

The implementation of evidence in clinical care

exploring the gap between knowledge and practice

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To my parents

To Stefan, Sofie and Emma

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Saturnus

Neptunus

The implementation
of
evidence
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health care

Chapter 1

Exploring
the gap
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and
practice

Introduction

Uranus

Background of EBM

• A brief history

The history of evidence-based medicine starts many centuries ago. The *clinical trial* can be traced back to biblical times, when around 600 B.C. Daniel of Judah compared the health effects of a vegetarian diet with those of a royal Babylonian diet. After ten days the men who had been eating the vegetarian diet looked healthier than those who had indulged on the royal delicacies. So the warden took away the delicacies and wine and gave everybody a diet of vegetables instead.¹ The first scientific publications of trials appear in the 18th and 19th century. Concerned about the impact of scurvy on the lives of seamen, James Lind, a Scottish naval physician (1716-1794), carried out an experiment with twelve men. In pairs they were given six different dietary additions, including one with oranges and lemons (1753).² Almost a century later, in France Pierre Charles Alexandre Louis (1787-1872) introduces his 'numerical method' ("la méthode numérique") into diagnosis and therapy in order to "... ensure that all medical practitioners arrive at identical results." His method of careful observation, systematic record keeping and rigorous analysis of multiple cases provided the foundations for modern clinical epidemiology.^{3,4} The study of the effect of bloodletting for treating pneumonia was first published in the 1828 issue of the French journal 'Archives Générale de Médecine' and in 1836 in an American scientific journal. In spite of the impressive results of both Lind's and Louis' work, it wasn't until many years later that medical practice changed accordingly. Pierre Louis' contributions to medical science were made possible by the developments of statistics and the theory of chance.⁵ He was a contemporary of the Belgian astronomer and mathematician Adolphe Quetelet, who was born in Ghent in 1796. Quetelet introduced mathematical concepts that had been developed in astronomy to the study of sociological and societal phenomena and thus paved the way for modern biostatistics. His concept of the "average man", based on the Belgian census of 1829, is still applied in epidemiology today.⁶ The first record of a *randomised* clinical trial is attributed to Austin

Bradford Hill. Supported by the British Medical Research Council he performed a trial with streptomycin to treat pulmonary tuberculosis.⁷ However, it has been suggested that the roots of *evidence-based practice* lie in Chinese medicine. In the reign of Emperor Qianlong (1688-1766) a method known as ‘kaozheng’ (‘textual criticism’, or ‘evidential research’) was practiced that resembles modern day critical appraisal. It refers to an effort to establish the authenticity of the classical Confucian texts through rigorous methods.⁸

In 1971 Archie Cochrane, a Scottish physician and epidemiologist, published *“Effectiveness and efficiency: random reflections on health services”*.⁹ In this now ‘modern classic’ he introduces the notion that health care and health services must be evaluated on the basis of scientific evidence rather than on clinical impression, anecdotal experience, ‘expert opinion’, or tradition. He suggested that, because resources would always be limited, they should be used to provide equitably those forms of health care which had been shown to be effective in properly designed evaluations. In particular, he stressed the importance of using evidence from randomised controlled trials (RCTs) because these were likely to provide much more reliable information than other sources of evidence.¹⁰ Although clinical trials had been around for several hundred years, it was Cochrane’s 20th century advocacy that focussed attention on their importance for health care. His plea for more randomised clinical trials also included improved accessibility of these trials. The case of diethylstilbestrol (DES), a drug prescribed to women who threatened to miscarry, illustrated the need for a proposal for well designed RCTs and visibility of the results of these studies. The recommendations for use of DES were based on non-randomised studies, whereas available randomised trials did not show an effect. Despite these findings DES continued to be used.¹¹ The harm of this practice inflicted on the treated women, their daughters and their offspring is now well known. Greater accessibility of the information at the time might have saved lives. On the other hand Cochrane recognized the need to critically summarize the results of available trials. His ideas inspired Iain Chalmers, a British obstetrician, to compile a register of perinatal trials that was published in an electronic format in 1988.¹² Following the success of this register in the field of obstetrics, the first (NHS funded) Cochrane Centre in honor of Archie Cochrane, was established in 1992 in the U.K.. The worldwide Cochrane Collaboration was launched a year later. The Cochrane Library, containing databases with controlled clinical trials and

systematic reviews and meta-analyses on treatments in all major fields of clinical medicine, is now a leading source of evidence for clinicians, guideline developers and health policymakers. The methodology for tracing, selecting, appraising and synthesizing all this evidence was established by David Sackett and the McMaster University research group (Toronto, Canada).

• EBM: revolution or evolution?

The term *evidence-based medicine* (EBM) first appeared in the medical literature in 1992 in a paper by Guyatt *et al.*¹³ Fifteen years after its introduction it is widely known in the field of health care. The concept of EBM, defined by its founding parents as "...*the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients...*"¹⁴, is taught in medical schools all over the world and is a popular topic of postgraduate courses. Practising EBM or evidence-based practice (EBP) involves a process of lifelong learning based on questions raised through encounters with patients. The core idea is that by relying on clinical practices that have proven to be effective and by eliminating ineffective ones quality of patient care can improve.

EBM is rooted in clinical epidemiology and builds on the methodological concepts of this discipline. It is not new, but rather an evolution of existing concepts and research methods, "*an extension of... clinical epidemiology with rich contributions coming from biostatistics...*"^{15,16} The development of information technology in the past two decades paved the way for its rapid advancement and popularity. The introduction of computers supported availability of new and complex biostatistical techniques and greatly improved the possibilities for research and clinical trial methodology. In stead of spending many days (and nights) running statistical tests on the few computers available at universities, nowadays the results are instantly available to researchers at their desk. This has certainly resulted in an increase of the number of (published) RCTs that contribute to the evidence base of clinical medicine.¹⁷

Computer technology, and more specifically the internet, has at the same time had a revolutionary impact on the availability of information. It has empowered many users. A growing number of electronic journals and databases are available on the internet and health professionals no longer need to visit academic libraries or rely solely on the opinion of 'experts' in order to fill the gaps in their knowledge. Open access to clinical guidelines, but also to Medline, the indexing system of the U.S. National Library of Medicine, enables them to 'check the evidence' at home or in the consultation room. Access for professionals in developing countries could have a dramatic impact on the battle against inequity.¹⁸ Likewise, the internet fosters a new level of knowledge among patients, enabling them to have input into making decisions about their own health. This is changing the way patients and doctors interact and it provides opportunities for new partnerships.¹⁹⁻²¹ However, alongside with these promising developments, concerns rise about the quality and validity of the available information.²²

• Limitations of EBM

The widespread attention on EBM has also triggered critical reflection. The notion of 'evidence' must be seen in the context of its biostatistical roots. Evidence of a treatment effect is not 'proof of an effect' in the legal sense, but rather a probabilistic likelihood.²³ We can never be 'sure', but rather must be satisfied with estimates of effect and their accuracy. Only the p-value can help us cope with this uncertainty. There is a risk then that this p-value becomes a dogma, fostering the mistaken idea that a single number can capture both the long-run outcomes of an experiment and the evidential meaning of a single result.²⁴

By nature EBM builds on reductionistic thinking, reducing the nature of complex things like disease and its management to simpler and more fundamental things that can be investigated in controlled trials.⁵ Moreover, the results of clinical trials tend to be interpreted as if they represent some kind of universally valid biomedical law, in the same sense as the results of physiological experiments. However, this is inconsistent with the reality that the effects of interventions are often not the same in different populations. Pathophysiological reasoning that builds on the results of laboratory experiments and knowledge of physiological processes could be expected to fill this gap, but the theoretical concepts it produces

are not always translated into the expected outcome in patients. Both methods are fundamentally different and generate different kinds of knowledge. Neither one can substitute for the other. Therefore, Wiersma argues that the medical practitioner must balance both types of knowledge in a plausible way, creating a “medicine with two faces”.⁵

The limitations of the process of evidence-based practice can be related to three main aspects.

First, the RCT, the cornerstone of EBM, is the most suitable research design to answer questions about treatments, but not everything can be randomized and concerns about issues like safety of treatments or prognosis of disease cannot be studied in RCTs and require other study designs.^{25,26} In their definition of EBM Sackett *et al* acknowledge that (probabilistic) evidence from clinical trials alone cannot be sufficient to support decision making. They point to the need to integrate various kinds of medical and non-medical knowledge, like clinical experience and patient preferences.¹⁴ However, it is not clear what the value of other types of medical knowledge might be and how this integration must take place.²⁷ Over the past years the methodology for performing and synthesizing the results of RCTs has been studied and established, but for non-randomized designs or observational studies there still is a long way to go.

Second, the ability of EBM to answer questions about care for individual patients is limited. Participants of trials are often a selected group of relatively young and healthy patients with clear pathologies. In clinical practice, and especially in primary care, patients present with symptoms rather than diagnoses and have multiple possibly interacting pathologies. What to do with a diabetic COPD patient whose treatment with corticosteroids may benefit his COPD, but will interfere with glycemic control?

Third, disseminating the evidence to health professionals poses problems. In spite of wide spread availability of clinical practice guidelines, evidence syntheses (e.g. the BMJ publication ‘Clinical Evidence’) and research findings through online databases (Pubmed), the gap between evidence and practice is still wide. It is clear that mere availability of evidence does not automatically result in evidence-based practice. Many other factors interfere with this process. At the moment we are still struggling to identify the best ways to transmit evidence and enhance uptake in clinical care.²⁸⁻³²

We should also be aware that the meaning of EBM as a label of high quality evidence may have been eroded. Since everybody can apply his own definition of 'EBM', the label has lost meaning and can even be deceptive.³³ Finally, critics point to the fact that evidence for the effect of EBM on patient outcome is lacking.^{34,35} Most of the studies evaluating guideline implementation strategies report output parameters related to the process of care (proportion of patients screened or antibiotics prescribed, ...).^{31,36} Recently, a multinational cohort analysis showed that improved hospital management of patients with acute coronary syndromes based on evidence from RCTs has resulted in significant reductions in the rates of new heart failure and mortality.³⁷ However, evidence on the effect of current clinical practice guidelines on patient outcomes in primary care is still scarce.³⁸

Objective of the thesis

In this thesis we take a closer look at the implementation of evidence in clinical practice. The goal of evidence-based medicine is to improve clinical performance resulting in better quality of care. However, 'quality of care' is a complex concept and may need more input than what evidence-based medicine currently offers. Perhaps we should look at it with a wider scope. The thesis departs from a comprehensive framework for understanding and designing strategies aimed at improving quality of care. The theoretical concept is adapted from the 'Donabedian triangle', a systems-based framework for studying health care, including structure, process and outcome.³⁹ Various factors related to the structure and process of health care were added, thus creating a comprehensive framework that enables us to understand the complexity of changing physicians' behavior in the quest for improving quality of care through enhanced uptake of findings from clinical research. When approaching this theoretical framework from a research perspective three different types of evidence emerge: medical, contextual and policy evidence. We argue that each of these three evidence types is needed in the quality debate. They are incorporated in an 'evidence framework' that could be useful for identifying gaps in the evidence and contribute to a better understanding of the determinants of patient care. In addition it could be helpful when designing and

evaluating interventions aimed at improving quality of care. In this thesis we focus on the usefulness of the ‘evidence framework’ as an instrument to structure evidence from research in relation to quality improvement. The papers presented in the thesis explore the three types of evidence in primary care. As primary care implies “...*dealing with all health problems regardless of the age, sex, or any other characteristic of the person ...*”⁴⁰ it is important to study the framework in a range of health issues. Therefore, our studies use different research designs and are performed in several domains relevant to primary care, such as upper respiratory tract infections and rational prescribing.

• Medical evidence

It goes without saying that reliable *medical evidence* is an indispensable support for clinical care. But evidence can either be ‘weak’ or ‘strong’ and it is important for clinicians to be aware of the strength of the evidence underpinning recommendations for practice. Therefore, in order to differentiate between weak and strong evidence a hierarchy of ‘levels of evidence’ has been created.¹⁴ These levels of evidence are based on the study design and the methodological quality of individual studies.⁴¹ In EBM evidence derived from RCTs is considered as the strongest. And in the same logic, the synthesis of RCTs in systematic reviews and meta-analyses provides the highest level of evidence for the efficacy of health care interventions. Evidence that is based on non-randomised or observational study designs has a lower ranking. Expert opinion represents the lowest level in the evidence hierarchy.^{14,41} Guideline developers use this information and combine it with a judgement about generalizability, applicability, consistency and clinical impact in order to create a link between the supporting evidence and a recommendation for practice. The strength of the recommendation is graded taking these aspects into account.⁴¹⁻⁴³ Therefore, it is extremely important to evaluate the validity and reliability of the evidence underpinning practice recommendations. The *Cochrane Library* is historically and presently a leading source of synthesized medical evidence. We chose to take a closer look at systematic reviews in the *Cochrane Database of Systematic Reviews*. Various methodological issues can bias the results of reviews. An important aspect is

publication bias. Only including (published) trials that may be more likely to show results in favor of a new treatment and not including unpublished trials, could bias the pooled estimates of the meta-analysis.^{44,45} Cochrane reviewers are therefore encouraged to also search for unpublished material. We wanted to know if these extensive searches for trials that had not (yet) been available as a paper published in a biomedical journal jeopardize the quality of the review.

• Transmission of medical evidence

The EBM movement has made more evidence of higher quality available in user friendly formats, like clinical practice guidelines. Clear evidence-based guidance should be sufficient to convince physicians to adapt their performance accordingly. Then, why is it that we do not succeed in integrating this knowledge in the care for patients? An impressive number of studies conclude that implementing guidelines is difficult. The reasons for not following guidelines are multiple and differ among guidelines, health care settings and doctors, ranging from unfamiliarity with the contents to disagreement and difficulties with changing prior behaviors.^{28,46-48} Could this be overcome by better implementation strategies? It is clear that merely distributing guidelines does not affect prescribing.^{32,49,50} In many European countries peer review groups or quality circles have become an important instrument for the improvement of quality of care.^{51,52} These small groups of physicians are based on voluntary participation and are dedicated to continuously assessing and improving their own patient care without interference of 'experts' or so-called 'opinion leaders' to guide the process. Mutual respect, commitment and continuity are thought to provide the strong base required for change.⁵² Considering these characteristics they can play an important role in the implementation of guidelines. Several authors have made use of quality circles in designing guideline implementation studies, but mostly multiple sessions and presence of an 'expert' were involved. The evidence for the effectiveness of 'pure' (i.e. without external interference) peer group interventions as a tool to promote evidence-based practice is scarce.³¹ In this thesis we contribute to the evidence base on small peer group oriented implementation strategies. Like for the effect of treatments, the effect of interventions aimed at disseminating evidence or changing practice should be assessed by evidence-based methods. Therefore, we used the

design of a randomised controlled trial to assess the impact of discussing a new national guideline on the rational use of antibiotics in acute rhinosinusitis⁵³ in local quality circles of primary care physicians. In our pragmatic trial we contacted the group moderator and provided written materials for use during the group sessions, but did not attend the meeting. The trial thus evaluates the actual potential of this instrument to improve the quality of physicians' performance in day to day practice.

• Contextual evidence

Even if the 'evidence' is transmitted and understood, other factors may interfere in the decision making process and hamper implementation in patient care. These factors can be related to the patient, the doctor and the health care setting. In an observational study we focussed on one of these aspects of context, the doctor-patient encounter, where clinical decisions are shaped and made. Internationally the impact of doctor-patient interactions on prescribing has been studied for respiratory tract infections in primary care. Several authors have pointed to the 'misunderstandings' between physicians and their patients that result in inappropriate prescribing of antibiotics for acute respiratory tract infections.⁵⁴⁻⁵⁸ A better understanding of what patients expect and how they communicate this during the consultation could provide valuable clues to assist doctors in managing acute respiratory infections according to the guidelines, i.e. in general without an antibiotic prescription. In Belgium high antibiotic prescribing rates and growing antimicrobial resistance have put antibiotic prescribing high on the agenda.⁵⁹ The Belgian Antibiotic Policy Coordinating Committee (BAPCOC) has published several guidelines on the management of acute infections in ambulatory care.⁶⁰ Research on facilitating and impeding factors could contribute to effective implementation of these guidelines. Following the publication of a guideline on rational use of antibiotics for acute sore throat in 2001⁶¹, we explored contextual factors that could influence guideline uptake in treating patients who consult their primary care physicians for an acute sore throat.

· Policy evidence

Each encounter with patients is set in a health policy environment, which involves efficiency and equity. Efficiency deals with costs related to effect, the most efficient intervention provides a maximum of benefit for a minimum of costs. Equity refers to fair distribution of the available resources in an accessible health care system.

In addition to implementation strategies aimed at physicians, such as the interventions in local quality circles, health policy regulations could play a role in shaping evidence-based practice. Scarce resources force governments and health insurers to look for strategies to control rising health care costs. Drug expenses are an important concern and initiate various types of policy regulations. In general, these regulations are inspired by cost-containment agenda's. They are usually not directly linked to scientific evidence from clinical practice guidelines. However, they are potentially powerful instruments to change prescribing habits. We looked at the impact of reimbursement policies on physicians' prescribing for acid suppressant drugs in Belgium over a period of nine years and how this relates to the available and disseminated medical evidence.

Outline of the thesis

Chapter 2 presents a conceptual framework for the analysis of quality of care that draws attention to the need for evidence in three domains: medical, contextual and policy evidence. These three types of evidence are captured in an ‘evidence framework’ that could be used as an instrument to structure research and to evaluate and design strategies aimed at improving quality of care. The subsequent chapters of the thesis explore by means of research in different domains how this evidence framework can be useful.

In **chapter 3** we focus on the nature of the available *medical evidence*. We take a closer look at systematic reviews and meta-analyses published in the Cochrane Library, a leading source of synthesized evidence. We demonstrate the pitfalls related to inclusion of unpublished data in systematic reviews.

How to transmit medical evidence to physicians is dealt with in **chapter 4**. In a pragmatic cluster randomized clinical trial a strategy to promote uptake of a new guideline on acute rhinosinusitis is evaluated. The strategy makes use of local quality circles of primary care physicians that are a core feature of the continuing medical education systems in Belgium and many other European countries.

Contextual evidence is explored in **chapter 5**. We report the results of an observational study in primary care that focuses on physician-patient communication during consultations for acute sore throat. It explores the patient’s perspective of his needs and how they are translated into hope for antibiotic treatment.

How health care *policy* affects prescribing behavior of physicians is illustrated in **chapter 6**. We analysed national prescribing data for acid suppressant drugs in relation to specific reimbursement policies and publication of an evidence report.

In **chapter 7** we discuss our findings, summarize the implications for implementation of evidence in clinical practice and formulate questions for further research.

References

1. Book of Daniel 1.15-16.
2. http://www.bbc.co.uk/history/historic_figures/lind_james.shtml
3. Best M, Neuhauser D. Pierre Charles Alexandre Louis: Master of the spirit of mathematical clinical science. *Qual Saf Health Care* 2005;14:462-4.
4. Morabia A. PCA Louis and the birth of clinical epidemiology. *J Clin Epidemiol* 1996;49:1327-33.
5. Wiersma T. Twee eeuwen zoeken naar medische bewijsvoering. Amsterdam: Boom/Belvédère, 1999.
6. http://www.statbel.fgov.be/info/quetelet_n.asp
7. Medical Research Council. Streptomycin treatment of pulmonary tuberculosis. *BMJ* 1948;2:769-82.
8. www.bartleby.com/67/854.html
9. Cochrane AL. Effectiveness and Efficiency. Random reflections on Health Services. London: Royal Society of Medicine, 1971.
10. www.cochrane.org/docs/archieco.htm
11. Dickersin K, Manheimer E. The Cochrane Collaboration: evaluation of health care and services using systematic reviews of the results of randomized controlled trials. *Clin Obstet Gynecol* 1998;41:315-31.
12. Chalmers I. The Oxford Database of Perinatal Trials. Oxford: Oxford University Press, 1988.
13. Evidence-Based Medicine Working Group. Evidence-based medicine. A new approach to teaching the practice of medicine. *JAMA* 1992;268:2420-5.
14. Sackett DL, Straus SE, Richardson WS, Rosenberg W, Haynes RB. Evidence-based medicine. How to practice and teach EBM. 2nd ed. Edinburgh: Churchill Livingstone, 2000.
15. Jenicek M. Evidence-based medicine: fifteen years later. Golem, the good, the bad, and the ugly in need of a review? *Med Sci Monit* 2006;12:RA241-51.
16. Jenicek M. The hard art of soft science: evidence-based medicine, reasoned medicine or both? *J Eval Clin Pract* 2006;12:410-9.
17. Druss BG, Marcus SC. Growth and decentralization of the medical literature: implications for evidence-based medicine. *J Med Libr Assoc* 2005;93:499-501.
18. Tan-Torres Edejer T. Disseminating health information in developing countries: the role of the internet. *BMJ* 2000;321:797-800.
19. Jadad AR. Promoting partnerships: challenges for the internet age. *BMJ* 1999;319:761-4.
20. Budtz S, Witt K. Consulting the internet before visit to general practice. Patients' use of the internet and other sources of health information. *Scand J Prim Health Care* 2002;20:174-6.

21. Murray E, Lo B, Pollack L, Donelan K, Catania J, White M, Zapert K, Turner R. The impact of health information on the internet on the physician-patient relationship. *Arch Intern Med* 2003;163:1727-34.
22. Eysenbach G. Consumer health informatics. *BMJ* 2000;320:1713-6.
23. Upshur REG. The Ethics of Alpha: Reflections on statistics, evidence and values in medicine. *Theor Med Bioeth* 2001;22:565-76.
24. Vandenbroucke JP. Benefits and harms of drug treatments. *BMJ* 2004;329:2-3.
25. Vandenbroucke JP. When are observational studies as credible as randomised trials? *Lancet* 2004;363:1728-31.
26. Goodman SN. Towards evidence-based medical statistics. 1: The p value fallacy. *Ann Intern Med* 1999;130:995-1004.
27. Tonelli MR. Integrating evidence into clinical practice: an alternative to evidence-based approaches. *J Eval Clin Pract* 2006;12:248-56.
28. Bero LA, Grilli R, Grimshaw JM, Harvey E, Oxman AD, Thomson MA. Closing the gap between research and practice: an overview of systematic reviews of interventions to promote implementation of research findings. *BMJ* 1998;317:465-8.
29. Getting research into practice. *Effective Health Care* 1999;5(1).
30. Grol R, Grimshaw J. From best evidence to best practice: effective implementation of change in patients' care. *Lancet* 2003;362:1225-30.
31. Grimshaw JM, Thomas RE, MacLennan G, Fraser C, Ramsay CR, Vale L, Whitty P, Eccles MP, Matowe L, Shirran L, Wensing M, Dijkstra R, Donaldson C. Effectiveness and efficiency of guideline dissemination and implementation strategies. *Health Technol Assess* 2004;8(6). Available at: www.hta.nhsweb.nhs.uk/fullmono/mon806.pdf
32. Arnold SR, Straus SE. Interventions to improve antibiotic prescribing practices in ambulatory care. *The Cochrane Database of Systematic Reviews* 2005, Issue 4. Art. No.: CD003539. DOI: 10.1002/14651858.CD003539.pub2.
33. van Winkelen P, van Denderen JS, Vossen CY, Huizinga TW, Dekker FW. How evidence-based are advertisements in journals regarding the subspecialty of rheumatology? *Rheumatology (Oxford)* 2006;45:1154-7.
34. Miles A, Polychronis A, Grey JE. The evidence-based health care debate – 2006. Where are we now? *J Eval Clin Pract* 2006;12:239-47.
35. De Simone J. Beyond 'faith-based medicine' and EBM. *J Eval Clin Pract* 2006;12:438-44.
36. Arnold SR, Straus SE. Interventions to improve antibiotic prescribing practices in ambulatory care. *Cochrane Database Syst Rev* 2005, Issue 4. Art. No.: CD003539. DOI: 10.1002/14651858.CD003539.pub2.

