# PART 1

# Practising evidence-based respiratory medicine

# CHAPTER 1.1
# Introduction

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What is evidence-based respiratory medicine (EBRM) and why do we need it? The term evidence-based medicine (EBM) has a long history, and controversy exists regarding its components and value in decision making.[1,2] In most cases, however, it can be described as the combined use of experience, best evidence and patient's preference and values to develop an approach to a clinical problem, often referred to as evidence-based medical care.

An example may help readers understand the issue better. A 25-year-old woman presents to an emergency department with an exacerbation of her previously well-controlled asthma due to an upper respiratory tract infection. She improves slowly with inhaled β agonists and oral prednisone (pulmonary function tests improve from 55% to 75% predicted over 4 hours in the emergency department) and is ready for discharge home. From an evidence perspective, the clinician wishes to prescribe a short course of oral corticosteroids [best evidence based on systematic review (SR) of randomized controlled trials (RCT)].[3] Moreover, experience reminds the clinician that patients with moderate asthma can also deteriorate, require hospitalization and even die (clinical experience). The clinician is concerned and wishes to protect her from any and all of these events (and so does her lawyer). Unfortunately, the patient protests this decision because corticosteroids cause her to develop acne, retain fluids and have insomnia. She has a major weekend function and feels that these medications may create havoc with her social life. Despite the clinician's protestations, she refuses the oral corticosteroids (patient preference and values). Readers in clinical practice will be very familiar with this type of scenario.

What is the evidence-based decision in this case? Some traditionalists may suggest that their decision is final and the patient should accept the oral corticosteroid treatment. The EBM clinician might also use the evidence to clarify the benefits and risks of treatment options, in conjunction with the patient's preference and his/her experience. In the event that agreement cannot be achieved, the EBM clinician would propose an alternative 'next-best evidence' and similarly reasonable approach. For example, the clinician may recognize that very short courses of corticosteroids (1–2 days) are less likely to create side-effects. Moreover, the addition of inhaled corticosteroids,[4] asthma education[5] and very close follow-up may be safe in such patients.

## Why EBM?

This approach may seem intuitive to many practitioners, which begs the question why is this being proposed in respiratory medicine? In a therapy issue, clinicians must ultimately decide whether the benefits of treatment are worth the costs, inconvenience and harms associated with the care. This is often a difficult task; however, it is made more difficult by the exponentially increasing volume of literature and the lack of time to search and distil this evidence.[6] Although clinicians of the early twenty-first century have an urgent need for just-in-time, on-demand clinical information, their time to access such information has probably never been as compressed. Increases in patient volume and complexity, patient care demands and the lack of access to resources have exacerbated the work frustrations for many clinicians. These concerns often take precedence over seeking the most relevant, up-to-date and comprehensive evidence for patient problems.

Despite the fact that most patient problems presenting clinically may be seen by many clinicians daily around the world, the appropriate treatment approaches are often not fully employed and practice variation is impressive. For a variety of reasons, the results from high-level evidence such as RCTs are not readily available to busy clinicians and keeping up to date is becoming increasingly difficult. Moreover, a valid, reliable and up-to-date clinical bottom line to guide treatment decisions has been elusive.[6]

However, access to information is not the only barrier to practising 'best evidence medicine'. Clinicians also need rigorously produced, synthesized best evidence information to assist them at the point-of-care. As time is increasingly more precious, the need for this digestible information has never been greater.

## Levels of evidence

Levels of evidence have been developed and employed in clinical medicine to reflect the degree of confidence with which re-

sults from research may be accepted as valid. From levels of evidence, strength of recommendations are generated that are graded according to the strength of the scientific evidence supporting them. The highest level of evidence (Level I) in therapy is based on RCTs [or meta-analysis (M-A) of such trials] of adequate size to ensure a low risk of incorporating false-positive or false-negative results.[7] Although Level I status is awarded to RCTs, many trials are not large enough to generate Level I evidence. While considerable debate exists regarding the relative merits of evidence derived from large individual trials versus systematic reviews,[8] owing to the costs associated with large, multicentred trials, they remain uncommon across many clinical specialties and topic areas. Consequently, it is likely that systematic reviews will play an increasingly important role in the future decisions made by patients, clinicians, administrators and society in all areas of health care.

