to the relative risk (RR) when the events are rare; but as event rates increase, the OR becomes further and further from 1 relative to the RR.

Odds reduction The complement of odds ratio (1–OR), analogous to the relative risk reduction when events are rare.

Overview see systematic review.

Paired or matched subjects Children receiving different treatments within a study can be “matched” or “paired” to balance potential confounding variables, for example, sex and age. Study results are analyzed and presented as differences between pairs.

P value The probability that an observed difference occurred by chance, if it is assumed that there is in fact no underlying difference between the means of the observations. If this probability is < 1 in 20 (which is when the \(P\) value is < 0.05, i.e., under the null hypothesis), then the result is conventionally regarded as being “statistically significant”.

Placebo A biologically inert treatment (looking, tasting, and given in the same way as the active treatment) that is given to the control group in a randomized, placebo-controlled trial.

Positive predictive value (PPV) The chance of having a disease given a positive test result. The value is strongly influenced by the “prevalence” of that disease in the population under study.

Post-test odds The odds of a patient having a condition once the result of the test for diagnosing that condition is available. Post-test odds = pretest odds × likelihood ratio. Post-test odds can be used to calculate the post-test probability.

Post-test probability The probability of a child having a condition once the result of the diagnostic test is available. This estimate is more useful and meaningful than the pretest probability. Post-test probability can be estimated mathematically. Post-test probability = post-test odds/(post-test odds + 1). When the likelihood ratio is known, post-test probability can be estimated by using the likelihood ratio nomogram.

Power Refers to the ability of a study reliably to detect a clinically important difference (for example, between two treatments) if one actually exists. Statistical power is a function of sample size and should be calculated before the study commences.

Pretest odds The odds of a patient having a condition before the diagnosis is confirmed. Pretest odds = prevalence/(1−prevalence). Pretest odds can be used to calculate post-test odds.

Pretest probability The estimate of the probability of a patient having a condition before the test for diagnosing that condition is performed and/or the result is available, i.e., the prevalence of that disease in the population. Clinicians often derive this estimate from their own clinical experience in their own setting, and there may be wide variation in different settings.

Prevalence The proportion of people with an outcome or a disease in a given population at a given time.

Primary evidence Evidence available from primary (original) studies, including randomized controlled trials, cohort studies, case–control studies, cross-sectional surveys, and case reports (see secondary evidence).

Protocol (Cochrane) A systematic review that is currently being undertaken by members of the Cochrane Collaboration and contains everything but the results. Protocols are listed in the Cochrane Library’s Database of Systematic Reviews.

PsycLIT A database of literature, indexed like MedLine, covering the fields of psychology, psychiatry, sociology and related disciplines.

Publication bias may result for a number of reasons. Studies with positive results are more likely to be published than studies with negative results, making it appear from reviews of the published literature that certain treatments are more effective than is truly the case. Other sources of publication bias include duplicate publication, failure to publish completed trials, publication in the non-English language, and publication in journals not listed in MedLine (see Chapter 1).

Randomization A “formal chance” process (equivalent to the flip of a coin) by which children participating in a study are allocated to groups. Using this process, each child has an
independent, fixed, and usually equal chance of inclusion in the intervention or comparison group. This process may be facilitated using a table of random numbers or a computer-generated sequence.

**Randomized controlled trial (RCT)** A trial in which participants are randomly assigned to groups. One group (the experimental or treatment group) receives the intervention being tested, and the other (the comparison or control group) receives an alternative treatment or placebo. This study design for assessment of the relative effects of an intervention is least likely to be subject to bias.

**Reference standard (gold standard) diagnostic test** The most widely accepted (or established) method, for diagnosing a condition. A “gold standard” provides a benchmark against which a new or proposed screening or diagnostic test can be compared. Although a gold standard usually comprises a single intervention or test, it could also be a period of follow up to observe the evolution of a child’s condition, the consensus of an expert panel of clinicians, or a combination of these. In articles about diagnostic tests, the gold standard must be explicitly stated and applied independently in a blinded fashion and regardless of the results of other tests.

**Relative risk (RR)** (synonyms: risk ratio, or event rate ratio) The ratio of the risk of an event in the treatment group and the control group. If \( RR > 1 \) or \( RR < 1 \), then the therapy either increases or decreases the event rate respectively. If the \( RR = 1 \) (or the CI of the RR crosses 1), then there is no significant difference between groups.

**Relative risk increase (RRI)** The proportional increase in risk (event rate) of an adverse outcome between children in experimental and control groups in a trial. \( RRI = RR - 1 \).

**Relative risk reduction (RRR)** The proportional reduction in risk of an adverse event between children in experimental and control groups in a trial. \( RRR = 1 - RR \).

**Secondary evidence (evidence syntheses, predigested evidence)** Evidence from primary or original studies (see primary evidence) which has been searched out and critically appraised – often using predetermined methodology – and sometimes combined and reanalyzed. Secondary evidence may be presented in systematic reviews, meta-analyses, and literature reviews.

**Sensitivity** The proportion of children with a disease, who have a positive diagnostic test. Sensitivity should not to be confused with positive predictive value (see above).

**Significant** By convention “significant” means statistically significant at the 5% level (see statistically significant).

**SnNOut** When a clinical sign or diagnostic test has a high Sensitivity, a Negative result rules Out the diagnosis.

**Specificity** The proportion of children without a disease who have a negative diagnostic test. Specificity should not to be confused with negative predictive value (above).

**SpPin** When a sign or diagnostic test has a high Specificity, a Positive result rules In the diagnosis.

**Standardized mean difference (SMD)** A measure of effect size used when outcomes are continuous (such as height, weight, or symptom scores) rather than dichotomous. The mean differences in outcome between the groups being studied are standardized to account for differences in scoring methods (such as pain scores). The measure is a ratio, and therefore has no units.

**Statistically significant** The findings of a study are unlikely to be due to chance. Significance at the commonly cited 5% level \( (P < 0.05) \) means that the observed result would occur by chance in only 1 in 20 similar studies. Where the word “significant” or “significance” is used without qualification in the text, it is being used in this statistical sense. A finding that is statistically significant may not be clinically significant or important (see above).

**Systematic review** A review in which all the primary studies on a topic have been systematically identified, appraised, and summarized according to explicit and reproducible methodology. It can, but need not, involve meta-analysis as a statistical method of combining and numerically summarizing the results of the trials that meet minimum quality criteria. The Cochrane Library lists systematic reviews performed by the Cochrane collaboration in the Cochrane Database of Systematic reviews and in the Database of Abstracts of Reviews of Effects lists Systematic Reviews, done by others and deemed to have sound methods (see above).

**Toxlit** A medical database on toxicology, indexed like MedLine.

**Validity** The extent to which the results of a study reflect the truth (and are not affected by bias, confounding, or random error). Internal validity reflects the study; external validity refers to the extent to which the differences between groups reflect integrity of the study design. External validity reflects the ability to apply the results to the target (or non-study) population.

**Weighted mean difference (WMD)** A measure of effect size used when outcomes are continuous (such as symptom scores or height) rather than dichotomous (such as seizure or death). The mean differences in outcome between the groups being studied are weighted to account for different sample sizes and differing precision between studies. The WMD is an absolute figure, and so takes the units of the original outcome measure.