37. Worrall G, Chaulk P, Freake D. The effects of clinical practice guidelines on patient outcomes in primary care: a systematic review. *Can Med Assoc J* 1997;156:1705-12.
38. Fox KAA, Steg PG, Eagle KA, Goodman SG, Anderson FA, Granger CB, et al; for the GRACE Investigators. Decline in rates of death and heart failure in acute coronary syndromes, 1999-2006. *JAMA* 2007;297:1892-900.
39. Donabedian A. The quality of care. How can it be assessed? *JAMA* 1988;260:1743-8.
40. Allen J, Gay B, Crebolder H, et al. The European definition of general practice / family medicine. Barcelona: WONCA Europe, 2002. Available at: www.euprimarycare.org/smartsite.dws?ch=CLN&id=76
41. Harbour R, Miller J, for the Scottish Intercollegiate Guidelines Network Grading Review Group. A new system for grading recommendations in evidence based guidelines. *BMJ* 2001;323:334-6.
42. Guyatt GH, Sackett DL, Sinclair JC, Hayward R, Cook DJ, Cook RJ; for the Evidence-Based Medicine Working Group. Users' guides to the medical literature. IX. A method for grading health care recommendations. *JAMA* 1995;274:1800-4.
43. GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ* 2004;328:1490-7.
44. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;273:408-12.
45. Kjaergard LL, Villumsen J, Gluud C. Reported methodologic quality and discrepancies between large and small randomised trials in meta-analyses. *Ann Intern Med* 2001;135:982-9.
46. Cabana MD, Rand CS, Powe NR, Wu AW, Wilson MH, Abboud P-AC, Rubin HR. Why don't physicians follow clinical practice guidelines? A framework for improvement. *JAMA* 1999;282:1458-65.
47. Cranney M, Warren E, Barton S, Gardner K, Walley T. Why do GPs not implement evidence-based guidelines? A descriptive study. *Fam Pract* 2001;18:359-63.
48. Grimshaw J, McAuley LM, Bero LA, Grilli R, Oxman AD, Ramsay C, Vale L, Zwarenstein M. Systematic reviews of the effectiveness of quality improvement strategies and programmes. *Qual Saf Health Care* 2003;12:298-303.
49. Oxman AD, Thompson MA, Davis D, Haynes B. No magic bullets: a systematic review of 102 trials of interventions to improve professional practice. *CMAJ* 1995;153:1423-31.

50. Figueras A, Sastre I, Gestal-Otero JJ. Effectiveness of educational interventions on the improvement of drug prescription in primary care: a critical literature review. *J Eval Clin Practice* 2001;7:223-41.
51. Beyer M, Gerlach FM, Flies U, Grol R, Krol Z, Munck A, Olesen F, O'Riordan M, Seuntjens L, Szecsenyiet J. The development of quality circles/peer review groups as a method of quality improvement in Europe. Results of a survey in 26 European countries. *Fam Pract* 2003;20:443-51.
52. Grol R. Quality improvement by peer review in primary care: a practical guide. *Qual Health Care* 1994;3:147-52.
53. De Sutter A, Gordts F, Van Lierde S. Aanbevelingen voor goed gebruik van antibiotica. Acute rhinosinusitis. [in Dutch and French] BAPCOC/WVVH, 2004. Available at: www.health.fgov.be/antibiotics/ndl/rhinosinGL.pdf
54. Butler CC, Rollnick S, Pill R, Maggs-Rapport F, Stott N. Understanding the culture of prescribing: qualitative study of general practitioners' and patients' perceptions of antibiotics for sore throats. *BMJ* 1998;317:637-42.
55. Dosh SA, Hickner JM, Mainous III AG, Ebell MH. Predictors of antibiotic prescribing for nonspecific upper respiratory tract infections, acute bronchitis, and acute sinusitis. *J Fam Pract* 2000;49:407-14.
56. Little P, Dorward M, Warner G, Stephens K, Senior J, Moore M. Importance of patient pressure and perceived medical need for investigations, referral, and prescribing in primary care: nested observational study. *BMJ* 2004;328:444-7.
57. Barry CA, Bradley CP, Britten N, Stevenson FA, Barber N. Patients' unvoiced agendas in general practice consultations: qualitative study. *BMJ* 2000;320:1246-50.
58. Rollnick S, Seale C, Rees M, Butler C, Kinnersley P, Anderson L. Inside the routine general practice consultation: an observational study of consultations for sore throats. *Fam Pract* 2001;18:506-10.
59. Goossens H, Ferech M, Vander Stichele R, Elseviers M, for the ESAC Project Group. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet* 2005;365:579-87.
60. Belgian Antibiotic Policy Coordinating Committee (BAPCOC). Available at: www.health.fgov.be/antibiotics
61. De Meyere M, Matthys J, Cox T. Aanbevelingen voor goed gebruik van antibiotica. Acute keelpijn. [in Dutch and French] BAPCOC/WVVH, 2001. Available at: <http://riziv.fgov.be/care/nl/doctors/promotion-quality/guidelines-antibiotics/gorge-keelpijn/pdf/rbpcomplet.pdf>

Saturnus

Neptunus

The implementation
of
evidence
in
health care

Exploring
the gap
between
knowledge
and
practice

Chapter 2

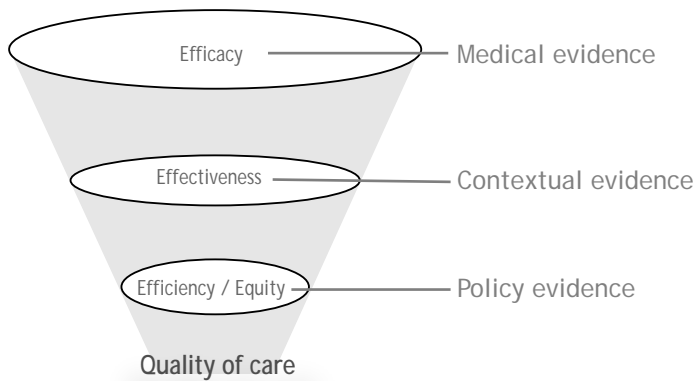
A conceptual framework

Paper 1

De Maeseneer JM, van Driel ML, Green LA, van Weel C. Bridging the gap between evidence and patient care: the need for research in primary care. Lancet 2003;362:1314-9.

Uranus

In this chapter we present a conceptual framework for the analysis of quality of care. It shows the complexity of the determinants of quality and emphasizes that in order to improve quality of health care we need evidence derived from three domains: medical, contextual and policy evidence. These three domains are incorporated in an 'evidence framework' that comprises the core of the thesis. The research papers explore the three types of evidence in the framework.



Saturnus

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Chapter 3

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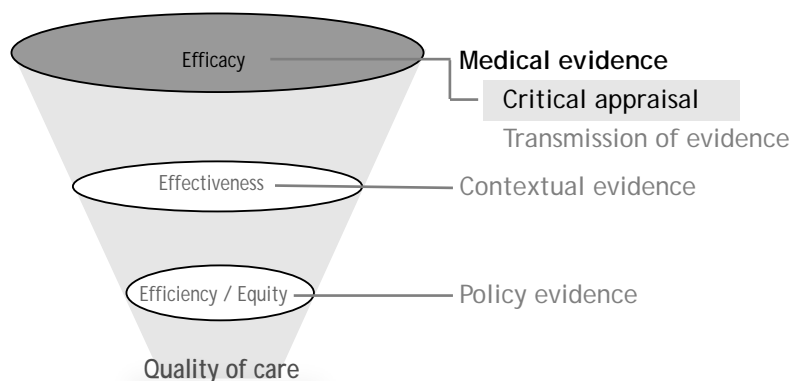
Medical evidence

Paper 2

van Driel ML, De Sutter A, De Maeseneer J, Christiaens T. Searching for unpublished trials in Cochrane reviews: is it worth the effort? A retrospective analysis. (submitted)

Uranus

Medical evidence provides information on the 'efficacy' of interventions; how well they work in the controlled conditions of a clinical trial. It is the cornerstone of evidence-based practice and is indispensable for scientifically sound recommendations for clinical care. Therefore, medical evidence should be carefully appraised and selected. In this chapter we focus on the nature of the available 'medical evidence'. We take a closer look at systematic reviews and meta-analyses published in the Cochrane Library. We demonstrate the pitfalls related to the inclusion of unpublished data in systematic reviews.



Searching for unpublished trials in Cochrane reviews: is it worth the effort? A retrospective analysis.

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What is already known

- Including unpublished trials in systematic reviews and meta-analyses does not necessarily solve the problem of publication bias.
- Inclusion of methodologically weak trials can bias the results of reviews and meta-analyses.

What this study adds

- Only a minority of Cochrane reviews include data from unpublished trials.
- The methodological quality of trials that remain unpublished is unclear or weak.
- Systematically searching for unpublished trials in reviews or meta-analyses may not be worth the effort.

Abstract

Objective: To assess the value of searching for unpublished data by exploring the extent to which Cochrane reviews include unpublished data and by evaluating the methodological quality of unpublished trials.

Design: Retrospective analysis of trials included in Cochrane reviews.

Data sources: We screened all 2462 completed Cochrane reviews published since 2000 in the Cochrane Database of Systematic Reviews Issue 3, 2006 for inclusion of unpublished data.

Review methods: In a random sample of 61 reviews from 292 reviews (11.9%) that included references to unpublished trials we studied all 116 references in detail. Data on source of the unpublished trial, methodological criteria, population size, funding source and incorporation in the review were extracted.

Results: References to unpublished trials make up 8.8% of all included trials in our sample. We found that 36.2% of the trials marked as “unpublished” have in fact been published. Allocation concealment was ‘adequate’ in 45.7% and 61.2% was double blinded or outcome assessor blinded. In 46.8% withdrawal rates were high ($> 20\%$). Trials that were eventually published had larger mean population sizes (p-value 0.026). A sponsor was reported for 60.3%, of which 88.6% was a drug company. Methodological quality and publication bias are mentioned in half of the reviews and explored in a third. Quality ratings did not have consequences for pooling since 82.8% was included in the review’s forest plots.

Conclusions: Only a small proportion of Cochrane reviews include references to “unpublished trials” and many of these are eventually published. The truly unpublished studies are often of poor or unclear methodological quality. Therefore, it may be advisable to invest in assessment of trial quality and regular updating of reviews, rather than in searching for unpublished data.

Introduction

The Cochrane Database of Systematic Reviews (CDSR) is one of the most important sources of reviews and meta-analyses in the field of clinical medicine. The results of Cochrane reviews are consulted by clinicians, guideline developers and health policy makers and contribute to the growing body of “medical evidence”.¹ Reviewers use a standardized methodology as described in the reviewer’s handbook² that makes the review process and the synthesis of evidence transparent and increases the methodological rigor.³ Minimizing bias related to the studies that make up the review and the way these studies are collected is an important issue in Cochrane reviews. The Handbook states that, “*A comprehensive search for relevant RCTs, which seeks to minimize bias, is one of the essential steps in doing a systematic review...*”² Since studies with significant results (in favour of the new treatment) have a higher chance of being published^{4,5}, this includes attempts to locate unpublished studies.² Excluding them can lead to exaggerated estimates of the effectiveness of an intervention in the meta-analysis.^{6,7}

Already in 1993 Cook *et al* discussed the controversies related to including unpublished data in meta-analyses.⁸ They point to the lack of information and/or sufficient methodological quality of these unpublished studies and recommend that both published and unpublished data should be subject to the same rigorous methodological evaluation. Presenting the results with and without inclusion of unpublished data in a sensitivity analysis could improve the quality of meta-analyses.⁹ An HTA Report shares these concerns and mentions that by including (unpublished) trials of low quality bias could even be introduced, rather than prevented.¹⁰

We wanted to know whether the use of unpublished material is a valuable contribution to Cochrane reviews. Therefore we explored the quantity and methodological quality of unpublished data currently used in Cochrane reviews.

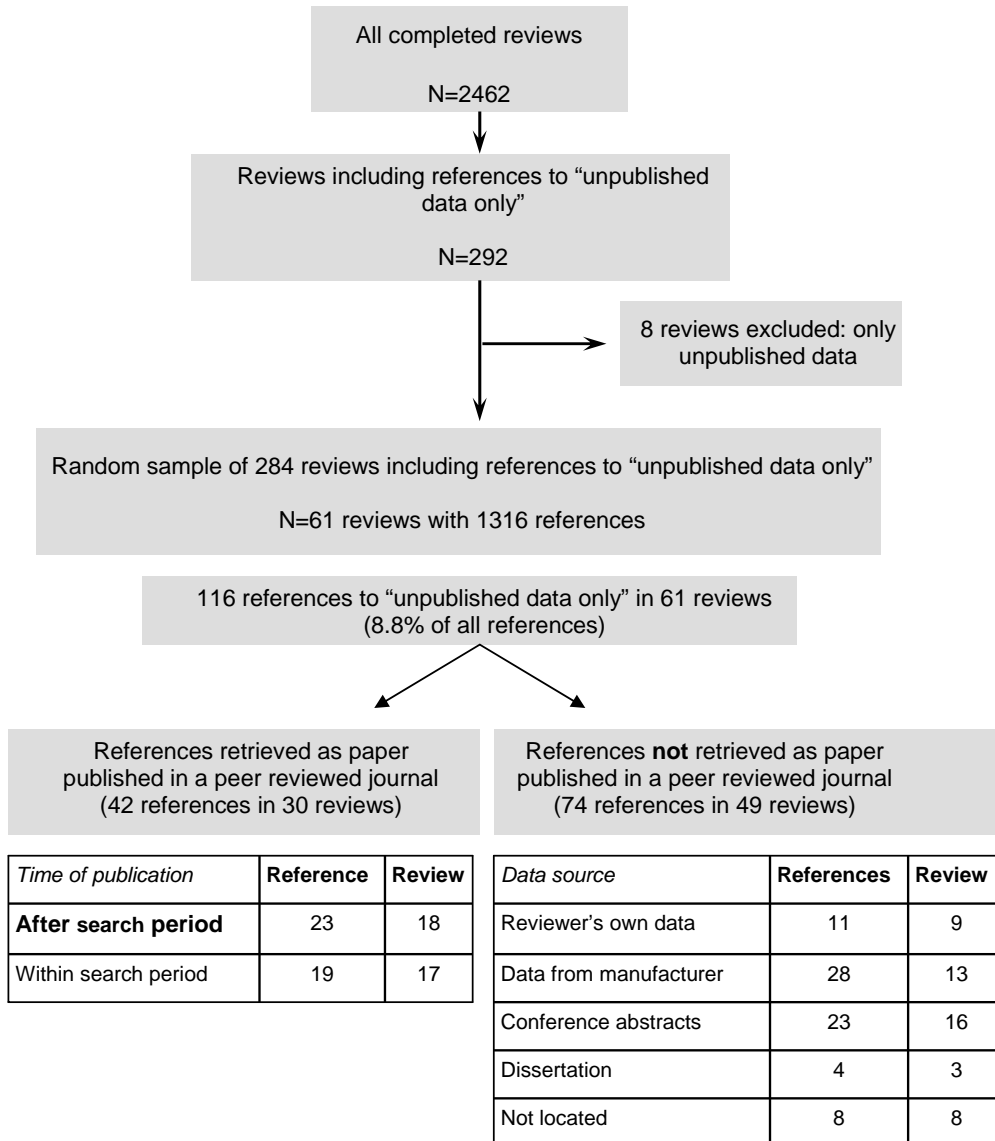
Methods

We retrieved all completed reviews listed in the Cochrane Library issue 3 of 2006 from the Wiley InterScience electronic interface. In all reviews published since the first issue of 2000 we checked the reference lists for included unpublished studies (marked as “unpublished data only”). We focussed on the references to “unpublished

data only”, rather than additional data that are obtained from the authors of published papers and are marked as “published and unpublished data”. By means of computer generated random numbers we took a random sample of the reviews including unpublished data. We estimated that 20% of all reviews would be a sufficient sample size to provide relevant results. The reviews in the random sample were scrutinised for number and type of unpublished material. For each reference to an unpublished study we searched MEDLINE and Google Scholar (November 2006) in an attempt to locate formal publications of the trial in biomedical peer reviewed journals. We classified the trials for which we found a journal publication as published within or after the reported search period. The remainder of truly unpublished trials were categorized as reviewer’s own data, data from manufacturers, conference abstracts (available online or in journal supplements), dissertation or “could not be located”. For all trials labelled as “unpublished data only” we extracted the reported methodological quality for three items that are directly related to the control of bias (allocation concealment, blinding and withdrawals).¹¹ We also extracted population size and funding source from the tables with characteristics of included studies.

We used SPSS 12.0 to generate frequency tables and Pearson Chi-square tests with continuity correction to test for differences between proportions. We used ANOVA and t-test to test for differences between means. P-values < 0.05 are considered statistically significant.

Figure 1: Flowchart of Cochrane reviews selected from all completed reviews published in the Cochrane Library Issue 1, 2000 to Issue 3, 2006.



Results

Reviews including unpublished references

We identified 2689 completed reviews in the Cochrane Library 2006 issue 3, of which 2462 have been published since 2000. References to unpublished data are included in 292 reviews (11.9% of the reviews). (Figure 1) Eight reviews are entirely based on unpublished material and were excluded from this analysis since we were interested in the role of unpublished trials in reviews based on published and unpublished data. The remaining 284 reviews use data from both published and unpublished trials. In a random sample of 62 reviews (21.2% of all reviews including unpublished material) one review from the Cochrane methods group was excluded because it was not accessible to us. The mean number of included studies per review is 12.19 (SD 22.36) for all completed reviews, 20.88 (SD 29.36) for all reviews including references to “unpublished data only” and 21.57 (SD 28.78) in our random sample. The mean number of references to “unpublished data only” was 2.59 (SD 5.84) for all reviews that include this type of data and 1.89 (SD 1.68) in our sample of 61 reviews.

Ninety-six references to unpublished trials (82.8%) provided data that were included in the forest plots of the reviews. Twenty unpublished studies were not presented in a forest plot. The reviews in our sample cover 32 of the 51 Cochrane Review Groups. Three groups are represented by five or more reviews (the Cochrane Airways Group, the Cochrane Dementia and Cognitive Improvement Group, and the Cochrane Stroke Group).

Sources of references to “unpublished data only”

We located publications in peer reviewed journals for 42 of the references marked as “unpublished data only”. Of these publications 19 had been published within the reported search period. Eight trials in the review were listed with a reference to a published paper, two to a paper in press and for another eight trials data were obtained from the author. The 23 papers published after the indicated search period were derived from a draft manuscript obtained before full publication of the study (9 trials), as data from the authors (2 trials), data from manufacturers (5 trials), conference abstracts (4 trials) and data obtained through online accessible registers or reports (3 trials). The majority of the remainder of truly unpublished data were obtained from manufacturers or as conference abstracts. (Table 1) The trial sponsor was reported for 60.3% of the references (70/116); the vast majority of these trials were

sponsored by the pharmaceutical industry (62 of 70 trials). Only 8 studies report funding from non-commercial sources.

Methodological quality

Allocation concealment was rated adequate by the reviewers in less than half of the studies marked as “unpublished” (45.7%). (Table 2) Blinding of outcome assessment was reported for 13.0%. 48.3% of the trials were marked as double blind. Some studies (25 of 116) were also scored with another quality rating system: the Jadad-score¹⁰ in 22 trials (12 trials had a score > 3) and in 3 studies in one review with the CCDAN-QRS¹¹ (a quality rating system of the Cochrane Depression, Anxiety & Neurosis Group).

The withdrawal rate was reported for 62 of 116 trials (53.4%). Nearly half of these trials (46.8%) had withdrawal rates higher than 20% and in 14.5% of the trials more than half of the participants withdrew before the study ended. These high withdrawal rates were mainly reported in trials with psychiatric medication. One study on adherence to hormonal treatments had a withdrawal rate of 83%.

We compared trials for which we could locate a publication to the truly unpublished trials and found that the unpublished trials were older than trials that were (eventually) published (F-statistic 3.626; p-value 0.001). Published trials had larger mean population sizes than trials that remained unpublished (591 vs 236; t-statistic 2.30; 48.7 df; p-value 0.026). Trials with adequate allocation concealment were significantly larger than trials with unclear or inadequate blinding of allocation (mean population 513 vs 240; t-statistic 2.06; 60.1 df; p-value 0.044). Studies sponsored by manufacturers had significantly higher mean withdrawal rates than studies sponsored by non-commercial sources (t-statistic 2.026; 40 df; p-value 0.05).

Table 1: Methodological quality, mean population size and proportion sponsored by manufacturers of references to unpublished data in 61 Cochrane reviews.

Reference type	Methodological quality			Mean population size (SD)	Manufacturer sponsored (%)
	Allocation concealment adequate (%)	Assessor and/or double blinded (%)	Mean % withdrawal (SD)		
Retrieved as published full paper (n=42)	52.4	64.3	24.8 (23.3)	591 (957) median: 317	50.0
Reviewer's data (n=11)	90.9	63.3	58.8 (24.4)	371 (773) median: 55	45.5
Data from manufacturer (n=28)	25.6	78.6	25.0 (20.8)	303 (334) median: 164	100.0
Conference abstract (n=23)	39.1	56.5	24.3 (26.6)	176 (233) median: 71	30.4
Dissertation (n=4)	25.0	25.0	11.6 (8.5)	32 (2) median: 32	25.0
Not located (n=8)	37.5	12.5	9.0 (7.9)	88 (97) median: 45.5	NR

NR: not reported.

Table 2: Methodological quality assessed by reported concealment of allocation, blinding and withdrawal rates of 116 references to “unpublished data only”.

Concealment of allocation	Number of references	% of unpublished references
Adequate	53	45.7
Unclear	50	43.1
Inadequate	2	1.7
Not used	11	9.5
Blinding		
Outcome assessor blinded	15	13.0
“Double blind”	56	48.3
“Single blind”	3	2.6
No blinding	17	14.7
Not reported	25	21.6
Withdrawal rates		
<20%	30	25.9
20-50%	23	19.8
>50%	9	7.8
Not reported	54	46.6

Discussion

Our study shows that searching for unpublished trials in Cochrane reviews does not give a high yield and that the methodological quality of unpublished trials raises concern.

We found that only 11.9% of all recent Cochrane reviews included references to unpublished data. In an earlier literature review of 150 meta-analyses indexed in MEDLINE (1988 to 1999) 30.7% included unpublished data in their analysis.⁸ The attention to publication bias in the past decade and the recommendations to search for unpublished material^{9,13,14} apparently haven't resulted in more frequent inclusion of unpublished data in Cochrane reviews. Recently, Egger *et al* found that funnel plot asymmetry did not disappear when unpublished trials were included, indicating that inclusion of unpublished data does not necessarily solve the problem of publication bias.¹⁰

In our sample the proportion of unpublished trials included in the reviews is small. Only 8.8% of all references referred to "unpublished data only". Considering the finding that eventually a third of these trials can be retrieved as full publications in journals, the actual proportion is even smaller (5.6%). Almost half of these "unpublished" references were available as a publication within the indicated search period. The other references were mostly presented to the reviewers as draft manuscripts, but it is not clear if these manuscripts had already passed the process of journal peer review. We found discrepancies in numbers of participants and events reported in the reviews' forest plots and in the corresponding papers. Recently, Toma *et al* also reported discrepancies between conference abstracts and subsequent full-length publications.¹⁵ Waiting for the published paper may therefore be a more reliable strategy.