Level II evidence is based on RCTs that are too small to provide level I evidence. They may show either positive trends that are not statistically significant or no trends and are associated with a high risk of false-negative results. Level III evidence is based on non-randomized controlled or cohort studies, case series, case–control studies or cross-sectional studies. Level IV evidence is based on the opinion of respected authorities or expert committees as indicated in published consensus conferences or guidelines. Level V evidence is based on the opinions of those who have written and reviewed the guidelines, based on their experience, knowledge of the relevant literature and discussion with their peers.

## Levels of evidence and systematic reviews

One possible solution to the information dilemma for clinicians is to focus on evidence from SRs.[9] Systematic reviews address a focused clinical question, using comprehensive search strategies, assessing the quality of the evidence and, if appropriate, utilizing meta-analytic summary statistics, and synthesize the results from research on a particular topic with a defined protocol. They represent an important and rapidly expanding body of literature for the clinician dealing with respiratory complaints and are an integral component of EBM. Despite a recent increase in the production of diagnostic testing SRs, the most common application of SRs is in therapeutic interventions in clinical practice.

Despite publications illustrating the importance of methodological quality in conducting and reporting both RCTs[10] and SRs,[11] not all SRs are created using the same rigorous methods described above. Like most other research, there are shades of grey in methodological quality associated with research in this field. High-quality SRs of therapies attempt to identify the literature on a specific therapeutic intervention using a structured, a priori and well-defined methodology. Rigorously conducted SRs are recognizable by their avoidance of publication and selection bias. For example, they include foreign language, both published and unpublished, literature and employ well-described comprehensive search strategies to avoid publication bias. Their trial selection includes studies with similar populations, outcomes and methodologies and use of more than one 'reviewer'.

Systematic reviews regarding therapy would most commonly combine evidence from RCTs. In the event that statistical pooling is possible and clinically appropriate, the resultant statistic provides the best 'summary estimate' of the treatment effect. A SR with summary pooled statistics is referred to as a *meta-analysis*, while those without summary data are referred to as a *qualitative systematic review*. Both these options represent valid approaches to reporting SRs, and both are now increasingly commonly published in the medical literature.

## Levels of evidence and the Cochrane Collaboration

The Cochrane Collaboration represents one source of high-quality SR information available to most clinicians with very little effort. By way of brief review, the Cochrane Collaboration is a multinational, volunteer, collaborative effort on the part of researchers, clinicians from all medical disciplines and consumers to produce, disseminate and update SRs on therapeutic interventions.[12] The Cochrane Collaboration takes its name from the British epidemiologist, Archie Cochrane, who drew attention to the overwhelming and seemingly unmanageable state of information pertaining to clinical medicine. A famous quote from Cochrane summarizes his thoughts on the topic:

> It is surely a great criticism of our profession that we have not organized a critical summary, by specialty or subspecialty, adapted periodically of all relevant randomized controlled trials.

The Cochrane Library is a compendium of databases and related instructional tools. As such, it is the principal product of the large international volunteer effort in the Cochrane Collaboration. The quality of SRs contained within the Cochrane Library has been shown to be consistently high for individual topic areas as well as throughout the Cochrane.[13,14] Within the Collaboration, the Cochrane Airway Group (CAG; www.cochrane-airways.ac.uk) is responsible for developing, completing and updating systematic reviews in 'airway' topics [e.g. asthma, chronic obstructive pulmonary disease (COPD), bronchiectasis, interstitial lung disease, sleep apnoea and pulmonary embolism]. Based at St George's Hospital Medical School in London, UK, the CAG editorial office co-ordinates this huge international respiratory effort. The Co-ordinating Editor (Professor Paul Jones: 1993–2003; Dr Christopher Cates: 2003–present) and the editorial team are responsible for the direction, quality and supervision of the reviews provided in the Cochrane Library. The CAG Review Group Co-ordinator (Mr Stephen Milan:

1995–2001; Mr Toby Lasserson: 2001–present) administratively co-ordinates this effort and assists reviewers in completing their reviews. Reviewers within the CAG represent consumers, researchers, physicians, nurses, physiotherapists, educators and others interested in the topic areas. Respiratory topics are particularly well covered by members of the Cochrane Airway Group.[15]

Systematic reviews produced by members of the Cochrane Collaboration are products of a priori research protocols, meet rigorous methodological standards and are peer reviewed for content and methods before dissemination. Specifically, this process of review production is designed to reduce bias and ensure validity, using criteria discussed in the *Journal of the American Medical Association*'s 'User's Guide' series.[16] This text will focus on evidence derived from SRs and, as often as possible, those contained within the Cochrane Library.