Why are so few unpublished trials included in Cochrane reviews? It is unlikely that the trials that have surfaced cover all the available unpublished data. More likely is that there is a large volume of trial data that is too difficult to find. Concerns about this led to the 'Medical Editors Trial Amnesty' in 1997, a call for all unreported trials to register on a website.¹⁶ This initiative had only limited success.¹⁷ The introduction of a prospective clinical trials registry listing all trials before they start recruiting patients is important for increasing accessibility.^{18,19} However, without an obligation to make

the results of these trials publicly available, valuable information will remain largely unknown to the scientific community. A “*declaration of intent to publish all that is undertaken in the name of medical research...*” is a first step to overcome some of these barriers.²⁰ However, until this is endorsed by legislation²¹ the possibility remains that many trials will never be published. Moreover, the unpublished trials identified by the reviewers could be a selection of the available unpublished data. After all, the owners of the data (mostly drug companies) decide if and which data they provide.²²⁻²⁴ These data may be biased. Several authors have pointed to the relationship between drug company funding and study outcome²⁵⁻²⁹ or outcome of meta-analysis^{6,30,31}. In our sample of unpublished trials for which the funding source was reported the vast majority was sponsored by manufacturers. Several reviewers mention that authors or companies have failed to respond to their request for data. Some reviewers explicitly mention that they believe data have been withheld by manufacturers.^{32,33} This “donation bias” is a potentially serious matter. The cases of cyclooxygenase-2 selective inhibitors (rofecoxib and celecoxib) and of selective serotonin reuptake inhibitors in childhood depression show how detrimental withholding trial results from publication can be to public health.³⁴⁻³⁶ It shouldn’t be possible that authors, for-profit organizations or interest groups can grant themselves the right to deny the public the results of research that have implications for public health. Perhaps with the support and some pressure from regulating agencies, such as FDA, EMEA and WHO, research sponsors will show more social accountability.

We also found that the methodological quality of the unpublished trials raises concern. For 64.3% of the trials the allocation concealment was either unclear or even inadequate or not used. Although 48.3% of the trials are reported as double blind, assessor blinding is only mentioned in 13%. Likewise, the high withdrawal rates are a disturbing source of bias. If the Cochrane reviewers are to realize the peer review for unpublished data, the clear lack of sufficient information on methodology in unpublished material seriously hampers the ability to assess its quality. On the other hand, the quality assessment does not seem to have any consequences for the meta-analysis. The vast majority of unpublished references (82.8%) were included in forest plots, regardless of the methodological quality score. Only a few reviews (18%) actually incorporated these results in a sensitivity analysis or qualitative discussion. This is considerably less than the 50% found in a recent survey of 46 Cochrane reviews.³⁷ This finding is a cause for concern about the validity of the results of

reviews. There is sufficient evidence that inadequate allocation concealment can lead to overestimation of the treatment effect or more positive outcomes.^{25,30,38} Likewise, insufficient blinding can bias the results of a meta-analysis.^{25,39} Therefore, including methodologically weak studies in meta-analyses may bias the results.

In the publishing process journals editors play an important role in filtering the methodologically sound trials from the submitted papers. Also, wider adoption of the CONSORT statement⁴⁰ can help improve reporting of methodology.⁴¹ If we could be sure that all the good quality trials are published, we wouldn't need to be concerned about the unpublished ones. However, the publishing process itself could be responsible for the fact that some study results are not published. Peer review is open to arbitrariness and editors often prefer studies with clear (significant) messages.^{8,42} Several authors have shown that a statistically significant outcome predicts publication and time to publication.⁴³⁻⁴⁶ The editors' initiative to consider only registered trials for publication is important for transparency of the available research. However, it should be accompanied by a fair chance for all good quality trials to be published, regardless of the results.

A limitation of our literature survey is that we explored only a sample of the 292 reviews that use unpublished data. By taking a random sample we tried to minimize the chance of selection bias. The mean numbers of references and references to unpublished data in our sample were similar to the total group of reviews. We did not include the reviews that are entirely based on unpublished data. In this case the authors of the review perform the quality assessment and peer review. It would be interesting to investigate if the reported quality in these reviews differs from that in reviews including only a few unpublished trials.

Conclusion

The question is if we would be missing the mark by not including unpublished data in meta-analyses. Our review shows that less than 10% of Cochrane reviews include unpublished data and that references to unpublished studies make up only a small proportion of all included studies. The fact that a third of these "unpublished" references could be located as journal publications suggests that not including them in the review before formal publication would merely delay the evidence synthesis. The poor methodological transparency and quality of the trials that remain

unpublished is an important concern for the validity of the reviews. Therefore, it may be better to invest in improving (reporting of) methodological quality and regular updating of existing reviews than in extensive searches for unpublished data.

Competing interests

"All authors declare that the answer to the questions on your competing interest form bmj.com/cgi/content/full/317/7154/291/DC1 are all No and therefore have nothing to declare".

Contributors

MLvD, TC, ADS and JDM designed the review. MLvD collected and analysed the data, and wrote the final paper. TC, ADS and JDM supervised the review, commented on the data collection and analysis and were responsible for the quality control. All authors assisted in writing the paper, commented on the drafts and approved of the final version. MLvD is the guarantor.

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References

1. De Maeseneer JM, van Driel ML, Green LA, van Weel C. The need for research in primary care. *Lancet* 2003;362:1314-9.
2. Cochrane handbook for systematic reviews of interventions 4.2.6 (Updated September 2006). Available at: www.cochrane.org/resources/handbook
3. Jadad AR, Cook DJ, Jones A, et al. Methodology and reports of systematic reviews and meta-analyses. A comparison of Cochrane reviews with articles published in paper-based journals. *JAMA* 1998;280:278-80.
4. Dickersin K. How important is publication bias? A synthesis of available data. *AIDS Educ Prev* 1997;9(1 Suppl):15-21.
5. Benjamin DK, Smith PB, Murphy MD, et al. Peer-reviewed publication of clinical trials completed for pediatric exclusivity. *JAMA* 2006;296:1266-73.
6. McAuley L, Pham B, Tugwell P, Moher D. Does inclusion of grey literature influence estimates of intervention effectiveness reported in meta-analyses? *Lancet* 2000;356:1228-31.
7. Abraham NS, Moayyedi P, Daniels B, Veldhuyzen van Zanten SJO. Systematic review: the methodological quality of trials affects estimates of treatment efficacy in functional (non-ulcer) dyspepsia. *Aliment Pharmacol Ther* 2004;19:631-41.

8. Cook DJ, Guyatt GH, Ryan G, et al. Should unpublished data be included in meta-analysis? Current convictions and controversies. *JAMA* 1993;269:2749-53.
9. Cook DJ, Sackett DL, Spitzer WO. Methodologic guidelines for systematic reviews of randomised control trials in health care from the Potsdam consultation on meta-analysis. *J Clin Epidemiol* 1995;48:167-71.
10. Egger M, Jüni P, Bartlett C, Hohenstein F, Sterne J. How important are comprehensive literature searches and the assessment of trial quality in systematic reviews? Empirical study. *Health Technol Assess* 2003;7(1).
11. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomised clinical trials: Is blinding necessary? *Control Clin Trials* 1996;17:1-12.
12. Cochrane Collaboration Depression, Anxiety & Neurosis Review Group. Available at: <http://web1.iop.kcl.ac.uk/loP/ccdan/qrs.htm>
13. Jadad AR, Moher D, Klassen TP. Guides for reading and interpreting systematic reviews. II. How did the authors find the studies and assess their quality? *Arch Pediatr Adolesc Med* 1998;152:812-7.
14. Lefebvre C, Clarke MJ. Identifying randomised trials. In: Egger M, Davey Smith G, Altman DG, editors. *Systematic reviews in health care. Meta-analysis in context*. 2nd ed. London: BMJ Publishing Group, 2001:69-86.
15. Toma M, McAlister FA, Bialy L, Adams D, Vandermeer B, Armstrong PW. Transition from meeting abstract to full-length journal article for randomised controlled trials. *JAMA* 2006;295:1281-7.
16. Horton R. Medical editors trial amnesty. *Lancet* 1997;350:756.
17. Roberts I. An amnesty for unpublished trials. *BMJ* 1998;317:763-4.
18. De Angelis C, Drazen J, Frizelle FA, et al. Clinical trial registration: a statement from the International Committee of Medical Editors. *JAMA* 2004;292:1363-4.
19. De Angelis C, Drazen J, Frizelle FA, et al. Is this clinical trial fully registered? A statement from the International Committee of Medical Editors. *JAMA* 2005;293:2927-9.
20. Peam J. Publication: an ethical imperative. *BMJ* 1995;310:1313-5.
21. Steinbrook R. Registration of clinical trials – voluntary or mandatory? *N Engl J Med* 2004;351:1820-2.
22. Davey Smith G, Egger M. Meta-analysis. Unresolved issues and future developments. *BMJ* 1998;316:221-5.
23. Melander H, Ahlqvist-Rastad, Meijer G, Beermann B. Evidence b(i)ased medicine – selective reporting from studies sponsored by pharmaceutical industry: review of studies in new drug applications. *BMJ* 2003;326:1171-5.
24. Chan AW, Altman DG. Identifying outcome reporting bias in randomised trials on PubMed: review of publications and survey of authors. *BMJ* 2005;330:753, doi:10.1136/bmj.38356.424606.8F.
25. Gluud LL. Bias in clinical intervention research. *Am J Epidemiol* 2006;163:493-501.
26. Lexchin J, Bero LA, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. *BMJ* 2003;326:1167-70.
27. Als-Nielsen B, Chen W, Gluud C, Kjaergard LL. Association of funding and conclusions in randomized drug trials. A reflection of treatment effect or adverse events? *JAMA* 2003;290:921-8.
28. Ridker PM, Torres J. Reported outcomes in major cardiovascular clinical trials funded by for-profit and not-for-profit organizations: 2000-2005. *JAMA* 2006;295:2270-4.
29. Kelly RE, Cohen LJ, Semple RJ, et al. Relationship between drug company funding and outcomes of clinical psychiatric research. *Psychol Med* 2006;36:1647-56.

30. Moher D, Pham B, Jones A, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? *Lancet* 1998;352:609-13.
31. Jørgensen AW, Hilden J, Gøtzsche PC. Cochrane reviews compared with industry supported meta-analyses and other meta-analyses of the same drugs: systematic review. *BMJ* 2006;333:782, doi:10.1136/bmj.38973.444699.0B.
32. Frampton M, Harvey RJ, Kirchner V. Propentofylline for Dementia. *Cochrane Database of Systematic Reviews* 2003, Issue 2. Art. No.: CD002853. DOI: 10.1002/14651858.CD002853.
33. McShane R, Areosa Sastre A, Minakaran N. Memantine for dementia. *Cochrane Database of Systematic Reviews* 2006, Issue 2. Art. No.: CD003154. DOI: 10.1002/14651858.CD003154.pub5.
34. Jüni P. Are selective COX 2 inhibitors superior to traditional non steroidal anti-inflammatory drugs? *BMJ* 2002;324:1287-8.
35. Dieppe PA, Ebrahim S, Jüni P. Lessons from the withdrawal of rofecoxib. *BMJ* 2004;329:867-8.
36. Whittington CJ, Kendall T, Fonagy P, Cottrell D, Cotgrove A, Boddington E. Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data. *Lancet* 2004;363:1341-5.
37. De Craen AJM, van Vliet HAAM, Helmerhorst FM. An analysis of systematic reviews indicated low incorporation of results from clinical trial quality assessment. *J Clin Epidemiol* 2005;58:311-3.
38. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;273:408-12.
39. Kjaergard LL, Villumsen J, Gluud C. Reported methodologic quality and discrepancies between large and small randomised trials in meta-analyses. *Ann Intern Med* 2001;135:982-9.
40. The CONSORT Statement. Available at: www.consort-statement.org
41. Moher D, Jones A, Lepage L, for the CONSORT Group. Use of the CONSORT Statement and quality of reports of randomized trials. *JAMA* 2001;285:1992-5.
42. Calnan M, Davey Smith G, Sterne JAC. The publication process itself was the major cause of publication bias in genetic epidemiology. *J Clin Epidemiol* 2006;59:1312-8.
43. Stern JM, Simes RJ. Publication bias: evidence of delayed publication in a cohort study of clinical research projects. *BMJ* 1997;315:640-5.
44. Ioannidis JPA. Effect of statistical significance of results on the time to completion and publication of randomized efficacy trials. *JAMA* 1998;279:281-6.
45. Misakian AL, Bero LA. Publication bias and research on passive smoking. *JAMA* 1998;280:250-3.
46. Decullier E, Lh ritier V, Chapuis F. Fate of biomedical research protocols and publication bias in France: retrospective cohort study. *BMJ* 2005;331:19, doi:10.1136/bmj.38488.385995.8F.

← Met opmaak: opsommingstekens en nummering

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The implementation
of
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Exploring
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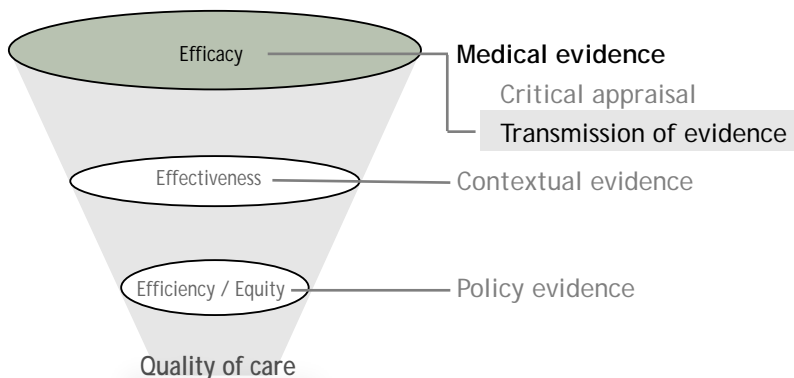
Chapter 4

Transmission of medical evidence

Paper 3

van Driel ML, Coenen S, Dirven K, Lobbestael J, Janssens I, Van Royen P, Haaijer-Ruskamp FM, De Meyere M, De Maeseneer J, Christiaens T. What is the role of quality circles in strategies to optimise antibiotic prescribing? A pragmatic cluster randomised controlled trial in primary care. Qual Saf Health Care 2007;16(3) (in press).

In this chapter we explore a strategy designed for the transmission of medical evidence to physicians. As clinical practice guidelines are the ultimate synthesis of selected and appraised medical evidence, we chose to evaluate the implementation of a new guideline on rational use of antibiotics in acute rhinosinusitis. In a pragmatic cluster randomized clinical trial we evaluated the uptake of the guideline's recommendations by local quality circles of primary care physicians, a core feature of continuing medical education in Belgium and many other European countries.



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The implementation
of
evidence
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Exploring
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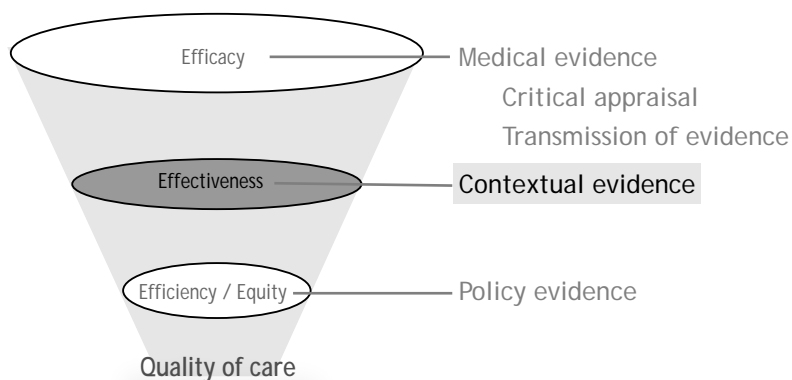
Chapter 5

Contextual evidence

Paper 4

van Driel ML, De Sutter A, Deveugele M, Peersman W, Butler CC, De Meyere M, De Maeseneer J, Christiaens T. Are sore throat patients who hope for antibiotics actually asking for pain relief? *Ann Fam Med* 2006;4:494-9.

Contextual evidence provides information that helps us understand the effectiveness of interventions, i.e. the effect in 'real life patients' in 'real life settings'. An important aspect of context that could influence decision making is doctor-patient communication. In this chapter we report the results of an observational study in primary care that focuses on the communication between physician and patient during consultations for acute sore throat. It explores the patient's perspective of his or her needs and how they are translated into hope for antibiotic treatment. The potential impact of the results of this study on clinical care is illustrated in the editorial by John Hickner that is also included in this thesis. The editorial accompanied the paper when it was published in the Annals of Family Medicine.



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Chapter 6

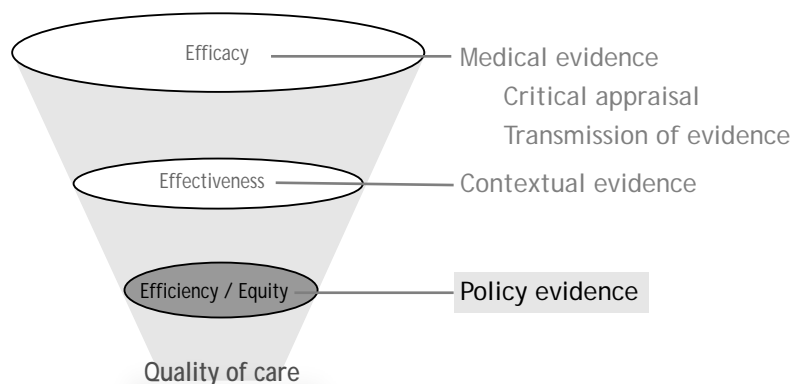
Exploring
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Policy evidence

Paper 5

van Driel ML, Vander Stichele R, De Sutter A, De Maeseneer J, Christiaens T. Medical evidence and health policy: a marriage of convenience? The case of proton pump inhibitors. *J Eval Clin Practice* 2007 (in press).

The third domain of policy evidence provides information on efficiency (i.e. the best treatment for the best price) and on equity (fair distribution of care and resources to all citizens). Interventions that are efficacious (in clinical trials) and effective (in clinical care) also need to be cost-effective and efficient in order to be feasible and sustainable in health care systems that are bound by budgetary restrictions. Health insurers and policymakers issue policies, such as reimbursement regulations, in an attempt to contain growing expenses for medication. In this chapter an analysis of Belgian national prescribing data for acid suppressant drugs illustrates how the prescribed volume responds to specific reimbursement and shows that these policies can also have unintended effects. The fact that publication of an evidence report did not have a distinguishable effect on prescribing volume draws attention to the need to integrate medical and policy evidence when developing clinical guidelines as well as public health policies.



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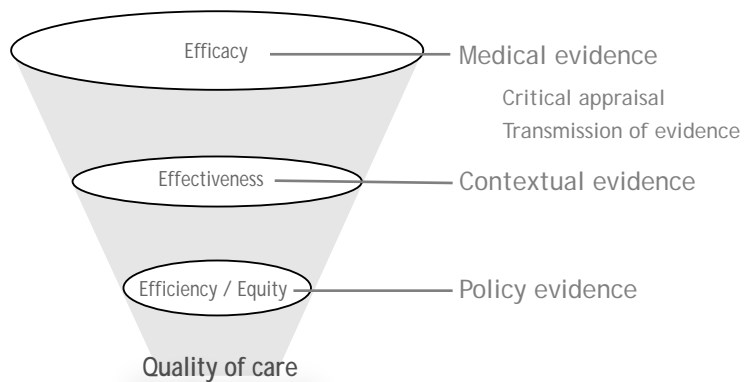
Chapter 7

Exploring
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General discussion and conclusion

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In this chapter we discuss our research findings within the proposed framework of medical, contextual and policy evidence. We summarize some implications for the implementation of evidence in clinical practice and formulate questions for further research.



A conceptual framework for research

David Sackett *et al* define EBM as “...*the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients...*” and emphasize the need to integrate this evidence with clinical expertise and patient preferences.¹ In a nutshell this description of EBM covers the entire process from the acquisition of evidence through clinical trials and synthesis of trial results to uptake by health care professionals, and to shared decision making with patients. It sounds attractive and logical. It would only be a matter of teaching the required skills to health care workers. Nevertheless, we now know and acknowledge that it is not so easy and straightforward. A linear mechanistic approach does not work. Clinical performance and medical decision making are complex processes influenced by many different factors.

In this thesis we take our departure from a conceptual framework that may help us grasp the wide range of determinants and processes that play a role in improving quality of patient care (chapter 2). The picture is incomplete and there are numerous interactions between the different components, but it emphasizes the need to proceed beyond the linear approach to quality of care. It may help us understand why efforts to improve quality still fail to reach their goals. Why do doctors still prescribe antibiotics for self limiting upper respiratory tract infections? The evidence is available, as are the tools (guidelines) to bring the evidence to the providers. However, if the doctor fears losing the patient if he doesn't give ‘value for money’ (characteristics of the health care system), or if he is not convinced that ‘watchful waiting’ is a safe option (belief of the individual professional), or if the patient believes that antibiotics are necessary to get better (external health locus of control), the drops of evidence will not reach the ground.

The conceptual framework also illustrates the rather limited role of evidence-based medicine. EBM is linked to the process of care and makes up the knowledge base of health care providers. Its role is restricted to improving the scientific rigor of guidelines and protocols and it aims to provide answers to problems in clinical practice. However, many questions still remain unanswered. EBM is a necessary condition for success, but not the only one. We argue that within the framework of quality analysis and quality improvement we need three types of evidence: medical, contextual and policy evidence. When making decisions in patient care we need to build on sound knowledge of the disease and its management (medical evidence), but we must also take into account the specific context of the health care setting and the encounter with patients (contextual evidence) and pay attention to efficiency and equity (policy evidence). These three types of evidence are incorporated in an 'evidence framework' that could be useful in the analysis and design of research on quality improvement strategies in primary care. The evidence framework comprises the core of the research presented in this thesis. Medical evidence is explored in chapter 3, contextual evidence in chapter 5 and policy evidence in chapter 6. The RCT in chapter 4 illustrates issues related to the transmission of medical evidence in the context of quality circles in primary care in Belgium.

Medical evidence

The shaping of medical evidence

Medical evidence derived from clinical trials is the core of evidence-based medicine. It provides information on the *efficacy* of treatments or interventions, referring to the effect in selected populations in specific settings and under controlled conditions. Synthesis of trials with the same research question increases the precision of the estimates of a potential effect. Evidence from systematic reviews and meta-analyses is regarded as high level evidence to underpin recommendations for clinical practice. Therefore, critical appraisal of the trials that are included in meta-analyses is an essential part of practising EBM. Our analysis of unpublished data included in

systematic reviews and meta-analyses published in the Cochrane Library raises concerns about the quality of these reviews.

The finding that unpublished trials are of poor or unclear *methodological quality* is a threat to their validity, hence also to the validity of the reviews. Data from unpublished trials are often included in the forest plots and pooled with other studies to calculate an overall estimate of effect. Although reviewers mention the risk of bias in their review, only a few reviews report sensitivity analyses to explore this source of bias. Are we taking our quest for ‘high level evidence’ too far and pooling for the sake of pooling? The impact of trial quality on outcomes of meta-analysis has been documented. Inclusion of low quality studies can alter the interpretation of the benefit of an intervention towards a more positive effect.²

Most of the unpublished trials in the Cochrane reviews were *sponsored* (and performed) by drug manufacturers. This also reflects a development of the past two decades. Performing an RCT has become a sophisticated and expensive undertaking. As a result independent institutions are often unable to fund their own research and turn to resources like pharmaceutical companies.^{3,4} The latter have fully embraced the methodology of the randomised controlled trial, especially since regulatory agencies, like FDA and EMEA, require such evidence in applications for registration or reimbursement of new drugs. The pharmaceutical industry has made the RCT and EBM into successful marketing tools. The label ‘evidence-based’ frequently appears in drug advertisements aimed at physicians and patients. This should be enough to convince them to prescribe or take the drug. The fact that these claims are usually not based on sound evidence⁵ is at most an academic debate.

However, more worrisome is the fact that the pharmaceutical industry now also seems to ‘master’ the available evidence base. Manufacturers can decide if and which data they present for publication or provide to reviewers. Evidence of the existence of this *donation bias* through selective release of evidence is demonstrated by the case of SSRIs, antidepressants for childhood depression, and the promotion of the cyclooxygenase-2-selective non-steroidal anti-inflammatory drugs (NSAIDs) rofecoxib and celecoxib. A meta-analysis of published trials reporting on the effect of SSRIs in depressed children and adolescents suggests a favorable risk-benefit profile. However, when unpublished data obtained from a review by the Committee on Safety of

Medicines are included, the results indicate that the risks (of serious events or suicide attempts) could outweigh the benefits.^{6,7} In the case of the cox-2-selective non-steroidal anti-inflammatory drugs, rofecoxib and celecoxib, data on safety were deliberately not reported in the published papers.⁸⁻¹¹ Meanwhile rofecoxib, better known by its brand name Vioxx®, has been withdrawn from the market, leaving devastating effects on public health. Recent developments, like the introduction of prospective clinical trials registries listing all trials before they start recruiting patients are important for increasing accessibility and transparency.¹²⁻¹⁴ Making individual patient data available to reviewers could improve the clinical relevance of meta-analysis. For instance, a recent meta-analysis of individual patient data on the effect of antibiotics for acute otitis media in children, finally answered a burning question from clinicians.¹⁵ We now know which children have the best chance of benefiting from antibiotics.¹⁶ However, without an obligation and/or legislation to make the results of all trials available to the public, valuable information may still remain unknown.^{14,17-19}

The pharmaceutical industry currently also has a large input in the *research agenda*.²⁰ As main sponsors of clinical research they largely decide what is studied and hence much of the available research is driven by commercial interests rather than the needs of clinicians and patients.²¹ Some ‘diseases’ have even been created or promoted in the media to provide markets for existing products, like ‘female sexual dysfunction’ or ‘restless leg syndrome’.^{22,23} The research agenda is further complicated by the fact that researchers who are linked to institutions that should be sources of independent research, like academic institutions, have alliances with manufacturers. Paradoxically, academics who are pre-eminently suitable for independent research must turn to pharmaceutical companies for support in order to continue their research programs. Awareness of the risks this poses to training and to independent research is urgently needed. In addition, policies to counter it must be developed.^{24,25} It also points to the need to consider investment of public resources in independent RCTs.

Reporting of evidence is crucial in the era of EBM. Publication of research findings in biomedical journals and peer reviewed databases like the Cochrane Library is an essential link in the chain of evidence to the medical professionals. The role of *medical journals* in this debate therefore needs further attention. How journals compete to be the first to publish the results of large and prestigious trials and how this influences the accuracy and trustworthiness of reporting, still remains a ‘black box’. Two observations

reveal that ‘scientific objectivity’ of journals could be at risk. First, careful reading of abstracts of journal articles shows that reported results sometimes lack objectivity and that the authors’ conclusions are not always supported by all the results.^{26,27} A second indicator of the influence of competing interest in the publication process is the revelation of conflicts between editors of leading biomedical journals and commercial funding sources of those journals. Two published conflicts over editorial independence have resulted in the dismissal of the ‘dissident editors’.²⁸⁻³⁰

We can measure the *relevance* of the results of clinical trials to clinical care by the reported outcome. But, how can we translate composite endpoints (such as endpoints composed of both fatal and non-fatal outcomes) to a tangible effect in individual patients?³¹ What to do with surrogate endpoints (e.g. serum cholesterol levels) that are frequently put forward as evidence for success, but often do not predict the true clinical effects of interventions (e.g. on mortality)?³² Patients are interested in the quality of their life, but this is seldom measured in clinical trials. Moreover, in an era of increasing multimorbidity the gap between single-disease oriented trials and the ‘real’ patient populations grows.

Evidence-based medicine emphasizes the RCT as the cornerstone of medical evidence, but in order to answer *other questions* that are important to clinicians, such as the etiology or prognosis of a disease and the risks or harm related to treatments, other study designs are needed.^{33,34} In addition, some questions cannot be studied in experimental designs for ethical or practical reasons.³⁵ For instance, placebo controlled trials in surgery are controversial³⁶ and a proposal for a placebo controlled trial to study a treatment for meningitis will most likely not receive ethical approval. Likewise, we will never be able to prove with RCTs the effect of lifestyle factors such as smoking on lung cancer and mortality. Interventions that require long term guidance and follow-up (nutrition, behavior change) aren’t suitable for experimental designs either.

Another issue is the *magnitude* or impact of the effect. Researchers and readers focus on ‘statistical significance’. We accept a probability of 5% that the results are due to chance ($p < 0.05$), but a p-value of 0.051 is dismissed as non-significant. On the other hand, the relevance of results that pass the statistical test of ‘chance’ can be inflated.³⁷ Like patients, doctors are looking for clear answers, certainties, a yes or no. Yet scientific research provides outcomes expressed as ‘relative risks’ or ‘relative risk reductions’,

resulting in "more uncertain certainty".³⁸ Reported relative risk reductions (RRR) of treatments can be impressive, but also misleading, and interpretation is difficult without an accompanying absolute risk reduction.^{39,40} For instance, the CAPRIE trial shows that patients with recent cardiovascular events who were treated with clopidogrel had a significantly lower risk of a new event (defined as a composite of several events) than those treated with aspirin.⁴¹ The relative risk reduction reported in the abstract is 8.7%, but the absolute risk difference that can be calculated is only 0.51%. In clinical terms this means that 196 patients need to be treated for about two years with clopidogrel in stead of aspirin in order to prevent one (composite) new cardiovascular event. This puts the authors' enthusiastic interpretation into a much less promising perspective. The number needed to treat (NNT) is a useful measure to estimate the impact in clinical practice, but unfortunately it is sometimes misunderstood⁴² and it has methodological drawbacks.^{43,44}

When interpreting trial results to clinical practice *generalizability* of the findings is important. How overzealous implementation can harm patients is illustrated by the events following publication of the RALES trial. The Randomized ALdactone Evaluation Study (RALES) demonstrated that spironolactone improves outcomes in patients with severe heart failure.⁴⁵ These patients often also use ACE inhibitors and combination of both drugs can lead to life-threatening hyperkalemia. An analysis of population-based data showed that after publication of the RALES the rate of spironolactone prescriptions markedly increased in patients who were also treated with ACE inhibitors, including hospitalisation rates and associated mortality.⁴⁶ In a trial patients are carefully selected and closely monitored, but in everyday practice this is usually not feasible. When translating trial results into clinical algorithms this should be taken into account.

New systems of grading recommendations in evidence-based guidelines, such as GRADE, take many of the factors mentioned above into account.⁴⁷⁻⁴⁹ GRADE proposes to make sequential judgements about the quality of the evidence across studies, the critical outcomes, the overall quality of evidence across these outcomes, the balance between benefits and harms and finally the strength of the recommendations.^{49,50} The evidence quality is assessed by judgements of the study design (with the RCT at the top), the study quality (e.g. risk of bias by inadequate concealment of allocation or blinding), the consistency of the results across studies, and the directness (referring to the extent to which people, interventions and outcome measures are similar to those of

interest). RCTs are categorized as providing the highest level of evidence, but flaws in the methodology or important inconsistency can reduce their grade. On the other hand strong associations derived from observational studies (such as the association between smoking and lung cancer) can increase the grade of this (observational) evidence.^{49,50}

Conclusion and directions for future research of medical evidence

The methodology of RCTs and the synthesis of evidence based on RCTs have evolved dramatically over the past two decades. The number of RCTs has increased and their methodological quality has greatly improved. Systematic reviews and meta-analysis have resulted in better and more accurate estimates of the effects of treatments. Clinicians in the 21st century have access to an impressive and useful database of scientific evidence to underpin their clinical performance. However, many questions that arise in clinical care still remain unanswered, often because there is no commercial interest in such research. On the other hand, many clinical questions cannot be studied in RCTs and other research designs are needed. The methodology of non-randomised or observational studies and the synthesis of such studies have not evolved at the same pace as experimental designs and require attention in the near future. Considering the increasing influence of the pharmaceutical industry on both the funding of clinical research and the research agenda, there is an urgent need for more independent funding for research, including RCTs.

Interpretation of the results of clinical trials in day to day practice is hampered by the strong emphasis on statistics and numbers. Medical evidence must be approached with a combination of reflective common sense and critical appraisal skills.⁵¹ It is important to pass on this attitude to students and foster it throughout the curriculum, specifically during the clinical training and in post graduate continuing professional education. This could be essential for successful implementation of medical evidence in clinical patient care. Studies have shown that EBM training integrated in the clinical internship and residency program has the greatest potential to improve knowledge and self-assessed attitudes and behavior.⁵² Translation of these behavior changes into complex outcomes such as better patient care is not a linear process and may take time. Its potential to improve quality of care still needs to be assessed.

Transmission of medical evidence

In a 1998 BMJ paper Bero *et al* reviewed the literature on interventions aimed at ‘closing the gap between research and practice’.⁵³ Nearly a decade later the ‘magic bullet’ to close this gap still hasn’t been found. In the mean time high quality and locally adapted practice guidelines have been developed and made available to health care professionals. Guidelines synthesize the evidence and translate it into practical messages that respond to questions arising in clinical patient care. They are a first and indispensable step in the process of transmitting evidence to clinicians. Many different types of interventions designed to introduce these guidelines to practitioners have been studied more or less extensively in various countries and health care settings. One of the most widespread instruments for knowledge transmission and behavior change is the local quality circle or peer review group. These small groups of peers (e.g. primary care physicians) working in the same local area are established as part of national continuing medical education (and accreditation) systems in many European countries. Nevertheless, their impact as an instrument to promote evidence-based practice has not been studied extensively.^{54,55}

We performed a *pragmatic* randomised controlled trial involving local quality circles of Flemish family physicians (chapter 4) and thus contribute to the evidence on the effect of small peer group interventions as a means to promote guideline uptake. Our trial shows that the current practice of a single group session on a new guideline without external interference does not result in a significant change in prescribing. A rational approach making use of a rational tool, i.e. an evidence-based guideline, is not followed by rational behavior. It also means that by merely financially supporting participation in quality circles, evidence will not automatically be integrated in clinical practice. Our research demonstrates the complexity of implementing medical evidence in clinical care. It also points to the need for research into other factors related to implementation, such as the context of peer review and physician-patient contact and the policy environment related to antibiotic use.

The question remains how transmission of medical evidence can be optimised and how it can lead to the desired change of practice. Other studies with small group interventions suggest that by reinforcing group meetings with external support or multiple guided sessions a relevant improvement of prescribing can be achieved.⁵⁶⁻⁵⁸ Interventions based on academic detailing have shown promising results.^{58,59} In

Belgium this has been proven feasible and acceptable in a pilot project⁶⁰, but the impact on prescribing of implementation on a larger scale has not yet been evaluated. On the other hand, routine, untargeted outreach visiting may not be effective⁶¹, but combining these approaches in multifaceted interventions could yield more effect.^{58,59} Perhaps, additional training of practitioners in communication skills can help overcome some (patient-related) barriers.⁵⁹ However, it is impossible to cover the wide field of primary care with such intensive interventions, so priorities must be set. Moreover, multifaceted programs require additional human and financial resources and cost-effectiveness needs to be studied.

The Belgian National Institute for Sickness and Invalidity Insurance (RIZIV/INAMI) has launched an information campaign in which they provide individual physicians with feedback reports of their prescribing profile.⁶² Physicians are encouraged to discuss these profiles with their peers in local quality circles. An evaluation of the impact of individual prescription feedback and consecutive national public campaigns aimed at both prescribers and the general public showed a declining trend in antibiotic prescribing.⁶³ An effect of peer group discussions on antibiotic use in the local quality circles could not be demonstrated.⁶³ Our trial confirms this finding. In other countries however, integrating prescription feedback in group meetings has shown potential to improve prescribing.^{64,65} Initiatives that support quality circles by providing critically appraised evidence, like *Minerva*, the Belgian independent journal for EBM⁶⁶, could play a facilitating role. However, its impact on quality of care remains to be evaluated.

EBM promotes a non-authoritarian approach to evidence, encouraging health care professionals to search for evidence from objective sources rather than from 'experts'.^{1,67} Yet, in spite of the success of EBM and the availability of 'objective data', these experts or opinion leaders are still important sources of information.⁶⁸ The pharmaceutical industry often makes use of opinion leaders to promote their products. Strategies for implementing research findings that use local opinion leaders have shown to be effective in hospital settings, but the feasibility and impact in primary care is less clear.⁶⁹⁻⁷¹ It may be worthwhile to further explore how these acknowledged 'experts' can contribute to passing on evidence-based information in primary care.

Studying how interventions are received by health care professionals and the reasons why they do or do not change can reveal valuable clues for designing effective

interventions. Factors such as lack of time, support and resources have been mentioned, but also organizational issues related to (internal) communication, computer software, etc. play a role.^{72,73} In this context digital tools like PDAs (personal digital assistants) could be useful in supporting clinical decision making and promoting evidence-based practice. Their use has been studied in various clinical settings, both in medical training⁷⁴, clinical practice and research.⁷⁵ PDA users appreciate the practical applications and the rapid availability of evidence, but studies on the impact of digital decision support on the quality of care and on clinical patient outcomes are still lacking.

In addition, we need to look at the evidence that is being transmitted. Problems with credibility and applicability of recommendations in guidelines have been mentioned by clinicians.^{76,77} Physicians are less compliant with recommendations that are considered controversial or require change of existing practice routines.⁷⁸ Perhaps, a clear indication of the benefits to individual doctors of following the recommendation could enhance uptake. Availability of various different guidelines on the same topic can be confusing and calls for guidance from credible evidence-based institutions.⁷⁹ The finding that most of the variation in prescribing between European countries could be explained by the national setting points to the importance of structural factors to guideline adherence.^{80,81} The North-South axis in antibiotic prescribing and resistance patterns illustrates the link to cultural and historical differences reflected in health care delivery approaches.⁸²

Conclusion and directions for future research in transmission of medical evidence

The search for effective strategies to transmit medical evidence and evidence-based guidelines as a translation of evidence to clinical practice is still open. Our pragmatic trial shows that we should not rely on the existing local quality circles the way they function at present. In spite of the vast amount of literature on implementation strategies, many gaps in our knowledge remain. Implementation of evidence rests on processes that are studied in behavioral science and designing interventions therefore requires a multidisciplinary approach. We need to know more about the process of knowledge adaptation and how it is linked to the limitations of medical evidence, to

the context of health care and to the policy environment. When designing implementation strategies we can build on the instances that have been studied and published. However, local contextual and policy related factors should also be taken into account. Instead of looking for the one magic bullet, tailoring strategies to each specific topic, target group, time frame and context, followed by continuous evaluation could be a more effective approach.

Contextual evidence

Medical evidence derived from clinical research provides information on '*efficacy*', the effect of an intervention in a controlled setting for a carefully selected group of patients. However, in reality patients in primary care are a mix of people with various biopsychological, cultural and socioeconomic backgrounds, who present with complaints rather than a diagnosis and often have more than one condition. They consult doctors with specific competences (e.g. in communication), beliefs and empathy. Moreover, without the careful follow-up of a trial setting, they are much less adherent to the prescribed treatment. All these factors make up the context of clinical care and contribute to the 'efficacy of interventions in real life', i.e. the '*effectiveness*'. Information from contextual evidence helps us understand the gap between 'efficacy' and 'effectiveness'. This is what clinicians really need. It answers their most important question: 'How will it work for my patients in my practice?'

In an observational study we explored contextual evidence in patients consulting their primary care physicians for an acute sore throat (chapter 5). Physicians often mention patient pressure for an antibiotic prescription as a reason why they do not adhere to guideline recommendations. Our study shows that an antibiotic prescription is not necessarily the patient's main concern and that adequate analgesia may be a more important reason for seeking medical care. It suggests that patients who hope for an antibiotic may in fact want a treatment to alleviate pain. Patients may feel that antibiotics are the best treatment for pain in acute sore throat. Communicating with patients about their needs and potential misconceptions, and taking their 'health

beliefs' into account, could help remove this obstacle to evidence-based prescribing of antibiotics.

Communication between physician and patient is a prominent aspect of context that is directly linked to the process in the theoretical framework (figure 1 in chapter 2). Although there is evidence of the impact of doctor-patient communication on the process and the outcome of health care interventions, we are still far from understanding how, when or why it works.⁸³ Several other factors related to attitudes and beliefs about disease and well being complicate the picture. Very little is known about the effect of patients' personality traits on outcome in medical conditions. By reducing 'subjects' (patients) to 'objects' that are studied in trials we could be missing important clues. Our study, like another cross-cultural study⁸⁴, suggests that some patients have an inaccurate idea about the effect of antibiotics. This has been shown to influence prescribing.⁸⁵ What about the doctors? How do they perceive the available evidence? Research on this issue is scarce, but a defensive attitude has been linked to overprescribing of antibiotics.⁸⁶ Some studies on physicians' attitudes towards evidence-based medicine show that primary care physicians are concerned about the credibility and trustworthiness of available evidence.^{76,87,88} The discrepancies between the Belgian national consensus report on rational use of antibiotics for acute respiratory tract infections and the evidence-based guidelines of the scientific associations illustrate how this issue may influence acceptance and transfer of evidence to professionals. The jury of the consensus conference failed to reach an agreement on several issues regarding the management of acute tonsillitis or acute otitis media, in spite of the fact that the guidelines offered an evidence-based choice. When the jury report was published in June 2002 it was accompanied by a commentary from the organizers of the conference.⁸⁹ The organizing committee explained that the differences between the jury report and the guidelines could be attributed to the methodology of the consensus process.⁸⁹ This allows the jury to take the current clinical practice in Belgium into account when formulating their conclusions. Possibly, the jury was reluctant to formulate recommendations that differ from current practice and could create confusion. As a result they published recommendations that were based on 'expert opinion' rather than medical evidence.

More questions arise on the impact of *cultural factors*. Deschepper *et al* have demonstrated how two culturally close communities in Flanders and a neighbouring province of the Netherlands, differ with regard to disease labelling, coping strategies and attitudes towards antibiotics.⁹⁰ On the Dutch side of the border patients with symptoms of a cold say they have “a flu” for which they do not seek medical care. On the other side Flemish patients have “bronchitis” and consult their doctor, who usually prescribes antibiotics. However, physicians nowadays face much larger cultural diversity. In an increasingly multicultural society health care professionals encounter patients from a large variety of cultural backgrounds with disease concepts, health seeking behavior and communicative approaches that are very different from their own and for which they are not properly prepared. They are challenged to apply ethnically sensitive strategies, but the underpinning knowledge is currently lacking. Likewise, the messages of public campaigns, such as the one on rational use of antibiotics⁹¹, may even have adverse effects in certain populations. How to adequately deal with these issues in the education of health care professionals and in the organization of care are intriguing challenges for research and for the design of implementation strategies.

A frequently encountered problem, especially in primary care, is the fact that *real life patients* usually don't fit the available evidence. Participants in trials are a selected and preferably homogeneous group with a clear diagnosis, whereas primary care patients mostly present with symptoms.^{92,93} Moreover, the growing population of elderly patients often has multiple diseases, even without a common biological basis.^{94,95} Studies including elderly patients are still very rare. Questions about the best available treatment for these patients often remain unanswered. Likewise, there is a lack of research on effective treatments for children. The ethical issues concerned are subject of ongoing debate.^{96,97}

Another issue determining the effectiveness of interventions is patients' *adherence* to treatment. A WHO report estimates that adherence to long-term therapy for chronic illnesses in developed countries averages about 50%.⁹⁸ This is known to most physicians who acknowledge that it hampers the effectiveness of secondary (and tertiary) preventive treatments, such as lipid lowering drugs, antihypertensive or antidiabetic drugs. However, they may assume that their patients will do better if they are faced with a life threatening disease, such as cancer. A recent database analysis of women

who were treated with tamoxifen for breast cancer shatters this illusion. It showed that adherence to tamoxifen was lower than previously reported in trials and that non-adherence was as high as 35.2% after 3.5 years follow-up.⁹⁹ A subanalysis of the CHARM study with chronic heart failure patients elegantly illustrates the importance of adherence to health. High adherence, even to placebo, resulted in a 35% lower mortality than low adherence.^{100,101} A meta-analysis of observational studies confirms this finding.¹⁰² Adherence might be a surrogate marker for overall healthy behavior. Because of the importance of non-adherence to the ‘effectiveness’ of medical evidence in clinical practice, it deserves more attention. Non-adherent patients should be considered a high risk group and require more attention and careful follow-up. Instruments to identify these patients need to be developed and studied.

Other definitions of ‘contextual evidence’ can be found in the literature. Sometimes it is linked to data from qualitative research. In World Health Organization reports contextual evidence can refer to additional data, such as community health statistics, that support a case or describe a situation. In this thesis the concept of contextual evidence is not confined to a particular research method (such as qualitative research), nor to specific types of data (such as population statistics). It comprises information derived from various sources and through diverse research methods that can help us understand the gap between the efficacy of interventions and the effectiveness in ‘real life’.

Conclusion and directions for future research of contextual evidence

Medical evidence of ‘efficacy’ derived from clinical trials must be supplemented by evidence on contextual factors. Addition of contextual evidence to medical evidence translates ‘efficacy’ (derived from the ‘artificial’ setting of clinical trials) into ‘effectiveness’ (the impact in daily life with ‘real patients’). Clinicians need information on effectiveness before they can apply research findings to day to day practice. Our research suggests that patients’ beliefs and expectations about antibiotics can play a role in rational prescribing for respiratory tract infections. It is possible that this is also important in other pathologies and domains of medical care. This requires further research. The influence of cultural factors is an increasingly important challenge. We

should learn more about the interactions between diverse culturally defined concepts of illness and health in order to develop educational and organizational interventions that can adequately address the identified needs. Patients' adherence to treatment is an important issue in an 'era of chronic diseases'. In order to improve quality of care in the 21st century the focus on medical evidence must be widened to include evidence on the context of patient care.

Policy evidence

In this thesis we have shown that information on the 'efficacy' of interventions that is based on sound medical evidence is the primary requisite for evidence-based practice. It should be augmented by evidence from the context of day to day practice that contributes to understanding the 'effectiveness' in real life. In a world with unlimited resources this would be sufficient to make implementation of evidence in clinical practice possible. However, all health care systems struggle with methods to control increasing expenditures and to ensure accessibility to all citizens. Therefore, 'efficiency' and 'equity' need to be considered as well. Health policies, including those regulating reimbursement for medication, can be powerful drivers of physicians' prescribing, at least on the short term. These policies are usually inspired by cost-containment concerns and it is not always clear if this complements the principle of rational evidence-based prescribing. Our analysis of national prescribing data for acid suppressant medication in Belgium shows that indeed physicians' prescribing responds to reimbursement policies. These policies however, do not discriminate between rational and irrational use of medication and therefore cannot be considered as sufficient to improve quality of care. On the other hand, the clinical practice recommendations that were published during the observed period did not have any noticeable impact on prescribed volumes.

We have learned several things from this analysis. First, it shows that although the policies may have resulted in relevant savings for the health care budget, the contribution to public health is still questionable. Cost-containment through a policy favoring reimbursement of a cheaper product does not imply an increase of 'efficiency',

which refers to the best treatment for the best price. Still, many people who do not need the treatment or who would be better off with another intervention could be taking the drugs. Hence the resulting consumption remains inefficient. Second, it is not clear if these policies maintained or enhanced 'equity', referring to equal access to effective and efficient health interventions for those who may need or benefit from it. Are those who would benefit from the treatment taking it? Facilitating access to cheaper products does not lead to improved uptake, especially in resource poor groups in the community. The latest policy in our analysis that reintroduced an endoscopic examination as a condition for reimbursement of all proton pump inhibitors implies a visit to a gastroenterologist. And this may be an important barrier to adequate care for the underserved. Willems *et al* have shown that besides financial constraints, various other factors related to the individual as well as the health care system co-determine utilization of health services by the underserved.¹⁰³

The paper in chapter 5 also points to the importance of structural factors related to regulations as a potential barrier to rational prescribing. 40% of patients with a sore throat contact their physician to obtain a note for sick leave from school or work and thus ask him to legitimise their illness. Along with the note often goes a prescription. Countries where sick leave is legitimised by an external controlling organisation and not by the primary care physician, such as the Netherlands, have lower antibiotic prescribing rates.⁸² We argue that all these issues should be taken into account in the design of health policies and health systems.

The conceptual model for decision making in health policy by Dobrow *et al* includes the issues mentioned above and fits in our framework (chapter 2). They approach implementation of evidence from the policymaker's point of view and describe three important questions about interventions that need to be addressed by policymakers: effectiveness, appropriateness and implementation.¹⁰⁴

The first question, "*will it work?*" refers to efficacy and requires input from medical evidence. However, the available evidence is usually based on trials including selected groups of patients and it is not so obvious that evidence showing benefit to groups of individuals will have the same impact on communities.¹⁰⁵ In addition, the effect of interventions between communities may differ. A health education method that is effective in a risk-averse community may have the opposite effect in a risk-tolerant one.