## Cochrane Library

The Cochrane Library is composed of several databases, three of which require some description here. The Cochrane Central Register of Controlled Trials (CENTRAL) is an extensive bibliographic database of controlled trials that has been identified through structured searches of electronic databases and hand searching by Collaborative Review Groups (CRGs). Currently, it contains over 440 000 references (CL, Version 1, 2005) and can function as a primary literature searching approach with therapeutic topics. The Database of Abstracts of Reviews of Effects (DARE) consists of critically appraised structured abstracts of non-Cochrane published reviews that meet standards set by the Centre for Reviews and Dissemination at the University of York, UK. The last, and possibly most important, resource is the Cochrane Database of Systematic Reviews (CDSR), a compilation of regularly updated systematic reviews with meta-analytic summary statistics. Contents of the CDSR are contributed by CRGs, representing various medical topic areas (e.g. airways, stroke, heart, epilepsy, etc.). Within the CDSR, 'protocols' describe the objectives of SRs that are in the process of being completed; 'completed reviews' include the full text and usually present summary statistics. Both protocols and reviews are produced using a priori criteria, adhere to rigorous methodological standards and undergo peer review before publication. Regular 'updates' are required to capture new evidence and address criticisms and/or identified errors.

## Reporting systematic reviews

There is a unique lexicon used in SRs, and it is helpful to describe several of the important terms here. This is especially true of the statistical issues reported in SRs.

For dichotomous variables (alive/dead; admit/discharge), individual statistics are usually calculated as odds ratios (OR) or relative risks (RR) with 95% confidence intervals (95% CI). Pooling of individual trials is accomplished using sophisticated techniques using either a fixed effects (FE) or a random effects (RE) model. The 'weight' of each trial's contribution to the overall pooled result is inversely related to the trial's variance. In practical terms, for dichotomous outcomes, this is largely a function of sample size; the larger the trial, the greater contribution it makes to the pooled estimate. The results of most efforts to pool data quantitatively are represented as Forrest plots, or 'blob-o-grams'; these figures will be used extensively by reviewers in this textbook. In such displays, the convention is that the effects favouring the treatment in question are located to the left of the line of unity (1.0), while those favouring the control or comparison arm are located to the right of the line of unity. When the 95% CI crosses the line of unity, the result is considered non-significant (Fig. 1).

For continuous outcomes, weighted mean differences (WMD) or standardized mean differences (SMD) and 95% CIs are usually reported. The use of WMD is common in many SRs and is the difference between the experimental and control group outcomes, when similar units of measure are used.[17] The SMD is used when different units of measure are used for the same outcome. For continuous variables with similar units (e.g. airflow measurements), a WMD or effect size (ES) is calculated. The 'weight' of each trial's contribution to the overall pooled result is based on the inverse of the trial's variance. In practical terms, for continuous outcomes, this is largely a function of the standard deviation and sample size: the smaller the SD and the larger the sample size, the greater contribution the study makes to the pooled estimate. For continuous measures with variable units (such as quality of life or other functional scales), the SMD is often used. For example, if quality of life was measured using the same instrument in all studies, a WMD would be performed; if the quality of life was measured using multiple methods, all producing some 'score', an SMD would be calculated. For both the SMD and a WMD, the convention is the opposite of that for dichotomous variables, that is effects favouring the treatment in question are located to the right of the line of unity (0), while those favouring the control or comparison arm are plotted to the left. Once again, when the 95% CI crosses the line of unity, the result is considered non-significant.

Number needed to treat (NNT) is another method of expressing a measure of effect.[18] In the Cochrane Library reviews, the absolute risk reduction (ARR) is represented by the risk reduction statistic, and the inverse of this (and its 95% CI) provides the NNT estimation. A less exact method is to examine the pooled percentages in each column. For example, in the meta-analysis on corticosteroid use in acute asthma to prevent admission, the OR was 0.75 (95% CI 0.63–0.86).[19] The RR was 0.13, resulting in an NNT of 8 (95% CI 5–20). By subtracting the approximate percentage admission in the control group (0.50) from the treatment group (0.37), one obtains an ARR of 0.13 and a similar NNT of 8. Caution is advised, as this