Likewise, it is unclear if expanding the current recommendation for an annual influenza vaccination in high-risk groups to other populations like schoolchildren will result in benefits at the public health level.¹⁰⁶

Although the available evidence base may be the same for policymakers in different countries, this does not result in policies that are the same across nations and regions. Policymakers have other concerns than clinicians and interpret the evidence in a societal context. This leads us to the second question, “*should we do it?*”. It deals with the appropriateness of the intervention in the specific national or local setting. It involves human, financial and technological resource capacity and reflects whether an intervention is feasible or practical in a specific context. Cost-effectiveness is important at this stage. At the same time it refers to the priorities that need to be set in each society. Should we invest in new treatments or technologies or rather in the promotion of preventative care such as smoking cessation or increased physical activity?¹⁰⁷ Given the financial constraints policymakers face, the issues of efficiency and equity need careful consideration at this stage. Maynard argues that, “*If evidence-based medicine and the individual ethic are allowed to determine treatment choices, resources will be used inefficiently and unethically.*”¹⁰⁸ He illustrates how economic analyses can contribute to this debate. Assume there are two treatment options, treatment A leading to five years of good quality of life survival and option B leading to ten years. An obvious and evidence-based choice would favor option B. However, introducing the costs of each of these options may change this preference. Suppose the cost of option A is estimated as 1,500 Euro, while option B costs 7,000 Euro. With a limited budget of 70,000 Euro option A would be the preferred treatment, as it can lead to 133 more years of good quality life. Thus, from a population perspective, a physician prescribing option B uses resources inefficiently, depriving other patients of care from which they could benefit.¹⁰⁸

The equity debate also puts EBM in a wider perspective and draws attention to issues behind the apparently medical question. For instance, is preventing falls in older people an exclusively medical problem that should be addressed by clinical research? By focussing on the effect of medication to increase bone mineral density or on the effect of muscle strengthening exercises in order to improve mobility, we could be overlooking societal roots of the problem. If the streets and sidewalks are not safe to

walk on, mobility will remain a problem. This requires input from other disciplines that are traditionally not consulted by health care professionals.

In order to provide policymakers with ‘tailored’ evidence summaries and cost-effectiveness assessments many countries have established advisory institutions, such as the National Institute of Clinical excellence (NICE) in the U.K., the Health Council of the Netherlands (Gezondheidsraad) and the Belgian Health Care Knowledge Center (Federaal Kenniscentrum). They have become valuable sources of ‘objective’ evidence for policymakers, but are currently facing increased pressure from various stakeholders. A recent example illustrates how this pressure can shape outcome of evidence assessments. The first NICE guidance on the use of cholinesterase inhibitors for Alzheimer’s disease (2005) advised against the use of these drugs. Following the strong criticism by stakeholders, including patients with the disease and doctors working in the field, that the drugs may be effective for certain groups, NICE asked drug companies to provide evidence to this claim. As a result NICE revised its guidance, which greatly pleased patients and manufacturers.¹⁰⁹ Considering this procedure of looking for evidence to fit the guidance and taking into account what we know about the risks of digging for unpublished evidence, we can question how ‘objective’ this revised guidance is. The merit of using consumer groups to support claims and pressure politicians has also been discovered by pharmaceutical companies. Policymakers sometimes face difficult dilemmas. How strong should the evidence be in order to outweigh the impact of groups of determined consumers with petitions on your doorstep?

Finally, the third question points to actual implementation, *“how do we do it here?”*. This should build on evidence of the effectiveness of policies, but also of the harm inflicted by the introduction of specific policies.¹¹⁰ Some interventions may increase health inequalities. For instance, the pay-for-performance program that was introduced in the U.K. in 2004 paid general practitioners according to the proportion of patients for whom they achieve specific targets.¹¹¹ An evaluation of the program revealed that some practices attained high levels of achievement by excluding large numbers of patients, raising questions about equity. Were ‘difficult’ or less compliant patients simply left out? This type of evidence is often lacking and deserves more attention. As Woolf states, society devotes most of its resources to develop and promote new drugs and technologies (predominantly through the pharmaceutical industry) and spends

relatively little on delivering the right care to the right patients at the right time.¹¹² He calls for more research on improving health care systems. He illustrates how small improvements in care delivery can outweigh the benefits of small increases of efficacy of interventions. The greater the gaps in delivery, the more the efficacy of the intervention must be increased to make it more beneficial to public health than improving uptake of the intervention. WHO also recognizes the need for more health systems and health delivery research in its 2004 'Mexico Statement on Health Research', with special emphasis on the needs of developing countries where resources are often insufficient to serve the most basic health needs.¹¹³

The results of our analysis of national prescribing data and the reflections mentioned above make a strong case for more dialogue between policymakers, clinicians and researchers.¹¹⁴ They each have different goals and starting points, but will benefit from mutual understanding and collaboration.^{115,116} Policymakers could be more transparent in their ideologies and decision making process, but researchers need to acquire more understanding of the policy process. For research to have an impact it must target the values of policymakers, but in order to be relevant it must meet the needs identified by clinicians. A dialogue could also result in promoting and sponsoring research into issues that may be of little commercial interest, but are nevertheless relevant to society as a whole. This would also increase the social relevance and accountability of research.

Conclusion and directions for future research of policy evidence

Improving quality of care needs the input of efficiency and equity in addition to efficacy and effectiveness. Policy evidence therefore should be an integral part of the analysis and design of interventions to improve quality through implementation of evidence. Health policies that are inspired only by cost-containment agendas may succeed in saving costs but cannot be considered as efficient or equitable interventions. There is a growing need for policy evaluation research and health systems research that could guide policymakers in designing effective, efficient and equitable policies. A dialogue between policymakers, clinicians and researchers could assist in determining priorities for research and in designing policies that are based on solid clinical evidence, are appropriate to the individual setting and will be implemented by clinicians in

patient care. Consensus should not be the aim of this dialogue. Policy regulations should rather be designed according to an evidence-based methodology with an appropriate sequence. Ideally this starts with researchers formulating policy advice that is based on medical, contextual and policy evidence. Stakeholders must use this evidence to justify their positions. Then, policymakers must value the societal relevance and economic feasibility and define transparent and evidence-based priorities in accordance with general policy objectives. Likewise, guideline developers must also take the health policy environment into account to ensure that clinical practice guidelines are feasible in day to day practice. Finally, clinicians and other actors in the field of patient care, including patients, should take care of implementation at the practice level. Integrating medical and policy evidence could be a more effective and efficient way to achieve implementation of evidence in clinical practice and result in better quality of care and public health.

The conceptual framework presented in chapter 2 shows that improving quality of care requires input from different angles related to both the structure and the process of care. It explains why availability of evidence does not automatically result in evidence-based practice and better patient outcome. Interventions aimed at changing physician behavior therefore, must take several things into account. The ‘evidence framework’ can be useful in the analysis and design of research in this domain. *Medical evidence* from scientific studies provides the base for recommendations to improve quality of patient care, whereas *contextual evidence* adds clues for successful implementation in day to day practice. *Policy evidence* introduces the elements of efficiency and equity. In this thesis we illustrate that the proposed evidence framework can be useful in the analysis of determinants of quality of care. It can help us understand some factors related to the implementation of evidence and can guide further research. It is clear that translating knowledge into change is a complex undertaking. There is no ‘magic bullet’ to bend physician behavior towards evidence-based practice as practice is influenced by many different factors, including health system characteristics. The complexity of all the determinants involved explains why it is unlikely that a ‘quick and easy’ solution will ever be found. Strategies that integrate medical evidence with evidence on the context of clinical practice and the patient and on its policy boundaries could be more successful in promoting implementation in clinical care. Such strategies should be designed in collaboration with guideline developers, clinical researchers, clinicians, the public and policymakers. They will most likely be multifaceted and multi-tiered and will involve education of both patients and physicians and include unequivocal public policy that supports the desired change. Identification of the gaps in our knowledge of the three evidence components and addressing these in research are challenges for the future. Attention to the medical, contextual and policy elements of interventions could be an important step towards more successful implementation of evidence in clinical practice, better quality of patient care and more equity in health.

References

1. Sackett DL, Straus SE, Richardson WS, Rosenberg W, Haynes RB. Evidence-based medicine. How to practice and teach EBM. 2nd ed. Edinburgh: Churchill Livingstone, 2000.
2. Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, Tugwell P, Klassen. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? *Lancet* 1998;352:609-13.
3. Bodenheimer T. Uneasy alliance. Clinical investigators and the pharmaceutical industry. *N Engl J Med* 2000;342:1539-44.
4. Porta M. Five warrants for medical decision making: some considerations and a proposal to better integrate evidence-based medicine into everyday practice. Commentary on Tonelli (2006), Integrating evidence into clinical practice: an alternative to evidence-based approaches. *J Eval Clin Pract* 2006;12:265-68.
5. van Winkelen P, van Denderen JS, Vossen CY, Huizinga TWJ, Dekker FW for the SEDUCE study group. How evidence-based are advertisements in journals regarding the subspecialty of rheumatology? *Rheumatology* 2006;45:1154-7.
6. Whittington CJ, Kendall T, Fonagy P, Cottrell D, Cotgrove A, Boddington E. Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data. *Lancet* 2004;363:1341-5.
7. De Meyere M. Verborgen manipulatie: Minerva niet kritisch genoeg? [Editoriaal]. *Minerva* 2004;3:18-9.
8. Jüni P. Are selective COX 2 inhibitors superior to traditional non steroidal anti-inflammatory drugs? *BMJ* 2002;324:1287-8.
9. Dieppe PA, Ebrahim S, Martin RM, Jüni P. Lessons from the withdrawal of rofecoxib. *BMJ* 2004;329:867-8.
10. Krumholz HM, Ross JS, Presler AH, Egilman DS. What have we learnt from Vioxx? *BMJ* 2007;334:120-3.
11. van Driel M. Bijna helemaal waar. Het verhaal van de coxibs [Editoriaal]. *Minerva* 2003;2:120-1.
12. De Angelis C, Drazen J, Frizelle FA, Haug C, Hoey J, Horton R, et al. Clinical trial registration: a statement from the International Committee of Medical Editors. *JAMA* 2004;292:1363-4.
13. De Angelis C, Drazen J, Frizelle FA, Haug C, Hoey J, Horton R, et al. Is this clinical trial fully registered? A statement from the International Committee of Medical Editors. *JAMA* 2005;293:2927-9.
14. Evans T, Gulmezoglu M, Pang T. Registering clinical trials: an essential role for WHO. *Lancet* 2004;363:1413-4.
15. Rovers MM, Glasziou P, Appelman CL, Burke P, McCormick DPM, Damoiseaux RA, Gadbourey I, Little P, Hoes AW. Antibiotics for acute otitis media: a meta-analysis with individual patient data. *Lancet* 2006;368:1429-35.
16. Matilla PS. Antibiotics in childhood acute otitis media. *Lancet* 2006;368:1397-8.
17. Haug C, Gøtzsche PC, Schroeder TV. Registries and registration of clinical trials. *N Engl J Med* 2005;353:2811-2.
18. Pearn J. Publication: an ethical imperative. *BMJ* 1995;310:1313-5.
19. Steinbrook R. Registration of clinical trials – voluntary or mandatory? *N Engl J Med* 2004;351:1820-2.
20. Delaney B. Commentary: Is society losing control of the medical research agenda? *BMJ* 2006;332:1063-4.
21. Remuzzi G, Schieppati A, Boissel JP, Garattini S, Horton R. Independent clinical research in Europe. *Lancet* 2004;364:1723-6.
22. Moynihan R. The making of a disease: female sexual dysfunction. *BMJ* 2003;326:45-7.

23. Woloshin S, Schwartz LM. Giving legs to restless legs: a case study of how the media helps make people sick. *Plos Med* 3:e170. DOI: 10.1371/journal.pmed.0030170
24. Brennan TA, Rothman DJ, Blank L, Blumenthal D, Chimonas SC, Cohen JJ, Goldman J, Kassirer JP, Kimball H, Naughton J, Smelser N. Health industry practices that create conflicts of interest. *JAMA* 2006;295:429-33.
25. Ioannidis JPA. Open letter to the leaders of academic medicine. *BMJ* 2007;334:191-3.
26. Gøtzsche PC. Believability of relative risks and odds ratios in abstracts: cross sectional study. *BMJ* 2006;333:231-4.
27. van Driel ML, Chevalier P. Lipid lowering drugs in diabetes: Abstract was misleading [letter]. *BMJ* 2006;332:1272.
28. Kassirer JP. Editorial independence. *N Engl J Med* 1999;340:1671-2.
29. DeAngelis CD. Conflict of interest and the public trust. *JAMA* 2000;284:2237-8.
30. Kassirer JP, Davidoff F, O'Hara K, Redelmeier DA. Editorial autonomy of CMAJ. *CMAJ* 2006;174:945-50.
31. Montori VM, Busse JW, Permanyer-Miralda G, Ferreira I, Guyatt GH. How should clinicians interpret results reflecting the effect of an intervention on composite endpoints: Should I dump this lump? *ACP Journal Club* 2005;143(3):A8-A9.
32. Fleming TR, DeMets DL. Surrogate end points in clinical trials: Are we being misled? *Ann Intern Med* 1996;125:605-13.
33. Vandembroucke JP. When are observational studies as credible as randomised trials? *Lancet* 2004;363:1728-31.
34. Mant D. Can randomised trials inform clinical decisions about individual patients? *Lancet* 1999;353:743-6.
35. Rosser WW. Application of evidence from randomised trials to general practice. *Lancet* 1999;353:661-4.
36. Horng S, Miller FG. Is placebo surgery unethical? *N Engl J Med* 2002;347:137-9.
37. Goodman SN. Toward evidence-based medical statistics. 1: The p value fallacy. *Ann Intern Med* 1999;130:995-1004.
38. Richards JP. Evidence based general practice. *BMJ* 1997;314:525.
39. Nuovo J, Melnikow J, Chang D. Reporting number needed to treat and absolute risk reduction in randomised controlled trials. *JAMA* 2002;287:2813-4.
40. van Driel M, Christiaens T, Piessens V, Sunaert P, Feyen L. Misleading conclusions of PROactive study [e-letter]. *Lancet* 2005. Available at: www.thelancet.com/journals/lancet/article/PIIS0140673605675289/comments?action=view&totalComments=6
41. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996;348:1329-39.
42. Halvorsen PA, Kristiansen IS, Aasland OG, Førde OH. Medical doctors' perception of the "number needed to treat" (NNT). *Scand J Prim Health Care* 2003;21:162-6.
43. Cook RJ, Sackett DL. The number needed to treat: a clinically useful measure of treatment effect. *BMJ* 1995;310:452-4.
44. Lubsen J, Hoes A, Grobbee D. Implications of trial results: the potentially misleading notions of number needed to treat and average duration of life gained. *Lancet* 2000;356:1757-9.
45. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J, The Randomized Aldactone Evaluation Study Investigators. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 1999;341:709-17.
46. Juurlink DN, Mamdani MM, Lee DS, Kopp A, Austin PC, Laupacis A, Redelmeier DA. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. *N Engl J Med* 2004;351:543-51.

47. Harbour R, Miller J for the Scottish Intercollegiate Guidelines Network Grading Review Group. A new system for grading recommendations in evidence based guidelines. *BMJ* 2001;323:334-6.
48. WHO. Guidelines for WHO guidelines. Report: EPI/GPE/EQC/2003.1. Geneva: World Health Organization, 2003.
Available at: http://whqlibdoc.who.int/hq/2003/EIP_GPE_EQC_2003_1.pdf
49. GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ* 2004;328:1490-7.
50. GRADE Working Group. Available at: www.gradeworkinggroup.org/
51. Horton R. Common sense and figures: the rhetoric of validity in medicine. Bradford Hill memorial lecture 1999. *Statist Med* 2000;19:3149-64.
52. Coomarasamy A, Khan KS. What is the evidence that postgraduate teaching in evidence based medicine changes anything? A systematic review. *BMJ* 2004;329:1017.
53. Bero LA, Grilli R, Grimshaw JM, Harvey E, Oxman AD, Thomson MA. Closing the gap between research and practice: an overview of systematic reviews of interventions to promote implementation of research findings. *BMJ* 1998;317:465-8.
54. Oxman AD, Thompson MA, Davis D, Haynes B. No magic bullets: a systematic review of 102 trials of interventions to improve professional practice. *CMAJ* 1995;153:1423-31.
55. Grimshaw JM, Thomas RE, MacLennan G, Fraser C, Ramsay CR, Vale L, Whitty P, Eccles MP, Matowe L, Shirran L, Wensing M, Dijkstra R, Donaldson C. Effectiveness and efficiency of guideline dissemination and implementation strategies. *Health Technol Assess* 2004;8(6). Available at: www.hta.nhsweb.nhs.uk/fullmono/mon806.pdf
56. Lundborg CS, Wahlström R, Oke T, Tomson G, Diwan VK. Influencing prescribing for urinary tract infection and asthma in primary care in Sweden: a randomised controlled trial of an interactive educational intervention. *J Clin Epidemiol* 1999;52:801-12.
57. Veninga CCM, Denig P, Zwaagstra R, Haaijer-Ruskamp FM. Improving drug treatment in general practice. *J Clin Epidemiol* 2000;53:762-72.
58. Coenen S, Van Royen P, Michiels B, Denekens J. Optimizing antibiotic prescribing for acute cough in general practice: a cluster-randomized controlled trial. *J Antimicrob Chemother* 2004;54:661-72.
59. Welschen I, Kuyvenhoven MM, Hoes AW, Verheij TJ. Effectiveness of a multiple intervention to reduce antibiotic prescribing for respiratory tract symptoms in primary care: randomised controlled trial. *BMJ* 2004;329:431-3.
60. Habraken H, Janssens I, Soenen K, van Driel M, Lannoy J, Bogaert M. Pilot study on the feasibility and acceptability of academic detailing in general practice. *Eur J Clin Pharmacol* 2003;59:253-60.
61. Hall L, Eccles M, Barton R, Steen N, Campbell M. Is untargeted outreach visiting in primary care effective? A pragmatic randomized controlled trial. *J Public Health Med* 2001;23:109-13.
62. Vander Stichele R. Farmamet: een venster op de kwaliteit van het voorschrijven van ambulante geneesmiddelen in België. *Tijdschr Geneesk* 2003;59:499-508.
63. RIZIV. Ambulant voorschrijfgedrag antibiotica en antihypertensiva. Onderzoeksrapport april 2005. Akkoord artsen-ziekenfondsen 2004-2005. Brussel: RIZIV, 2005. Available at: www.riziv.fgov.be/care/nl/doctors/promotion-quality/antibiotiques-antihypertenseurs/index.htm
64. Lagerløv P, Loeb M, Andrew M, Hjortdahl P. Improving doctors' prescribing behaviour through reflection on guidelines and prescription feedback: a randomised controlled study. *Qual Health Care* 2000;9:159-65.
65. Veninga CCM, Stalsby Lundborg C, Lagerlov P, Hummers-Pradier E, Denig P, Berkhof H, Kochen MM, Haaijer-Ruskamp FM, DEP-Group. Evaluating an educational intervention to

- improve the treatment of asthma in four European countries. *Am J Resp Crit Care Med* 1999;160:1254-62.
66. www.minerva-ebm.be
 67. Evidence-Based Medicine Working Group. Evidence-based medicine. A new approach to teaching the practice of medicine. *JAMA* 1992;268:2420-5.
 68. Tomlin Z, Humphrey C, Rogers S. General practitioners' perceptions of effective health care. *BMJ* 1999;318:1532-5.
 69. Soumerai SB, McLaughlin TJ, Gurwitz JH, Guadagnoli E, Hauptman PJ, Borbas C, et al. Effect of local medical opinion leaders on quality of care for acute myocardial infarction. A randomised trial. *JAMA* 1998;279:1358-63.
 70. Grimshaw JM, Eccles MP, Greener J, MacLennan G, Ibbotson T, Kahan JP, Sullivan F. Is the involvement of opinion leaders in the implementation of research findings a feasible strategy? *Implementation Science* 2006;1:3.
 71. Doumit G, Gattellari M, Grimshaw J, O'Brien MA. Local opinion leaders: effects on professional practice and health care outcomes. *Cochrane Database Syst Rev* 2007, Issue 1. Art. No.: CD000125. DOI: 10.1002/14651858. CD000125.pub3.
 72. Flottorp S, Håvelsrud K, Oxman AD. Process evaluation of a cluster randomised trial of tailored interventions to implement guidelines in primary care – why is it so hard to change practice. *Fam Pract* 2003;20:333-9.
 73. Janssens I, De Meyere M, Habraken H, Soenen K, van Driel M, Christiaens T, Bogaert M. Barriers to academic detailers: a qualitative study in general practice. *Eur J Gen Pract* 2005;11:59-63.
 74. Kho A, Henderson LE, Dressler DD, Kripalani S. Use of handheld computers in medical education. A systematic review. *J Gen Intern Med* 2006;21:531-7.
 75. Baumgart DC. Personal digital assistants in health care: experienced clinicians in the palm of your hand? *Lancet* 2005;366:1210-22.
 76. Cabana MD, Rand CS, Powe NR, Wu AW, Wilson MH, Abboud P-AC, Rubin HR. Why don't physicians follow clinical practice guidelines? A framework for improvement. *JAMA* 1999;282:1458-65.
 77. Cranney M, Warren E, Barton S, Gardner K, Walley T. Why do GPs not implement evidence-based guidelines? A descriptive study. *Fam Pract* 2001;18:359-63.
 78. Grol R, Dalhuijsen J, Thomas S, in 't Veld C, Rutten G, Mokkink H. Attributes of clinical guidelines that influence use of guidelines in general practice: observational study. *BMJ* 1998;317:858-61.
 79. Rosser WW, Davis D, Gilbert E, on behalf of the Guideline Advisory Committee. Promoting effective guideline use in Ontario. *CMAJ* 2001;165:181-2.
 80. Christiaens T, De Backer D, Burgers J, Baerheim A. Guidelines, evidence, and cultural factors. *Scand J Prim Health Care* 2004;22:141-5.
 81. Veninga CCM, Lundborg CS, Lagerløv P, Hummers-Pradier E, Denig P, Haaijer-Ruskamp FM, and the Drug Education Project Group. Treatment of uncomplicated urinary tract infections: exploring differences in adherence to guidelines between three European countries. *Ann Pharmacother* 2000;34:19-26.
 82. Ferech M, Coenen S, Malhotra-Kumar S, Dvorakova K, Hendrickx E, Seutens C, Goossens H on behalf of the ESAC Project Group. European Surveillance of Antimicrobial Consumption (ESAC): outpatient antibiotic use in Europe. *J Antimicrob Chemother* 2006;58:401-7.
 83. Deveugele M. Doctor-patient communication in general practice. An observational study in six European countries [dissertation]. Ghent: Ghent University, 2003.

84. van Duijn H, Kuyvenhoven M, Tudor Jones R, Butler C, Coenen S, Van Royen P. Patients' views on respiratory tract symptoms and antibiotics. *Br J Gen Pract* 2003;53:491-2.
85. Britten N, Ukoumunne O. The influence of patients' hopes of receiving a prescription on doctors' perceptions and the decision to prescribe: a questionnaire survey. *BMJ* 1997;315:1506-10.
86. De Sutter AI, De Meyere MJ, De Maeseneer JM, Peersman WP. Antibiotic prescribing in acute infections of the nose or sinuses: a matter of personal habit? *Fam Pract* 2001;18:209-13.
87. Tracy CS, Dantas GC, Upshur REG. Evidence-based medicine in primary care: qualitative study of family physicians. *BMC Family Practice* 2003;4:6.
88. Walker AE, Grimshaw JM, Armstrong EM. Salient beliefs and intentions to prescribe antibiotics for patients with a sore throat. *Br J Health Psychol* 2001;6(Part 4):347-60.
89. RIZIV/INAMI. Available at: <http://riziv.fgov.be/drug/nl/statistics-scientific-information/consensus/2000-10-17/index.htm>
90. Deschepper R, Vander Stichele RH, Haaijer-Ruskamp FM. Cross-cultural differences in lay attitudes and utilisation of antibiotics in a Belgian and a Dutch city. *Patient Educ Couns* 2002;48:161-9.
91. Goossens H, Guillemot D, Ferech M, Schlemmer B, Costers M, van Breda M, Baker LJ, Cars O, Davey PG. National campaigns to improve antibiotic use. *Eur J Clin Pharmacol* 2006;62:373-9.
92. Christiaens T. Acute dysuria in non-pregnant, adult women: diagnostic and therapeutic aspects in primary care [dissertation]. Ghent: Ghent University, 2003.
93. De Sutter A. Acute infections of nose and sinuses in general practice. A diagnostic and therapeutic approach [dissertation]. Ghent: Ghent University, 2005.
94. van Weel C. Chronic diseases in general practice: the longitudinal dimension. *Eur J Gen Pract* 1996;2:17-21.
95. Van den Akker M, Buntinx F, Metsemakers JFM, Roos S and Knottnerus JA. Multimorbidity in general practice: prevalence, incidence and determinants of co-occurring chronic and recurrent diseases. *J Clin Epidemiol* 1998;51:367-75.
96. Ross LF. Do healthy children deserve greater protection in medical research? *J Pediatr* 2003;142:108-12.
97. www.fda.gov/fdac/features/2003/103_drugs.html
98. World Health Organization. Adherence to long-term therapies. Evidence for action. Geneva: WHO, 2003.
99. Barron TI, Connolly R, Bennett K, Feely J, Kennedy M. Early discontinuation of tamoxifen. *Cancer* 2007. DOI: 10.1002/cncr.22485
100. Granger BB, Swedberg K, Ekman I, Granger CB, Olofsson B, McMurray JJ, Yusuf S, Michelson EL, Pfeffer MA, for the CHARM investigators. Adherence to candesartan and placebo and outcomes in chronic heart failure in the CHARM programme: double blind, randomised, controlled clinical trial. *Lancet* 2005;366:2005-11.
101. White HD. Adherence and outcomes; it's more than taking the pills. *Lancet* 2005;366:1989-91.
102. Simpson SH, Eurich DT, Majumdar SR, Padwal RS, Tsuyuki RT, Varney J, Johnson JA. A meta-analysis of the association between adherence to drug therapy and mortality. *BMJ* 2006;333:15-9.
103. Willems S, De Roo L, De Maeseneer J. Towards a comprehensive model for understanding the complexity of medical care utilisation patterns by the poor and underserved. In: Willems S. The socio-economic gradient in health: a never-ending story? [dissertation]. Ghent: Ghent University, 2005.

104. Dobrow MJ, Goel V, Lemieux-Charles L, Black NA. The impact of context on evidence utilization: a framework for expert groups developing health policy recommendations. *Soc Sci Med* 2006;63:1811-24.
105. Kemm J. The limitations of 'evidence-based' public health. *J Eval Clin Pract* 2006;12:319-24.
106. Halloran ME, Longini Jr. IM. Community studies for vaccinating schoolchildren against influenza. *Science* 2006;311:615-6.
107. Woolf SH. The need for perspective in evidence-based medicine. *JAMA* 1999;282:2358-65.
108. Maynard A. Evidence-based medicine: an incomplete method for informing treatment choices. *Lancet* 1997;349:126-8.
109. Mayor S. NICE recommends drugs for moderate Alzheimer's disease [News]. *BMJ* 2006;332:195.
110. Macintyre S, Chalmers I, Horton R, Smith R. Using evidence to inform health policy: case study. *BMJ* 2001;322:222-5.
111. Doran T, Fullwood C, Gravelle H, Reeves D, Kontopantelis E, Hiroeh U, Roland M. Pay-for-performance programs in family practices in the United Kingdom. *N Engl J Med* 2006;355:375-84.
112. Woolf SH, Johnson RE. The break-even point: When medical advances are less important than improving the fidelity with which they are delivered. *Ann Fam Med* 2005;3:545-52.
113. The Lancet. Mexico, 2004: Research for global health and security. *Lancet* 2003;362:2033.
114. Black N. Evidence based policy: proceed with care. *BMJ* 2001;323:275-9.
115. Davey Smith G, Ebrahim S, Frankel S. How policy informs the evidence. *BMJ* 2001;322:184-5.
116. Bero LA, Jadad AR. How consumers and policymakers can use systematic reviews for decision making. *Ann Intern Med* 1997;127:37-42.

Saturnus

Neptunus

The implementation
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evidence
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Exploring
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Epilogue

Uranus

In this thesis we focussed on various aspects linked to the implementation of evidence in day to day clinical patient care. The conceptual framework helps us understand the process of quality of care in relation to different types of evidence. We illustrated some of the determinants in the framework with examples from original research carried out in Flanders, Belgium. However, when reflecting upon these issues, we feel a need to add a global perspective.

We have described the empowering effect of availability of (medical) evidence. However, will it also empower health professionals and patients in countries with fewer resources? Computers and the internet, as a direct access to all this information, are not generally available in deprived or developing regions, where often even a reliable power supply is lacking. On the other hand, even if accessibility isn't a problem, availability of relevant evidence may well be. The "10:90 gap" still exists, whereby only 10% of worldwide health research funds are allocated to the problems responsible for 90% of the world's burden of disease, mainly in poor countries.¹ An exception to this rule may well be HIV/AIDS, but only because it is also a problem of rich countries. Had HIV/AIDS not been introduced into the gay community of the Western world in the 1970s, the drive for AIDS-research would not have been so strong and the epidemic in Africa would have had an even more devastating effect. The lack of drug research on 'non-profitable' infectious diseases that prevail in the South is tangibly illustrated by their population health statistics. Funding for research into diseases that are common in developing countries, like tuberculosis, malaria and other tropical infectious diseases, is urgently needed.² However, both the South and the North could also benefit from studies of 'cheap' or 'old' treatments. The evidence that is being generated nowadays mainly covers new expensive medication and technologies. This could create the false impression that good health care equals expensive health care and thus increase the gap between the 'haves' and the 'have-nots'.

The context of implementing evidence across cultures is already at our doorstep. Opening up to other cultural concepts of health and healthy behavior might also enrich our understanding of what makes efficacious interventions into effective ones. The issue of equity is an important challenge for the 21st century. Delivering effective care to those who need it when they need it enhances efficiency, but also addresses equity. Our responsibility for equity goes beyond our own region, and extends across borders into resource poor regions in the South.

In this thesis we voice a plea for independent research into matters that affect patients all over the world. This includes studying diseases and treatments that lack a commercial interest. Research on health systems and health care delivery strategies focussed on the needs of the community and not on the financial profits of stakeholders is urgently needed. We hope this thesis can contribute to the debate.

References

1. McCoy D, Sanders D, Baum F, Narayan T, Legge D. Pushing the international health research agenda towards equity and effectiveness. *Lancet* 2004;364:1630-1.
2. Trouiller P, Olliaro P, Torreele E, Orbinski J, Laing R, Ford N. Drug development for neglected diseases: a deficient market and a public-health policy failure. *Lancet* 2002;359:2188-94.

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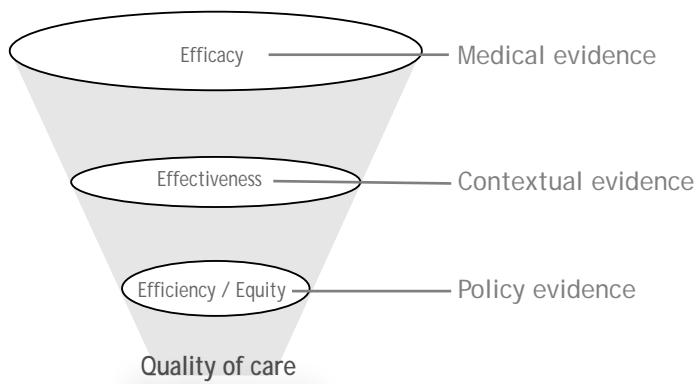
Neptunus

The implementation
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Summary

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A conceptual framework for research

Making evidence from scientific studies available to clinical practice was expected to directly improve the quality of patient care. However, this expectation has not been met. The concept of quality of care is complex and requires a wider view. In this thesis we present a conceptual framework that can help us grasp the wide range of determinants and processes that play a role in improving quality of care (*chapter 2*). When approaching quality improvement from a research perspective three different types of evidence emerge: medical, contextual and policy evidence. Making decisions in patient care requires sound knowledge of the disease and its management (medical evidence), but we must also take into account the specific context of the health care setting and the encounter with patients (contextual evidence) and pay attention to efficiency and equity (policy evidence). These three types of evidence are incorporated in an ‘evidence framework’ that can be used in the design and analysis of research on quality improvement strategies in primary care. The four research papers in this thesis explore the usefulness of the ‘evidence framework’ as an instrument to investigate and understand the evidence we need in the domain of quality improvement in primary care.

Medical evidence

Medical evidence derived from clinical trials provides information on the *efficacy* of treatments or interventions, referring to the effect in selected populations, in specific settings and under controlled conditions. Medical evidence is the cornerstone of evidence-based medicine (EBM) and should therefore be reliable and of high quality. Evidence from systematic reviews and meta-analyses that synthesize the results of individual trials is mostly regarded as high level evidence to underpin recommendations for clinical practice. However, the quality and validity of a meta-analysis depends on the quality of the individual trials it includes. Therefore, critical appraisal of this medical evidence is an essential part of practising EBM. Poor trial quality and selective availability of data are important

A prerequisite for good quality of care is availability of medical evidence.

issues that have been shown to jeopardize the validity of reviews. In *chapter 3* we take a closer look at Cochrane reviews, a major source of synthesized medical evidence. We studied a random sample of all Cochrane reviews that included references to “unpublished data only”. As these data have not been reviewed by journal editors and reviewers, they could be an important source of bias and influence the results of reviews. Our study shows that searching for unpublished data in Cochrane reviews does not give a high yield. Moreover, 38% of the ‘unpublished’ references were (eventually) published as a peer-reviewed paper either within the reported search period or shortly after. Also, the methodological quality of the unpublished trials, in particular data from manufacturers or conference abstracts, was generally poor or not reported. Therefore, extensive searching for unpublished trials may not be worth the effort. Rather, reviewers could be advised to invest in regular updating of their reviews.

Transmission of medical evidence is a next step in evidence-based practice. Many different interventions aimed at ‘closing the gap between evidence and practice’ have been designed and tested, but a ‘magic bullet’ has not been found. In many European countries, including Belgium, small peer groups or local quality groups have been established as an instrument for quality improvement in health care. They are a core feature in national systems for accreditation and continuing medical education. Nevertheless, research into their impact on quality of patient care is scarce. In a pragmatic cluster randomized controlled trial we evaluated the effect on antibiotic prescribing of a self-led discussion of a guideline on acute rhinosinusitis in local quality circles of Belgian family physicians (*chapter 4*). By not interfering in the peer review process we aimed to approach the situation in ‘real life’. We found that a single intervention did not have a significant effect on the quantity of antibiotic prescribing (56.9% of patients received an antibiotic in the nine intervention groups and 58.3% in the nine control groups). Likewise, there was no difference in the proportion of prescribed first choice antibiotics (34.5% versus 29.4%). This study suggests that more attention to the context of primary care practice and insight into the process of self-reflective learning may be needed to optimise the effectiveness of quality circles.

When medical evidence is available one would expect that transmitting the evidence to health care professionals is sufficient to change practice and improve quality of care.

Contextual evidence

If medical evidence and strategies for transmitting the evidence are available, why doesn't this result in evidence-based practice? Why are sore throat patients still abundantly treated with antibiotics?

Medical evidence provides information on '*efficacy*', the effect of an intervention in a controlled setting for a carefully selected group of patients. However, in reality patients in primary care are a mix of people with various biopsychological, cultural and socioeconomic backgrounds, who present with complaints rather than a diagnosis

and often have more than one condition. They consult doctors with specific competences (i.e. in communication), beliefs and empathy. Moreover, without the careful follow-up in a trial setting, they are much less adherent to the prescribed treatment. All these factors make up the context of clinical care and contribute to the 'efficacy of interventions in real life', i.e. the '*effectiveness*'. Information from contextual evidence helps us understand the gap between 'efficacy' and 'effectiveness'. Information on the effectiveness of interventions is what clinicians really need. It answers their most important question: 'How will it work for my patients in my practice?'

Why do physicians still prescribe antibiotics for an uncomplicated sore throat, in spite of the availability of a guideline that recommends refraining from antibiotics? In an observational study of patients consulting their doctor for an acute sore throat we explored this contextual evidence (*chapter 5*). Physicians often mention patient pressure for an antibiotic prescription as a reason why they do not adhere to the guideline. Our study questions if this is the case. An antibiotic prescription is not necessarily the patient's main concern. Adequate analgesia may be a more important reason for seeking medical care. Possibly, patients who hope for an antibiotic may in fact want a treatment to alleviate pain. They may mistakenly feel that antibiotics are the best treatment for their pain. Communicating with patients about their needs and potential misconceptions, and taking their 'health beliefs' into account, could help remove this obstacle to more rational and evidence-based prescribing of antibiotics.

Information on the 'efficacy' of interventions that is based on sound medical evidence is a basic requirement for evidence-based practice. It needs input from evidence on contextual factors that determines 'effectiveness' of interventions in day to day practice. However, not all interventions that are efficacious and effective can be implemented. Health care budgets are limited and policymakers need to control costs and ensure accessibility for all its citizens. Can health policies, such as national reimbursement regulations for acid suppressant drugs, contribute to evidence-based prescribing?

Policymakers are mostly concerned with the 'efficiency' and 'equity' of interventions. Health policies, including those regulating reimbursement of medication, can be powerful drivers of physicians' prescribing, at least on the short term. These policies are usually inspired by cost-containment concerns and it is not always clear if this coincides with the principle of rational evidence-based prescribing. Our analysis of national prescribing data for acid suppressant medication in Belgium shows that indeed physicians' prescribing

responds to reimbursement policies (*chapter 6*). These policies, however, do not discriminate between rational and irrational use of acid suppressants and therefore cannot be considered as sufficient to improve quality of care. On the other hand, the clinical practice recommendations that were published during the observed period in a consensus report on rational use of acid suppressant drugs did not have any noticeable impact on prescribed volumes. Our analysis also shows that some effects of reimbursement policies can be unintended. This suggests that the design and evaluation of policies should follow a structured process and adopt evidence-based methods. Medical and contextual evidence should be the starting point for all policies. Stakeholders should refer to evidence to support their arguments. Policymakers must then consider efficiency and equity issues and societal and political priorities. A dialogue between policymakers, researchers, guideline developers, health care professionals and patients could be an effective way to pursue both cost-containment and quality of care.

The four research papers in this thesis illustrate that the proposed evidence framework can be useful in the analysis of determinants of quality of care. Attention to medical, contextual and policy evidence provides clues that could be instrumental in designing strategies and interventions that aim to increase the implementation of evidence in clinical care and thus contribute to improvement of its quality.

Een conceptueel kader voor onderzoek

Het beschikbaar maken van de resultaten van wetenschappelijke studies (evidentie of ‘evidence’) in de klinische praktijk zou rechtstreeks de kwaliteit van zorg verbeteren. Dit is echter niet het geval. Het concept ‘kwaliteit van zorg’ is complex en vraagt om een bredere benadering. In deze thesis stellen wij een theoretisch kader voor dat kan helpen om de brede waaier van determinanten en processen in kaart te brengen die een rol spelen bij het verbeteren van kwaliteit van zorg (*hoofdstuk 2*). Wanneer we dit theoretische kader bekijken vanuit een onderzoeksperspectief, tekenen zich drie soorten evidentie (wetenschappelijk bewijs) af: medische, contextuele en beleidsgerelateerde evidentie. Bij het nemen van beslissingen over patiënten dienen we te bouwen op degelijke kennis van de ziekte en de aanpak ervan (medische evidentie). We moeten echter ook de specifieke context van het arts-patiënt contact en het gezondheidszorg-systeem (contextuele evidentie) in rekening nemen en aandacht hebben voor een doelmatige (efficiëntie) en billijke (equity) verdeling van de beschikbare middelen (beleidsgerelateerde evidentie). Deze drie soorten evidentie zijn opgenomen in een ‘evidentie kader’ dat gebruikt kan worden bij het ontwikkelen en analyseren van onderzoek op het gebied van kwaliteitsbevordering in de eerstelijnsgezondheidszorg. De vier onderzoeksartikels in deze thesis exploreren het nut van dit ‘evidentie kader’ als instrument bij het onderzoeken van kwaliteitsverbetering in de gezondheidszorg, waarbij het gebruik maken van de resultaten van wetenschappelijk onderzoek voorop staat.

Medische evidentie

Medische evidentie verkrijgen we uit klinische studies en geeft ons informatie over de werkzaamheid (*efficacy*) van behandelingen of interventies. Hieronder verstaan we het effect bij geselecteerde populaties, in specifieke en gecontroleerde omstandigheden. Medische evidentie is de hoeksteen van evidence-based medicine (EBM) en dient daarom betrouwbaar en van goede kwaliteit te zijn. Evidentie op basis van systematische reviews en meta-analyses waarin de resultaten van individuele studies worden samengebracht,

Een eerste voorwaarde voor goede kwaliteit van zorg is beschikbaarheid van medische evidentie.

wordt beschouwd als krachtig bewijs bij het onderbouwen van aanbevelingen voor de klinische praktijk. De kwaliteit van deze syntheses is echter afhankelijk van de kwaliteit van de individuele studies die erin zijn opgenomen. Het kritisch beoordelen van deze studies is daarom een essentieel onderdeel van het beoefenen van EBM. Een slechte methodologische kwaliteit en selectieve beschikbaarheid van data zijn belangrijk en kunnen de validiteit van de reviews in gevaar brengen. In *hoofdstuk 3* nemen we de beschikbare Cochrane reviews, een belangrijke bron van gesynthetiseerde medische evidentie, onder de loep. We bestudeerden een aselechte steekproef van alle Cochrane reviews, die referenties naar “unpublished data only” opnemen. Omdat deze gegevens niet zijn beoordeeld door redacteurs van tijdschriften of andere inhoudsdeskundigen, zijn zij een potentiële bron van vertekening voor de resultaten van de meta-analyse. Onze analyse toont dat het zoeken naar ongepubliceerde studies niet veel oplevert. Bovendien wordt 38% van de als ongepubliceerd aangeduide referenties (uiteindelijk) toch gepubliceerd, ofwel binnen de gerapporteerde zoekperiode, ofwel kort daarna. De methodologische kwaliteit van deze ongepubliceerde studies, in het bijzonder de data van geneesmiddelenfabrikanten of abstracts van symposia en congressen, was over het algemeen slecht of niet te beoordelen. Daarom lijkt het niet de moeite om uitgebreid te zoeken naar meestal moeilijk te lokaliseren ongepubliceerde studies. In plaats daarvan kan overwogen worden om Cochrane reviewers te adviseren om te investeren in het regelmatig actualiseren van hun reviews.

Het **overdragen van medische evidentie** is een volgende stap in het beoefenen van evidence-based practice. Met behulp van verschillende soorten interventies heeft men getracht om de kloof tussen evidentie en praktijk te overbruggen, maar een ideale oplossing bestaat niet. In vele Europese landen, waaronder België, zijn Lokale Kwaliteitsgroepen (LOK's) opgestart, kleine groepen van collega's (bijvoorbeeld huisartsen in een zelfde regio). Zij zijn bedoeld als instrument ter verbetering van de zorgkwaliteit en maken deel uit van nationale systemen voor accreditering en permanente navorming in de gezondheidszorg. Onderzoek naar de impact van dergelijke groepen op de kwaliteit van de patiëntenzorg is echter schaars. In een pragmatische, op cluster niveau gerandomiseerde studie evalueerden wij het effect van een eenmalige

Indien medische evidentie beschikbaar is, dan zou het overbrengen van deze kennis bij professionals in de gezondheidszorg voldoende moeten zijn om hun handelen aan te passen en zo de kwaliteit van hun zorg te verbeteren.

door de LOK-groep zelf geleide bijeenkomst over een nieuwe praktijkrichtlijn voor de aanpak van acute rhinosinusitis op het voorschrijven van antibiotica (*hoofdstuk 4*). Door niet in te grijpen in het groepsproces trachtten we de toestand in de dagelijkse praktijk zoveel mogelijk te benaderen. We stelden vast dat een eenmalige interventie geen significant effect heeft op de hoeveelheid voorgeschreven antibiotica (56.9% van de patiënten kreeg een antibioticum in de negen interventietroepen en 58.3% in de negen controlegroepen). Er was evenmin een verschil tussen beide groepen in de proportie voorgeschreven eerste keuze antibiotica (34.5% versus 29.4%). Deze studie suggereert dat meer aandacht voor de context van de praktijk en meer inzicht in het proces van zelfreflectie en leren nodig zijn om het toepassen van EBM met behulp van lokale kwaliteitsgroepen te optimaliseren.

Contextuele evidentie

Indien de medische evidentie en strategieën voor het overbrengen ervan beschikbaar zijn, waarom resulteert dit dan niet in evidence-based praktijkvoering? Waarom worden patiënten met acute keelpijn nog altijd met antibiotica behandeld?

Medische evidentie geeft informatie over de werkzaamheid (*efficacy*) van een interventie in een gecontroleerde setting bij een zorgvuldig geselecteerde groep patiënten. Echter, in de realiteit zijn patiënten in de eerstelijns een mengeling van personen met

verschillende biopsychologische, culturele en sociaaleconomische achtergronden, die zich aanmelden met een klacht in plaats van een diagnose, en die vaak meer dan één aandoening hebben. Zij raadplegen artsen die elk hun eigen specifieke vaardigheden (bijvoorbeeld met betrekking tot communicatie), overtuigingen en empathische talenten hebben. Bovendien worden patiënten in de dagelijkse praktijk minder intensief opgevolgd dan in een klinische studie en zijn ze ook veel minder trouw aan de voorgeschreven behandeling. Al deze factoren vormen de context van de patiëntenzorg en dragen bij tot de werkzaamheid van interventies in het dagelijkse leven, namelijk de doeltreffendheid (*effectiveness*). Informatie over contextuele evidentie helpt ons om de kloof tussen werkzaamheid en doeltreffendheid te begrijpen. Informatie over de doeltreffendheid is wat klinici werkelijk nodig hebben. Het geeft een antwoord op hun belangrijkste vraag: "Hoe werkt het bij mijn patiënten in mijn praktijk?"

Waarom behandelen artsen een ongecompliceerde acute keelpijn nog altijd met antibiotica, terwijl er een richtlijn beschikbaar is die aanbeveelt om er geen voor te schrijven? In een observationeel onderzoek bij patiënten die hun huisarts raadpleegden voor een acute keelpijn, exploreerden we de contextuele evidentie (*hoofdstuk 5*). Artsen vermelden vaak dat zij onder druk van hun patiënten antibiotica voorschrijven. Ons onderzoek stelt dit argument in vraag. Een voorschrift voor een antibioticum was niet noodzakelijkerwijs de belangrijkste zorg van de patiënt. Goede pijnstilling zou wel eens een belangrijker reden kunnen zijn om hulp te zoeken. Het is mogelijk dat patiënten die een antibioticum verwachten eigenlijk iets tegen de pijn willen en onterecht denken dat een antibioticum het beste medicijn hiervoor is. Door met patiënten te praten over hun wensen en mogelijke misvattingen en door aandacht te geven aan hun ideeën over hun eigen gezondheid, zouden deze obstakels uit de weg geruimd kunnen worden en de weg kunnen open staan naar rationeler en meer evidence-based voorschrijven van antibiotica.