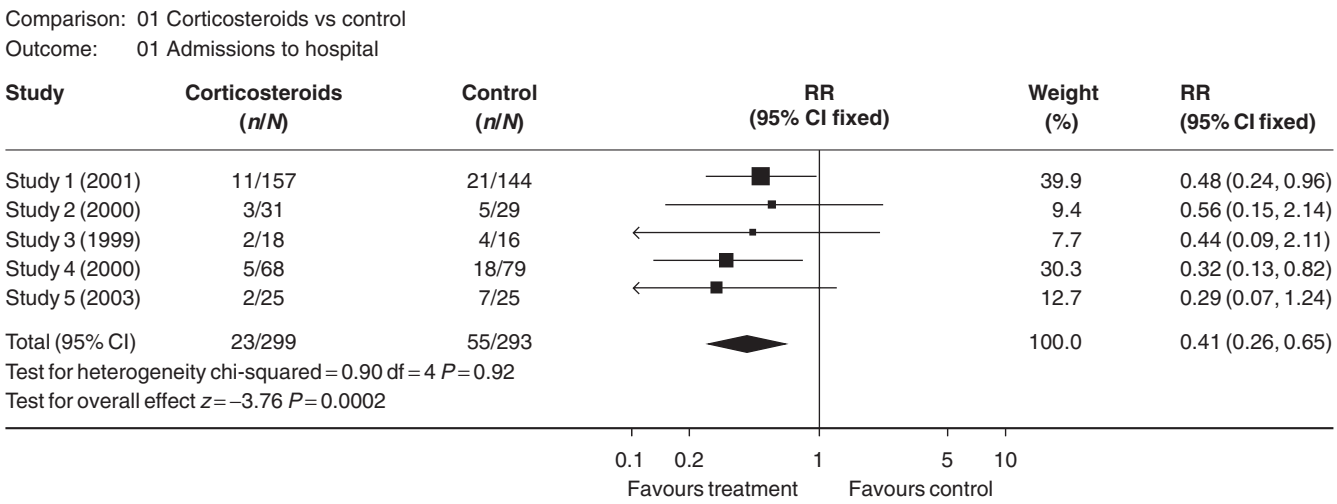


**Figure 1.** Hypothetical and typical Forrest plot of the effect of corticosteroids on admission to hospital in an illustrative respiratory disease.

approach is an approximation method for calculating NNT. Heterogeneity among pooled estimates is usually tested and reported.[20] Sensitivity and subgroup analyses are often performed to identify sources of heterogeneity, when indicated.

## Question development

Patients presenting with many of the respiratory complaints presented in this book represent typical cases commonly encountered in clinical medicine. Many potentially important questions arise from these encounters; all these questions vary based on the perspective of the person asking the question (e.g. clinician, patient, administrators, primary care providers, public health officers and government policy makers). For example, using the previous example above, what is the *aetiology* of this patient's acute asthma problem? What *diagnostic tests* should be performed (if any) and which can the health care system afford? What additional *therapy* could be added in order to reduce the chances of an adverse outcome? What is her *prognosis* over the next 3 weeks with respect to her respiratory status? Would instituting a policy of closer follow-up provided by nurse clinicians improve the long-term *prognosis* for this woman? Finally, would influenza vaccination *prevent* further asthmatic exacerbations or reduce their severity?

The success of any search for answers is the development of a well-defined, clinically relevant and succinct question.[21] This approach is similar for the clinicians at the bedside, the policy maker in the office, the patient searching for options and the researcher performing a systematic review. Some have referred to this process as developing an 'answerable question', and this is a useful approach that will be used throughout this book. The rationale for developing a question is that the approach will save time and needless repetition throughout the complicated process of progressing from question to answer.

## Components of a good question

Designing an appropriate clinical question includes consideration of the components of a good question (described below), compartmentalizing the topic area and describing the design of studies to be included. All questions should include focused details on the **p**opulation, **i**ntervention (and **c**omparison treatment) and **o**utcomes associated with the question. This approach is often abbreviated as PICO, but these are only part of the components necessary for developing the question. Each component is described in further detail below, and examples are illustrated in Table 1.

### Population

Clearly defining the population under consideration is the first step in developing a successful question; however, this can be a difficult task at times. The selection should be based on the interests and needs of the clinician and the patient's problem.