Beleidsgerelateerde evidentie

Informatie over de werkzaamheid van interventies gebaseerd op degelijke medische evidentie is een eerste voorwaarde voor evidence-based praktijkvoering. Het heeft input nodig van contextuele factoren die de doeltreffendheid van interventies in de dagelijkse praktijk bepalen. Echter, niet alle interventies die werkzaam en doeltreffend zijn kunnen in de praktijk worden uitgevoerd. Gezondheidsbudgetten zijn beperkt en beleidsmakers moeten de kosten beheersen en toegankelijkheid voor alle burgers bewaken. Kan regelgeving, zoals de terugbetalingsregelingen voor zuurremmers, bijdragen aan evidence-based voorschrijven?

Beleidsmakers zijn vooral geïnteresseerd in de doelmatigheid (*efficiency*) en de billijkheid (*equity*) van interventies. Beleidsmaatregelen, waaronder terugbetalingsregelingen voor geneesmiddelen, kunnen krachtige drijfveren zijn van voorschrijfgedrag van artsen zeker op korte termijn. Dergelijke maatregelen zijn meestal geïnspireerd door kostenbeheersing en het is niet altijd duidelijk of dit principe overeenkomt met het principe van rationeel evidence-based voorschrijven. Onze analyse van de Belgische federale databank (Farmanet) toont dat de voorgeschreven volumes van zuurremmers

inderdaad reageren op de verschillende terugbetalingsregelingen (*hoofdstuk 6*). Echter, deze maatregelen maken geen onderscheid tussen rationeel en irrationeel gebruik van zuurremmers en kunnen dus niet beschouwd worden als afdoende maatregel ter verbetering van de kwaliteit. Anderzijds zien we geen impact op de voorgeschreven volumes van het in dezelfde periode verspreide consensusrapport van het RIZIV over het doelmatige gebruik van zuurremmers. Onze analyse toont ook dat terugbetalingsregelingen soms een onbedoeld effect hebben. Dit alles suggereert dat het ontwerpen en evalueren van beleidsmaatregelen een gestructureerde procedure en evidence-based methode zouden moeten volgen. Medische en contextuele evidentie dienen het uitgangspunt te zijn van alle beleid en de referentie voor argumenten van alle betrokken partijen. Beleidsmakers dienen vervolgens de doelmatigheid en billijkheid te beoordelen en dit alles te plaatsen in de maatschappelijke en politieke prioriteiten. Een dialoog tussen beleidsmakers, onderzoekers, richtlijnontwikkelaars, gezondheidsprofessionals en patiënten zou een effectieve manier kunnen zijn om zowel kostenbeheersing als kwaliteit van zorg na te streven.

De vier onderzoeksartikels in dit proefschrift illustreren dat het voorgestelde ‘evidentie kader’ nuttig kan zijn bij het onderzoeken van de determinanten van kwaliteit van zorg. Aandacht voor medische, contextuele en beleidsgerelateerde evidentie levert belangrijke informatie. Deze kan bruikbaar zijn bij het onderzoeken en ontwikkelen van strategieën en interventies, die het toepassen van de resultaten van wetenschappelijk onderzoek in de praktijk kunnen bevorderen. Op deze wijze kan een bijdrage geleverd worden aan het verbeteren van de kwaliteit van patiëntenzorg.

Un cadre conceptuel pour une recherche

La mise à disposition, au niveau de la pratique clinique, des résultats des études scientifiques (les « faits » ou preuves) améliorerait directement la qualité des soins. Tel n'est cependant pas le cas. Le concept « qualité des soins » est complexe et exige un abord beaucoup plus vaste. Dans cette thèse, nous développons un cadre théorique nous permettant d'inclure le grand éventail des déterminants et processus impliqués dans l'amélioration de la qualité des soins (*chapitre 2*). Lorsque nous examinons ce cadre théorique dans une perspective de recherche, trois types de « preuves » émergent : médicales, contextuelles et politiques ('policy evidence'). Une prise de décision en matière de soins aux patients doit se baser sur une connaissance solide de la pathologie et de sa prise en charge (preuves médicales). Nous devons toutefois tenir compte du contexte spécifique des soins de santé et de la relation médecin-patient (preuves contextuelles) en restant attentifs à une répartition efficiente et équitable des moyens disponibles (preuves au niveau d'une politique). Ces trois types de preuves sont incorporés dans un « cadre de preuves » que nous pourrions utiliser pour élaborer et analyser des recherches dans le domaine des stratégies pour la promotion de la qualité en première ligne de soins. Les quatre publications de recherche reprises dans cette thèse explorent l'utilité de ce « cadre de preuves » en tant qu'instrument permettant de situer et de comprendre les recherches nécessaires pour améliorer la qualité des soins en ayant recours aux résultats des études scientifiques.

Les preuves médicales

Les preuves médicales sont issues des études cliniques et nous apportent des informations sur l'efficacité (*efficacy*) de traitements ou d'interventions, dans certaines populations sélectionnées et dans des circonstances spécifiques et contrôlées. Les preuves médicales constituent la pierre d'angle de l'evidence-based medicine (EBM) et doivent, à ce titre, être fiables et de bonne qualité. Les preuves issues de synthèses méthodiques et de méta-analyses sommant les résultats d'études individuelles sont considérées comme une preuve solide lors

Les preuves médicales comme pré requis à une bonne qualité des soins

de l'élaboration de recommandations pour la pratique clinique. La qualité de ces synthèses est cependant dépendante de la qualité individuelle des différentes études qu'elles incluent. Une évaluation critique de ces études constitue une des tâches essentielles de la pratique de l'EBM. Une piètre qualité méthodologique comme une disponibilité sélective des données sont des éléments importants qui peuvent mettre en péril la validité des synthèses. Dans le *chapitre 3*, nous analysons de plus près des synthèses de la Cochrane, source importante de « preuves médicales » synthétisées. Nous évaluons un échantillon aléatoire de l'ensemble de ces synthèses Cochrane qui incluent des références à des 'unpublished data only'. Ces données ne sont pas évaluées par les rédacteurs de revues ni par d'autres experts au niveau contenu, et, pour ce motif, elles introduisent un biais potentiel pour l'ensemble des résultats de la méta-analyse. Notre propre analyse montre que la recherche des études non publiées apporte peu d'éléments. En outre, 38% des références indiquées comme n'ayant pas été publiées sont (finalement) quand même publiées soit pendant la période de recherche mentionnée, soit peu de temps après. La qualité méthodologique de ces études non publiées, en particulier les données en provenance des fabricants de médicaments ou les résumés de symposium ou de congrès, est, en général, mauvaise ou non mentionnée. Il semble donc peu utile de se fatiguer à chercher des études non publiées par ailleurs difficiles à localiser. Les reviewers Cochrane auraient tout intérêt à plutôt investir ce temps dans l'actualisation régulière de leurs synthèses.

La **transmission des preuves médicales** est l'étape suivante dans une démarche evidence-based medicine. Différents types d'intervention ont été proposés pour combler le fossé entre « les preuves » et la pratique ; une solution idéale n'existe pas. Dans de nombreux pays européens, dont la Belgique, de petits groupes de confrères (par exemple de médecins généralistes d'une même région) se sont constitués (les Groupes Locaux d'Evaluation Médicale ou GLEMs). Leur but est de servir d'outil pour l'amélioration de la qualité des soins ; ils font partie d'un processus d'accréditation de formation continue permanente dans le cadre des soins de santé. Les évaluations de l'impact de la mise en place de tels groupes en termes de qualité pour les soins dispensés au patient sont cependant rares. Dans une étude pragmatique avec randomisation par grappes, nous avons évalué l'efficacité de l'organisation, par le GLEM-même, d'une réunion dont le thème était un

Quand des preuves médicales sont disponibles, les porter à la connaissance des professionnels des soins de santé devrait suffire pour leur permettre d'adapter leur pratique et améliorer la qualité des soins.

nouveau guide de pratique pour la prise en charge de la rhinosinusite aiguë. L'évaluation portait sur la prescription d'antibiotiques (*chapitre 4*). En ne nous impliquant pas dans le processus de « revue par les pairs » ('peer review'), nous pensons mieux approcher la réalité de la pratique quotidienne. Nous avons observé l'absence d'effet d'une intervention unique sur la quantité d'antibiotiques prescrits (56.9% des patients ont reçu un antibiotique dans les neuf groupes avec intervention et 58.3% dans les neuf groupes contrôle). Il n'y a également pas de différence observée entre les deux groupes dans la proportion de prescription de l'antibiotique recommandé comme premier choix (34.5% versus 29.4%). Cette étude suggère qu'il faut réserver plus d'attention au contexte de la pratique et mieux comprendre le processus d'autoévaluation critique pour pouvoir optimiser la mise en pratique de l'EBM grâce à ce processus de groupes locaux de qualité.

Preuves contextuelles

Les preuves médicales et les stratégies pour leur implantation étant disponibles, pourquoi pas de pratique basée sur les preuves? Pourquoi les patients présentant un mal de gorge aigu sont-ils toujours traités avec des antibiotiques ?

Les preuves médicales livrent des informations concernant l'efficacité (*'efficacy'*) d'une intervention dans un contexte contrôlé et sur un groupe de patients soigneusement sélectionnés. Dans la réalité, la patientèle en première ligne de soins est cependant un patchwork de personnes avec leur propre

contexte biopsychologique, culturel et socio-économique, qui se présentent avec une plainte plutôt qu'avec un diagnostic et souvent aussi avec plus d'une affection. Ils consultent des médecins qui ont, eux aussi, leurs propres aptitudes (par exemple en matière de communication), convictions et talents d'empathie. En outre, en pratique quotidienne, les patients sont suivis moins intensément que dans le cadre d'une étude clinique et ils sont moins observants pour le traitement qui leur est prescrit. Tous ces facteurs constituent le contexte des soins aux patients et interviennent au niveau de l'efficacité des interventions dans la vie de tous les jours, appelée efficacité pratique, clinique ou utilité (*'effectiveness'*). Une information concernant les preuves contextuelles nous aide à comprendre le hiatus entre efficacité et utilité. Cette information ayant trait à l'utilité représente une réponse au besoin réel des cliniciens. Elle apporte en effet

une réponse à leur question la plus importante: “Quel effet pour mes patients, dans ma pratique ?”.

Pourquoi les médecins traitent-ils encore toujours un mal de gorge non compliqué avec des antibiotiques alors qu'ils disposent d'un guide de pratique leur recommandant de n'en point prescrire ? Dans une étude d'observation incluant des patients consultant leur médecin généraliste pour un mal de gorge aigu, nous avons étudié les preuves contextuelles (*chapitre 5*). Les médecins racontent souvent qu'ils prescrivent des antibiotiques sous la pression de leurs patients. Notre enquête met cet argument en doute. La prescription d'un antibiotique n'était pas nécessairement le souci principal du patient, plus préoccupé, dans sa recherche d'aide, d'obtenir un soulagement correct de sa douleur. Il est possible que les patients qui désirent un antibiotique attendent en fait un traitement de la douleur et qu'ils estiment que l'antibiotique est le meilleur médicament pour atteindre ce but. En dialoguant avec les patients à propos de leurs souhaits et de conceptions peut-être erronées, en réservant l'attention nécessaire à leurs idées concernant leur santé, ces obstacles pourraient largement sauter et la voie s'ouvrir vers une prescription d'antibiotiques plus rationnelle et basée sur les preuves.

Preuves au niveau d'une politique

Une information concernant l'efficacité des interventions, basée sur des preuves médicales solides est la condition première pour une pratique basée sur des preuves. Les facteurs contextuels qui déterminent l'efficacité clinique (utilité) des interventions dans la pratique quotidienne doivent y être ajoutés. Toutes les interventions efficaces et utiles ne peuvent cependant être réalisées dans la pratique. Les budgets pour la santé sont limités et les décideurs doivent maîtriser les coûts et préserver une accessibilité pour tout citoyen. La réglementation, par exemple celle concernant le remboursement des inhibiteurs de la sécrétion acide gastrique, peut-elle contribuer à une prescription basée sur les preuves ?

Les décideurs sont surtout intéressés par l'efficacité et l'équité des interventions. Les règlements, dont la réglementation concernant le remboursement des médicaments, peuvent modifier fortement le comportement de prescription des médecins, certainement à court terme. De telles mesures sont généralement inspirées par un contrôle des

coûts et il n'est pas toujours évident que ce principe corresponde à une prescription rationnelle basée sur les preuves. Notre analyse d'une base de données fédérale belge (Pharmanet) montre que les volumes d'inhibiteurs de la sécrétion acide gastrique sont effectivement influencés par les différentes réglementations de remboursement (*chapitre 6*). Ces mesures ne font cependant pas la distinction entre un usage rationnel et une utilisation irrationnelle de ces médicaments et ne peuvent donc être considérées comme des mesures visant avec conviction une amélioration de la qualité. D'autre part, nous n'observons aucun impact sur les volumes prescrits du rapport de consensus de l'INAMI sur ce sujet des inhibiteurs de la sécrétion acide gastrique, rapport diffusé durant la même période. Notre analyse montre aussi que les réglementations concernant le remboursement ont parfois un effet non désiré. Tout ceci suggère que la conception et l'évaluation des réglementations devraient suivre un processus structuré et une méthode basée sur des preuves. Les preuves médicales et contextuelles doivent être le point de départ de toute politique et servir de référence dans les arguments de toutes les parties concernées. Les décideurs doivent ensuite évaluer l'efficacité et l'équité ainsi que mettre tout ceci en perspective des priorités sociales et politiques. Un dialogue entre les décideurs, les chercheurs, les personnes qui élaborent des guides de pratique, les professionnels de la santé et les patients serait une manière efficace de viser à la fois un contrôle des coûts et une qualité des soins.

Les quatre articles de recherche figurant dans cette thèse illustrent que le « cadre de preuves » proposé peut être utile dans la recherche de déterminants de qualité de soins. Être attentif aux preuves médicales, contextuelles et d'une politique, livre des informations utilisables pour investiguer et élaborer des stratégies et des interventions pouvant favoriser l'implantation de résultats de recherches scientifiques dans la pratique et contribuer ainsi à une meilleure qualité des soins prodigués aux patients.

證據在臨床護理中的實施：探索知識與實踐之間的缺口

The implementation of evidence in clinical care. Exploring the gap between knowledge and practice.

總結

本研究旨在經由科學研究尋求證據，作為臨床實踐中改善病患護理品質的直接依據，然而，由於護理品質的概念相當複雜，需要考慮更寬廣的範圍，結果並未達成此項期望。在本論文中，我們提出一個概念框架，用以幫助我們掌握各種具有影響效應的因素和過程

(第二章)。運用這個理論框架進行研究時，出現下列三種不同類型的證據：**醫療、情境和政策證據**。在進行病患護理決定時，我們需要以疾病及其管理相關而合理的知識(醫療證據)作為基礎，同時也必須考慮醫療護理環境的特殊背景，以及與病人的互動情況(情境證據)，而且也應注意效率與公平性(政策證據)。這三種類型的證據均已納入「證據框架」中，用以分析並設計著眼於改善基層醫護品質的策略之研究。本論文下分四項研究報告，均以評估「證據框架」是否可以用來探索並了解基層醫護品質改善領域所需要的各項證據作為重點。

來自臨床試驗的**醫學證據**，是『循證醫學』的核心。它提供在特定環境和限定條件下，針對特定群體進行治療或手術所見的影響之**功效性**資訊。來自系統性觀察和綜合個別試驗結果所得的**彙總分析**的證據，是用來支撐各項臨床實施建議的最高水平的證據。因此，針對彙總分析裡的各項試驗進行嚴謹的評價，是施行『循證醫學』(evidence-based medicine, EBM)

必要的措施。試驗品質粗劣以及刻意選擇數據，是危害評論有效性的兩項重要課題。在第三章中，我們深入探討了可賀蘭評論(Cochrane reviews) -

醫學證據變造案例的主要來源 - 中未經發表的各項試驗。我們針對全部為數292的評論案例（包括註明「限用未發表數據」之文獻），隨機抽樣(n=61)進行研究。結果顯示：在可賀蘭評論中尋找『未公佈的數據』的效益並不高，因為評論案例中只有11.9%含有這種參考文獻。此外，在「未公佈的」參考文獻中，有38%後來以同儕評論的形式發表。『未經發表的試驗』之方法論，其品質普遍粗劣，或並未記載，尤以廠家提供之數據或會議論文摘要為最。因此，廣泛搜尋未發表的案件未必值得從事，評論員可能已被告知定期更新其觀察評論。

醫學證據的傳播是實踐『循證醫學』的下一步驟。雖有許多各種措施，為了「消除證據和實踐之缺口」之目的，經設計提出並經測試，但那枚「神奇子彈」一直並未找到。在許多歐洲國家，包括比利時，已經設有同儕團隊或地方性品質小組，作為提升醫療護理品質的工具。這些是國家認證體系和醫學持續教育的核心特徵。不過，有關其對病人醫護品質影響之研究仍很稀少。在一項實際的群組隨機對照試驗中，我們就法蘭德斯(Flemish)地區家庭醫師的品質圈，針對抗生素處方，引用急性鼻竇炎的指導方針，進行自主討論的效果加以評估(第四章)。目的在探討「現實世界」的情況，而不要干預同儕評論觀察的過程。我們發現：單一的措施行動並未對抗生素處方的劑量產生顯著影響(在九個干預組中，有56.9%的病人接受抗生素，在九個對照組中，有58.3%的病人接受抗生素)。同樣，在首選抗生素中，也沒有明顯比例差異(34.5%相對於29.4%)。本研究建議，有必要進一步關注基層醫療實踐的情境，並探索自我反思的過程，或將有助於提供改進品質圈效益的線索。

醫學證據提供，在特定環境和限定條件下，針對細心選定的病患群組，所進行治療或手術的**功效性**資訊。而**情境證據**在日常診療中，增補了治療和手術之可行性和適用性的數據(第五章)。其中包括：醫患互動(溝通、環境)，醫師的個人特質資訊(態度、才幹、同理心)，以及病人相關資訊(生物心理的、社會文化的、社會經濟的等)。有關「效益」資訊，才是臨床醫生所真正需要。這些資訊能解答他們最重要的問題：「診療時，如何作才會對我的病人產生效用？」。在急性喉嚨痛患者諮詢其醫師的觀察研究中，我們探討了情境證據。醫生經常提出：病人強力要求

抗生素處方，是他們沒有堅守指導原則限制使用抗生素之規定的原因。我們的研究顯示：抗生素處方不一定是病患的主要關切，充分的鎮痛作用，或許才是他們尋求醫療照護的更重要原因。證據顯示，病人希求抗生素，事實上可能只是想要減輕疼痛的治療。病人或許覺得抗生素乃是急性喉嚨疼痛最好的治療。與患者溝通他們的需求和潛在的誤解，並以他們的「健康理念」為考量，才能幫助消除『循證處方』抗生素的障礙。

政策證據：以健全醫療證據為基礎的手術「效能」資訊，是『循證診療』的首要要求。它應由在具有『情境證據』的日常診療中所得的「功效性資訊」所組成。在這資源無限的世界中，應該足以有效執行證據臨床診療。不過，所有衛生保健系統仍在急於尋求如何控制醫療健保支出的增加，並確保滿足所有公民的需求。因此，「效率」與「公平性」需要同時加以考量。醫護政策，包括用藥報銷的規範，至少在短期內，仍是支配醫師的處方的強大驅動力量。這些政策通常出於成本控制的關切，這個原則是否符合循證處方的合理原則，並不十分明確。我們針對比利時的酸藥處方全國用藥數據的分析顯示：醫師的處方確實能符合報銷政策(第六章)。然而，這些政策並未區分合理與非合理用藥，因此，並不能視為足以提昇護理的品質。另一方面，發表於觀察期間的臨床實務建議，也沒有對規定的處方量產生明顯的影響。我們的分析也顯示：報銷政策的影響也許並非目的所在。我們同時建議：政策設計和評價應採用循證方法。決策者、研究者和方針發展者之間的對話，應能有效追求兼顧成本控制與醫療品質。

本論文這四個研究報告顯示：所提出的證據框架可以有效分析醫療品質的決定因素。關注醫療、情境和政策證據，可以提供線索有助於制定策略和措施，以增進證據執行在臨床護理中，從而幫助改善品質。

Saturnus

Neptunus

The implementation
of
evidence
in
health care

Exploring
the gap
between
knowledge
and
practice

Dankwoord

Uranus

Een dikke boom
begint als
een teer twijgje.

Een bergbeklimming
begint
met een stapje.

*Lao-Tse, Chinese filosoof
(ca. 600 v. C)*

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Mijn familie, schoonfamilie en vrienden dank ik voor hun aanmoedigen en vertrouwen dat het 'toch ooit af zou geraken'. In deze laatste fase van mijn thesis heb ik peter's kritische vragen gemist. Hij leerde mij altijd relativeren en daagde mij steeds uit om mijn argumenten aan te scherpen.

Aan mijn ouders heb ik dit proefschrift opgedragen. Zij leerden mij dat grenzen er zijn om verkend en verlegd te worden, dat uitdagingen er zijn om aan te pakken en dat liefde en vertrouwen de beste basis zijn voor groei. Jullie hebben mij vaak zien vertrekken naar verre onbekende oorden, misschien wel met een klein hartje, maar dat was een prachtig cadeau. Wetenschappelijk werk zie ik als een andere manier om de grenzen om mij heen te verkennen. Daarmee legden jullie de basis voor dit doctoraat.

Stefan, al 15 jaar zijn we een hecht team. Ook dit project hebben we samen tot een goed einde gebracht. Vooral de laatste maanden waren hectisch en moest er vaak geïmproviseerd worden, maar we hadden al voor hetere vuren gestaan. Je stond altijd achter, naast en voor mij en was een rustpunt in woelige tijden. Klaar voor een volgend project?

Sofie en Emma, jullie krijgen nu (eindelijk) het laatste woord. Sofie, jouw tekening sluit dit dankwoord af. Emma, met jouw heeal heb je al heel wat grenzen verlegd.



Jullie kunnen gerust zijn, want jullie zien opgroeien en samen de wereld verkennen, is nóg veel leuker dan een doctoraat maken. En daar hebben we nu tijd voor.

Saturnus

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Curriculum vitae

Uranus

Mieke (Marie Louise) van Driel was born November 28 1959 in Rotterdam, the Netherlands. In 1966 the family moved to Taiwan, where she attended the Kaohsiung Dominican School. It was there that she learned to read and write from Dominican Sisters from the Philippines in a multi-ethnic and multicultural environment. When the family returned to the Netherlands in 1969 her great-aunt Toos, headmistress of a primary school in Rotterdam, helped her to catch up with her mother tongue. She attended 'Het Nieuwe Lyceum' in Bilthoven, where she obtained her diploma Gymnasium-B in 1977. When given a chance to enter medical school at the University of Utrecht, she took a rain check on plans to explore other countries and cultures. Between internships she traveled to the United States, where she spent several months at various health care facilities and at the J.F. Kennedy Center for Child Development in Denver, Colorado. She continued her internships in Dutch hospitals and graduated as an MD in November 1984.

At the time of her graduation, future career perspectives for young doctors looked grim. Although there was enough work in patient care, opportunities for an acknowledged training position as a specialist were scarce. As a result, many freshly graduated MDs ended up working as assistant doctors in hospitals without the prospect of specialization (the "AGNIO's", Assistent Geneeskundige Niet In Opleiding). Mieke was one of the founders and a member of the executive committee of the LBB (Landelijke Belangenvereniging voor Basisartsen), a national doctors' association that strived to bring this issue to the attention of politicians. Her thesis, a survey of recently graduated physicians from Utrecht University, provided the evidence-base for the LBB's advocacy and was awarded a prize for "encouraging research" by the Board of Governors of the University. At the same time she was involved in various activities at the Women's Health Center in Utrecht, including information services, a library, research (use of the pessarium oclusivum as a contraceptive method) and advocacy (sexual assault of female clients by health care professionals). As an MD she worked at the Red Cross Blood Bank and at the CBO (Institute for quality of care) in Utrecht.

In 1987 she took a backpack and flew to Taiwan, where during six months she immersed herself in the hospitable culture that had shaped her childhood. In a China Studies Seminar she learned the basics of the Chinese language and made friends from all continents. The following six months she explored the cultures of South-East Asia.