### Intervention/exposure

Clearly defined interventions must be articulated before searching for answers. For example, corticosteroids may be a particularly problematic topic in question development. As corticosteroids can be administered via may routes (e.g. inhaled, intravenous, oral and intramuscular), using varying doses and over different durations, these must all be considered when searching for evidence. Moreover, the use of different agents is common (e.g. dexamethasone, prednisone, budesonide, fluticasone, methylprednisolone, etc.) and is clearly an important consideration in question development.

### Outcome

There are a variety of outcomes reported in respiratory research studies. For example, in acute asthma studies, administrative designations (e.g. death, admission/discharge, obser-

**Table 1.** Example of PICO methodology for developing clinically appropriate questions (see text for details).

| Population | Intervention | Outcome | Design | Topic |
|---|---|---|---|---|
| Children with asthma in ED | Ipratropium bromide versus standard care | Admissions to hospital | RCT | Therapy |
| Children < 18 years | Exposure to cigarette smoke | Development of asthma | Prospective cohort | Aetiology |
| Children in ED with acute asthma | Use of pulse oximetry versus clinical examination | Admissions to hospital | Prospective cohort | Diagnosis |
| Asthmatic children discharged | Corticosteroids versus control from the ED | Relapse to additional care | RCT | Therapy/prognosis |
| Children and adults in primary care practice | Influenza vaccine versus placebo | Prevention of exacerbations of asthma | RCT | Prevention |

RCT, randomized controlled trial; ED, emergency department.

vation, relapse, etc.), physiological parameters [peak expiratory flow (PEF), vital signs, oxygen saturation, etc.], adverse effects (e.g. tremor, nausea, tachycardia, etc.), medication use (e.g. β-agonist use, corticosteroid rescue, etc.), complications (e.g. intubation, pneumonia, etc.) and symptoms (e.g. quality of life, symptoms, etc.) may all be reported. The clinician must select appropriate primary and secondary outcomes before beginning the search. The primary outcome should reflect the outcome that is most important to the clinicians, patients, policy makers and/or consumers.

Often the clinician may also be interested in secondary outcomes, side-effects and patient preference. While patient preference is not often reported in clinical trials and therefore SRs, side-effects and secondary outcomes are commonly encountered. The importance of secondary outcomes is that, if their pooled results are concordant with that of the primary outcome, this adds corroborating evidence to the conclusion. In addition, side-effect profiles provide the patients, clinician and others with the opportunity to evaluate the risks associated with the treatment. Inclusion of other outcomes, which are either infrequently reported or clinically unhelpful, should be considered with caution.

## Other question considerations

Two additional components to be considered in the development of an answerable question for a clinical case are the topic area and the study methodology or design.

### Topic areas

While selecting between topic areas may initially appear straightforward, there can be confusion. For example, is pulmonary function a diagnostic or a prognostic topic? Clearly, the use of pulmonary function tests has been examined as a diagnostic tool compared with clinical examination, and a review in this area would encompass a diagnostic domain. However, whether spirometry testing is effective in predicting relapse after discharge would be a prognostic question. As there are other domains of SRs (including therapy, prevention and aetiology), by selecting the topic of the clinical question, this further clarifies the approach for the clinician.

### Design

The design of the studies to be located should also be considered carefully in the initial question formulation. For example, if one is interested in a therapeutic topic, the best level of evidence (Level I) includes results from large RCTs or SRs.[7,21] The next level of evidence (Level II) would be small RCTs, which are insufficiently powered. Finally, cohort, case–control and case series would be considered lower levels of evidence for treatment. It is therefore appropriate and efficient for initial searches for therapy answers to be limited to SRs and RCTs.

## Locating the evidence: literature searching

Searching for evidence is a complex and time-consuming task. For example, to ensure that one has identified all relevant possible citations pertaining to a clinical problem, simple searching is often ineffective.[22] Search of MEDLINE, the bibliographic database of the National Library of Medicine, for RCTs using a non-comprehensive search strategy will miss nearly half the relevant publications.[23] In addition, by not adding EMBASE (a European electronic database maintained by Elsevier) searching, clinicians may be missing an additional 40% of the available evidence.[24] Hand searching has been shown to increase the yield of RCT searches.[24] Finally, unpublished and foreign language literature may contain im-

portant information relevant to your patient's problem and should not be excluded. Given the volume of literature, the search strategies required and the need for multilingual detective work, it is hardly surprising that clinicians find it difficult to obtain all the relevant articles in a particular topic area. Several strategies can be used to address this issue. One strategy is to target searches, using designated filters (see Table 2).[6] Another strategy, and the choice of this text, is to search for high-quality SRs, especially in therapy, to answer the question.[25]

## Interpreting the evidence for clinical practice

Evidence-based medicine relies on the reporting of evidence using terms that are at times unfamiliar to clinicians. For example, in diagnostic articles, terms such as sensitivity, specificity and likelihood ratios (LR) are often reported. In therapy articles, terms such as odds ratio (OR), relative risk (RR) or number needed to treat (NNT) are commonly reported. In this book, these terms will be applied regularly in an attempt to distil the evidence for the clinician. There are many internet-based resources freely available to the reader that can provide additional information, calculations and interpretations of these terms. A limited internet resource list is provided in Table 3.

## Evidence-based medicine in respiratory care

We are excited about highlighting the approaches to the diagnosis and treatment of respiratory conditions that will be detailed in this book. The editors have selected experts in both respiratory conditions (content) as well as evidence-based medicine (methodology). Following this introductory chapter, the remainder of the chapters will focus on individual topic areas. Many of the chapters in this book have been organized in a similar fashion using the following format.

### Case scenario

The chapter author has been asked to develop a patient scenario upon which the remainder of the chapter will be based. Authors have been instructed to provide a real-world clinical problem.

### Questions

Using the PICO methodology described above, questions will be developed from each case. These clinical scenarios will be used to identify important questions relevant to the diagnosis, prognosis, therapy, adverse effects, cost-effectiveness, etc. of respiratory conditions.

### Literature search

A brief description of the search strategies employed to identify the relevant research used to answer the clinical question will be provided. In general, the evidence from SRs, especially those available in the Cochrane Library, will be highlighted.

**Table 2.** Common search strategies for identifying evidence from electronic databases using search filters.

| Topic | Highest level design | Search terms |
|---|---|---|
| Therapy | RCT | Publication type: RANDOMIZED CONTROLLED TRIAL; CONTROLLED CLINICAL TRIAL; CLINICAL TRIAL<br>MeSH headings: RANDOMIZED CONTROLLED TRIALS; RANDOM ALLOCATION; DOUBLE BLIND; SINGLE BLIND; PLACEBO(S) |
| Therapy | SR | Publication type: REVIEW; SYSTEMATIC REVIEW; META-ANALYSIS<br>MeSH headings: MEDLINE |
| Diagnosis | Prospective cohort | Publication type: DIAGNOSIS<br>MeSH headings: SENSITIVITY AND SPECIFICITY<br>Text word: sensitivity |
| Prevention | RCT, SR | See above for RCT and SR |
| Aetiology | Prospective cohort | Text word: risk |

MeSH, Medical Subject Heading; RCT, randomized controlled trial; SR, systematic review.

**Table 3.** Selected EBM websites.

| EBM | Website address |
|---|---|
| Cochrane Airway Group (airways progress and releases) | www.cochrane-airways.ac.uk |
| Bandolier (various EBM topics) | http://www.jr2.ox.ac.uk/bandolier/ |
| VirtualRx (NNT calculations) | http://www.nntonline.com/ebm/visualrx/nnt.asp |
| Cochrane Collaboration | www.cochrane.org |
| ACP Journal/EBM Journal | http://ebm.bmjjournals.com/ |
| Agency for Health Care Policy and Research (AHRQ) | http://www.ahrq.gov |
| Centre for Evidence-Based Medicine (Oxford, UK) | http://www.cebm.net |
| Centre for Health Evidence (CHE) | http://www.cche.net/che/home.asp |
| Centre for Reviews and Dissemination (CRD) | http://www.york.ac.uk/inst/crd/ |

This list is neither comprehensive nor complete; it represents some of the EBM resources of use to the authors.

### Summary critical appraisal

A summary of the available evidence will be provided by the authors, focusing on the key results and their implications.

### Answers/conclusions

A summary approach to the patient will be presented at the end of each chapter.

## Summary

Much progress has been made in respiratory medicine over the past half century in the areas of aetiology, diagnosis, prevention, therapy and prognosis. The synthesis of this evidence has been undertaken by many researchers, and there is now good evidence for the management of many common respiratory conditions. This book attempts to summarize this evidence in a best evidence fashion using relevant examples from clinical practice.

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## Conflicts of interest

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