Convinced of her choice for primary care, she started vocational training in general practice at Utrecht University. Paul and Eline Willemsen in Zaltbommel warmly introduced her to a challenging and rewarding profession. She celebrated her registration as a General Practitioner in 1989 with a trip on the Trans-Siberian railway. Together with her father she arrived in Beijing at the height of the students' optimistic stride for freedom.

Back in the Netherlands she worked as a GP in various practices and prepared for enrollment at the Institute of Tropical Medicine in Antwerp, Belgium. With a diploma in tropical medicine she travelled to China in 1990 on an assignment for Médecins Sans Frontières-Belgium. Her primary health care project was located in Wulan, a rural county on the Qinghai-Tibet Plateau, 1500 km west of Beijing. In 1991 she moved to Lhasa, Tibet, where she and a French nurse started a new project of primary care assistance and tuberculosis control in two rural counties, Linzhou and Nimu. In 1992 Stefan Thielemans joined the team to establish and coordinate the urgently needed infrastructure, providing the health care staff with proper clinics and the population with clean water. They also initiated a program of physiotherapy and rehabilitation in villages with children and adults disabled by Kashin-Beck's disease ("Big bone disease"). She exchanged the wild beauty of the Himalayan Mountains in 1993 for the lush paddy fields of Cambodia, a country recovering from the harsh Khmer Rouge regime and guided by UN blue helmets towards free elections. She coordinated an MSF team working in the provincial and district hospitals of Pursat and learned about malaria control, hospital management and the terror of land mines. In June 1994 she took up an assignment in Rwanda, where a few months earlier the genocide had taken place, leaving the country empty and ravaged. She led a team of motivated health professionals towards rehabilitation of primary care services and care for refugees on their way home. She was medical coordinator for the joint missions of MSF Belgium, Holland and France. After this experience in emergency relief she enrolled at the London School of Hygiene

and Tropical Medicine. The course and the inspiring multicultural group of students fostered her interest in epidemiology and public health. She obtained a Master's degree in public health in 1995 with a thesis on the economics of tuberculosis in developing countries.

She then settled in Belgium. For the Dutch National Institute of Infectious Disease Control (LCI) she developed a practice guideline on the management of Lyme disease. At the Department of General Practice of the Free University of Brussels she participated in a breast cancer screening project. In 1998 she was recruited as an editor for "Minnerva", a new independent Belgian journal for evidence-based medicine in primary care. She is currently responsible for the Flemish edition and has produced a glossary of statistical and epidemiological terms (in Dutch and French) which is also used in teaching. At Project Farmaka in Ghent she is involved in developing literature reviews, e.g. for the consensus conferences of the Belgian National Institute for Sickness and Invalidity Insurance (RIZIV/INAMI) and participates in the project of academic detailing in primary health care. She joined the Department of General Practice and Primary Health Care of Ghent University in 1999 to organize training in evidence-based medicine and to initiate research in the domain. Since 2001 she has carried out the research projects that have led to this PhD thesis.

She is married to Stefan Thielemans and they have two daughters, Sofie (°1996) and Emma (°1998).

Saturnus

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Appendix

Uranus



Bron: M. van Driel. *Minerva Verklarende Woordenlijst voor Evidence-Based Medicine*. Gent: Minerva, 2003. ISBN 90-76023-06-5.

Aselect

Uitsluitend door toeval geselecteerd.

Betrouwbaarheidsinterval (BI) [Confidence Interval (CI)]

In een klinisch onderzoek kan men zelden de gehele populatie onderzoeken. Meestal moet men zich beperken tot een kleinere groep binnen de gehele populatie (een steekproef). Het betrouwbaarheidsinterval geeft het gebied van waarden aan, waarbinnen de werkelijke waarde in de populatie met een zekere graad van waarschijnlijkheid ligt. Meestal wordt een waarschijnlijkheid van 95% gebruikt. Dit betekent dat wanneer we het onderzoek 100 maal in dezelfde populatie met verschillende steekproeven zouden herhalen 95 van de herhalingen een resultaat geven dat binnen het interval ligt. Dit noemen we een 95% betrouwbaarheidsinterval (95% BI). Het betrouwbaarheidsinterval zegt iets over de nauwkeurigheid van de in het onderzoek gevonden schattingen van het effect. Het betrouwbaarheidsinterval hangt af van de variabiliteit (in de vorm van de standaard deviatie) en de grootte van de steekproef (het aantal personen in de onderzoekspopulatie). Hoe groter de steekproef, des te smaller is het betrouwbaarheidsinterval en des te nauwkeuriger is de schatting van het effect.

Bias

Wanneer er sprake is van bias of vertekening wijken de resultaten van een onderzoek of de interpretatie ervan af van de werkelijkheid door een systematische fout. Vertekening kan optreden als gevolg van een fout in elk van de stappen van een

onderzoek; zoals bij de opzet van de studie, het verzamelen van de gegevens, het analyseren, het interpreteren van de resultaten en het publiceren.

Publicatiebias (publication bias) is een vorm van vertekening die belangrijk is bij meta-analyses. Indien publicatie van studies afhangt van de grootte, de richting of de statistische significantie van de resultaten, is er sprake van publicatiebias. Het samenbrengen van eenzijdige onderzoeksresultaten (bijvoorbeeld alleen in het voordeel van een nieuw geneesmiddel), kan in een meta-analyse een vertekend beeld geven (een overschatting) van het werkelijke effect van de interventie.

Blindering [blinding]

In experimenteel onderzoek spreekt men van blindering wanneer patiënten, artsen en personen die het effect beoordelen niet op de hoogte zijn van de toegewezen behandeling. Deze procedure wordt toegepast bij interventiestudies (RCT's) om te voorkomen dat de uitkomst van het onderzoek wordt beïnvloed.

In een **enkelblinde** opzet (single blind) is slechts een van de betrokken partijen, bijvoorbeeld de onderzoeker/behandelend arts of de patiënt niet op de hoogte van de toegediende behandeling.

In een **dubbelblind** onderzoek zijn noch de behandelend arts, noch de deelnemers aan het onderzoek op de hoogte van de toegewezen behandeling.

Een **blinde uitkomstevaluatie** houdt in dat het klasseren of benoemen van de uitkomsten wordt uitgevoerd door personen, die niet op de hoogte zijn van de groep waarin de patiënten zijn ingedeeld.

Clinical Trial [CT]

Een klinische studie (interventiestudie) onderzoekt de werkzaamheid en veiligheid van een interventie of een geneesmiddel. Bij klinische studies over geneesmiddelen onderscheidt men vier fases.

In *fase I* wordt de molecule voor het eerst geïntroduceerd bij mensen nadat het op dieren is getest. In deze fase onderzoekt men vooral de veiligheid van het nieuwe geneesmiddel, o.a. hoeveel toegediend kan worden zonder ernstige ongewenste effecten te veroorzaken. Tevens bestudeert men de metabolisatie. Men gebruikt hiervoor gezonde vrijwilligers. In deze fase is het onderzoek meestal niet gerandomiseerd en is er geen controlegroep.

In *fase II* onderzoekt men vooral de werkzaamheid van het nieuwe product bij verschillende doseringen en toedieningsmodaliteiten. De onderzoeksgroepen bestaan meestal uit een 20-tal personen met een bepaalde aandoening. Ook in deze fase

worden de proefpersonen vaak niet aselekt verdeeld over een interventie- en een controlegroep.

In *fase III* vindt een uitgebreide klinische studie plaats. Hierbij zijn grotere groepen proefpersonen betrokken en worden de werkzaamheid en veiligheid verder onderzocht. Dit gebeurt meestal in de vorm van een RCT. Proefpersonen worden aselekt ingedeeld in verschillende onderzoeksgroepen. Men vergelijkt het effect met een placebo of standaardbehandeling.

Fase IV studies worden pas uitgevoerd als het geneesmiddel officieel geregistreerd en op de markt gebracht is. In deze fase wordt bijvoorbeeld het optreden van ongewenste effecten en het effect van langdurig gebruik opgevolgd. Fase IV studies worden ook wel 'postmarketing surveillance studies' genoemd. Dit zijn geen RCT's.

Een **controlled clinical trial** is een klinische studie waarbij men een of meer interventiegroepen vergelijkt met een of meer controlegroepen, die de interventie niet krijgen.

Een **randomised controlled trial (RCT)** is een controlled clinical trial, waarbij de onderzoekspopulatie op aselekte wijze is verdeeld in een interventiegroep en een controlegroep. In een placebogecontroleerde RCT krijgt de controlegroep een placebo toegediend.

Cluster randomisatie

Zie randomisatie.

Cochrane Collaboration

De Cochrane Collaboration is een internationale organisatie, die zich tot doel stelt om ondersteuning te bieden bij het nemen van geïnformeerde beslissingen over gezondheidszorg. Zij doet dit door systematische reviews en meta-analyses te publiceren over de effecten van gezondheidsinterventies.

Cochrane Library

De Cochrane Library is een initiatief van de Cochrane Collaboration en bestaat uit een aantal databanken. De Cochrane Database of Systematic Reviews (CDSR) bevat alle Cochrane Reviews.

Cochrane Review

Dit is een systematische review (of meta-analyse) die is uitgevoerd in het kader van de Cochrane Collaboration. Deze reviews volgen een vast onderzoeksprotocol dat is opgesteld door de Cochrane Collaboration. In deze reviews zijn data uit de afzonderlijke studies vaak statistisch gepoold tot een meta-analyse.

Concealment of allocation

Bij een RCT worden de personen in de onderzoekspopulatie aselekt ingedeeld in interventiegroep(en) en controlegroep(en). 'Concealment of allocation' refereert aan het geheim houden of blinderen van deze toewijzing van patiënten aan de verschillende onderzoeksgroepen. Degene die de patiënten indeelt weet niet in welke groep ze terechtkomen. Op deze wijze voorkomt men dat er een selectie optreedt van patiënten in de onderzoeksgroepen (allocation bias).

Conflict of interest [belangenvermenging]

Hierbij vermelden auteurs van een publicatie hun persoonlijke financiële of andere belangen, die de resultaten of de interpretatie van hun studie zouden kunnen beïnvloeden.

Consensus

Een overeenkomst van meningen van personen over eenzelfde onderwerp.

DDD [Defined Daily Dose]

DDD is de gemiddelde dagelijkse dosis van een geneesmiddel voor de voornaamste indicatie bij volwassenen.

Doelmatigheid [efficiency]

De doelmatigheid of efficiëntie (efficiency) van een behandeling of interventie verwijst naar het bereikte effect in relatie tot de benodigde middelen (geld, tijd, personen). Dit wordt ook wel uitgedrukt als de kosten per eenheid van het gewenste effect. Een efficiënte behandeling of interventie geeft het gewenste effect tegen een minimum aan kosten.

Doeltreffendheid [effectiveness]

De doeltreffendheid (effectiveness) van een geneesmiddel of interventie verwijst naar de mate waarin het doel van de behandeling wordt bereikt in de alledaagse praktijk (dat wil zeggen buiten de condities van een klinisch-epidemiologisch onderzoek).

EBM

Evidence-Based Medicine is het oordeelkundig gebruik maken van systematisch verzamelde resultaten van wetenschappelijk onderzoek bij het nemen van beslissingen voor individuele patiënten. EBM in de praktijk toepassen impliceert het integreren van klinische expertise met beschikbaar wetenschappelijk bewijs, waarbij de voorkeur en opvattingen van de patiënt een belangrijke rol spelen (*Sackett et al.*).

Eindpunt [outcome]

Datgene wat men meet om het resultaat van een interventie te meten wordt eindpunt of uitkomst genoemd. Naar gelang de aard van het gekozen eindpunt kan men een onderscheid maken in **harde eindpunten** zoals dood of aangetoonde morbiditeit en **intermediaire** of **surrogaat eindpunten**. De intermediaire eindpunten zijn afgeleide parameters die meestal alleen indirect samenhangen met harde eindpunten. Serumcholesterolwaarden bijvoorbeeld, kunnen beschouwd worden als intermediaire eindpunten in onderzoek naar het effect van medicatie, waarbij cardiovasculair overlijden een harde uitkomst is. Wanneer er geen directe relatie is aangetoond tussen het intermediaire eindpunt en relevante harde eindpunten, is de waarde van studies die slechts intermediaire eindpunten weergeven zeer beperkt.

Equity

Deze term uit de (gezondheids)economie impliceert dat gezondheidszorg beschikbaar is voor iedereen (billijkheid). Dat wil zeggen dat er geen verschillen bestaan in de toegankelijkheid en kwaliteit van de zorg en in de gezondheid van een bevolking.

Experimenteel onderzoek

In tegenstelling tot observationeel onderzoek grijpt men bij een experimentele onderzoeksopzet in de 'natuurlijke gang van zaken' in. Een randomised controlled trial (RCT) is een voorbeeld van een experimentele onderzoeksopzet.

Interventiestudie

Een interventiestudie is een experimenteel onderzoek waarbij men het effect van een experimentele interventie (bijvoorbeeld een geneesmiddel) onderzoekt. Een (randomised) controlled trial is een voorbeeld van een interventiestudie.

Meta-analyse

Een meta-analyse is een systematische review waarin de resultaten van een aantal vergelijkbare klinische studies worden gebundeld (gepooled) en herberekend. Hierdoor wordt het mogelijk om met een grotere nauwkeurigheid een schatting te doen van het effect van een interventie of behandeling. Zie ook pooling.

Number Needed to Harm [NNH]

Dit getal geeft aan hoeveel behandelde personen aanleiding geven tot één negatieve uitkomst (een schadelijke nevenwerking of dood) ten gevolge van een interventie.

$$\text{NNH} = 1 / \text{ARR} (\%) \text{ van de negatieve uitkomst} \times 100$$

Number Needed to Treat [NNT]

Dit getal geeft aan hoeveel personen moeten worden behandeld gedurende de bestudeerde termijn om één extra geval van een bepaalde ziekte te genezen of te voorkomen.

$$\text{NNT} = 1 / \text{ARR} (\%) \times 100$$

Observationeel onderzoek

Onderzoek waarbij geen interventie of experimentele behandeling wordt getoetst noemt men observationeel of beschrijvend onderzoek (bijvoorbeeld cohortonderzoek of case-control onderzoek).

Peer review

Hierbij beoordelen collega's uit de eigen beroepsgroep op kritische wijze elkaars klinische handelen, onderzoeksprotocollen, of artikelen en abstracts die ter publicatie worden aangeboden aan tijdschriften of congressen.

Placebo

Een placebo interventie is een interventie die volledig gelijk is aan de te onderzoeken interventie, maar zonder het werkzame deel. Wanneer het effect van een geneesmiddel wordt onderzocht dient de placebo dezelfde kleur, smaak, grootte, consistentie en wijze van toediening te hebben als het te onderzoeken geneesmiddel. Het placebo-effect is het effect dat niet verklaard kan worden op basis van een pa-

thofysiologisch model, maar wordt toegeschreven aan andere factoren, zoals het natuurlijke verloop van de klacht of aandoening, de arts-patiënt relatie, of de verwachting (door patiënt, arts of onderzoeker) dat een bepaalde interventie of behandeling effect zal hebben.

Pooling

Onder pooling verstaat men het combineren van de resultaten van verschillende studies voor statistische bewerking in een meta-analyse om te komen tot een schatting van het globale effect. Zie meta-analyse.

Power

De power is de mogelijkheid van een studie om de nulhypothese te verwerpen (en een eventueel werkelijk bestaande associatie aan te tonen). De power wordt bepaald door een aantal factoren, zoals het voorkomen van de bestudeerde aandoening (de prevalentie), de grootte van het effect, de onderzoeksopzet en de grootte van de steekproef. Bij aanvang van een studie kiezen de onderzoekers zelf de gewenste power om hiermee de benodigde steekproefgrootte te berekenen. Meestal wordt een power van 80% als minimale vereiste beschouwd. Dit betekent dat er 80% kans is dat de studie een effect kan aantonen.

P-waarde

De p-waarde is een maat voor de waarschijnlijkheid (probability) dat het gevonden resultaat van een onderzoek berust op toeval. De p-waarde is een maat voor de kans dat de nulhypothese ten onrechte is verworpen (en het gevonden verschil tussen onderzoeksgroepen dus in werkelijkheid op toeval berust). De p-waarde is een getal tussen 0 en 1 en wordt berekend met behulp van een statistische toets. Bij een p-waarde van 1 kunnen we aannemen dat het gevonden resultaat op toeval berust. Met een p-waarde dichtbij 0 kunnen we ervan uitgaan dat de gevonden waarde een werkelijke associatie aanduidt. Gewoonlijk hanteert men $p=0,05$ als grens van statistische significantie. Indien $p < 0,05$ dan is de kans dat het gevonden resultaat aan het toeval is te wijten (en we de nulhypothese ten onrechte verwerpen) kleiner of gelijk aan 5%, dit noemt men 'statistisch significant'. Als een resultaat statistisch significant is, betekent dit niet automatisch dat het ook van belang is voor de patiënt.

Randomisatie

Toewijzing door middel van randomisatie betekent dat iedere aan het onderzoek deelnemende persoon evenveel kans heeft om in een van de onderzoeksgroepen terecht te komen. Wanneer randomisatie op het niveau van groepen individuen (in plaats van aparte individuen) gebeurt spreekt men van **cluster randomisatie**.

RCT Randomized controlled trial

Zie clinical trial.

Risico [risk, hazard]

Een risico is een kans op een gebeurtenis.

In een interventieonderzoek (RCT), waarin men het effect van een interventie onderzoekt op een bepaalde uitkomst (zoals bijvoorbeeld 'verdwijnen van de koorts') kan men de kans (het risico) op deze uitkomst berekenen voor de interventiegroep en de controlegroep.

Het risico van de uitkomst in de interventiegroep is $R_i = a / a + b$. Het risico van diezelfde uitkomst in de controlegroep is $R_c = c / c + d$.

Berekening van het risico in een RCT

	Geen koorts	Koorts
Interventiegroep	a	b
Controlegroep	c	d

Relatief Risico (RR)

Het quotiënt van twee (absolute) risico's noemt men het relatieve risico RR (R_i/R_c).

In een interventieonderzoek is dit relatieve risico een schatting van het aantal malen dat de kans op een uitkomst (bijvoorbeeld 'verdwijnen van de koorts') in de interventiegroep groter ($RR > 1$) of kleiner ($RR < 1$) is dan in de controlegroep. RR heeft geen dimensie.

Risicoverschil

Het risicoverschil is het verschil tussen het risico van een uitkomst in de interventiegroep en in de controlegroep ($R_i - R_c$). Bij afname van het risico noemt men dit risicoverschil *absolute risicoreductie* (**ARR**) (absolute risk reduction), bij toename *absolute risicotoename* (**ARI**) (absolute risk increase). Het absolute risicoverschil (ARR of ARI) is $|R_i - R_c|$.

Relatieve risicoreductie (RRR)

Een relatieve maat voor risicodaling is de relatieve risicoreductie (RRR). Dit is de verhouding van het risicoverschil tussen de interventiegroep en de controlegroep ten opzichte van het risico in de controlegroep. Deze uitkomstmaat geeft de proportionele reductie weer van het risico van een uitkomst door de interventie. De RRR wordt berekend als $|R_i - R_c| / R_c$ ofwel ARR / R_c .

Statistische toetsen

Wanneer men in een onderzoek een verschil tussen de onderzoeksgroepen vaststelt voor een bepaalde uitkomst, kan men met behulp van statistische toetsen nagaan hoe groot de kans is dat het gevonden verschil op toeval berust.

Steekproef [sample]

Een steekproef is een geselecteerde groep personen uit een populatie.

Werkzaamheid [efficacy]

De werkzaamheid (efficacy) van een geneesmiddel of interventie verwijst naar het gunstige effect ervan in optimale omstandigheden. De werkzaamheid wordt idealiter vastgesteld in een randomised controlled trial (RCT).

Publications in international peer reviewed journals

- Matthys J, De Meyere M, van Driel ML, De Sutter A. Differences among international pharyngitis guidelines: not just academic. *Ann Fam Med* 2007 (*accepted for publication*)
- van Driel ML, De Sutter A, De Maeseneer J, Christiaens T. Searching for unpublished trials in Cochrane reviews: is it worth the effort? A retrospective review. (*submitted*)
- van Driel ML, Coenen S, Dirven K, Lobbestael J, Janssens I, Van Royen P, Haaijer-Ruskamp FM, De Meyere M, De Maeseneer J, Christiaens T. What is the role of quality circles in strategies to optimise antibiotic prescribing? A pragmatic cluster randomised controlled trial in primary care. *Qual Saf Health Care* 2007;16(3) (*in press*)
- van Driel ML, Vander Stichele R, De Sutter A, De Maeseneer J, Christiaens T. Medical evidence and health policy: a marriage of convenience? The case of proton pump inhibitors. *J Eval Clin Practice* 2007;13 (*in press*)
- van Driel ML, De Sutter A, Deveugele M, Peersman W, Butler CC, De Meyere M, De Maeseneer J, Christiaens T. Are sore throat patients who hope for antibiotics actually asking for pain relief? *Ann Fam Med* 2006;4:494-9.
- De Sutter AI, Lemiengre MB, Van Maele GO, Van Driel M, De Meyere M, Christiaens T, De Maeseneer J. Predicting prognosis and effect of antibiotic treatment in rhinosinusitis. *Ann Fam Med* 2006;4:486-93.
- van Driel ML, Chevalier P. Lipid lowering drugs in diabetes. Abstract was misleading [letter]. *BMJ* 2006;332:1272.
- Deveugele M, Derese A, De Maesschalck S, Willems S, Van Driel M, De Maeseneer J. Teaching communication skills to medical students, a challenge in the curriculum? *Patient Educ Counsel* 2005;58:265-70.
- van Driel ML, De Sutter AI, Christiaens TCM, De Maeseneer JM. Quality of care: the need for medical, contextual and policy evidence in primary care. *J Eval Clin Pract* 2005;5:417-29.
- Mieke van Driel, Thierry Christiaens, Veerle Piessens, Patricia Sunaert, Luc Feyen. Misleading conclusions of PROactive study [e-letter]. *Lancet* October 24 2005.

Available at: www.thelancet.com/journals/lancet/article-PIIS0140673605675289/-comments?action=view&totalComments=6

- Janssens I, De Meyere M, Habraken H, Soenen K, van Driel M, Christiaens T, Bogaert M. Barriers to academic detailers: A qualitative study in general practice. *Eur J Gen Pract* 2005;11(2):59-63.
- Lemiengre M, van Driel M, Chevalier P, De Meyere M, Christiaens T. New analyses of Heart Protection Study [letter]. *Lancet* 2004;363:1827-8.
- De Maeseneer JM, van Driel ML, Green LA, van Weel C. Bridging the gap between evidence and patient care: the need for research in primary care. *Lancet* 2003;362:1314-9.
- An I De Sutter, Marc De Meyere, Mieke van Driel, Thierry Christiaens, and Jan De Maeseneer. Antibiotics for acute rhinitis: effective? [letter] *BMJ* 2003;327:193E.
- Habraken H, Janssens I, Soenen K, van Driel M, Lannoy J, Bogaert M. Pilot study on the feasibility and acceptability of academic detailing in general practice. *Eur J Clin Pharmacol* 2003;59(3):253-60.
- Dirckx K, van Driel M, Habraken H, De Meyere M. Hoesten bij kleine kinderen: ongerustheid van ouders leidt tot onnodig medicatiegebruik! *Tijdschrift voor Jeugdgezondheidszorg* 2003;35:93-8.
- van Driel M, De Maeseneer J. Evidence-based medicine versus evidence-based policy: family medicine in the frontline [Editorial]. *Eur J Gen Pract* 2003;9:124-5.
- De Sutter AI, De Meyere MJ, Christiaens TC, van Driel ML, Peersman W, De Maeseneer JM. Symptoms don't predict response to antibiotics – Reply. *J Fam Pract* 2002;51(8):719.
- De Sutter AI, De Meyere MJ, Christiaens TC, van Driel ML, Peersman W, De Maeseneer JM. Does amoxicillin improve outcomes in patients with purulent rhinorrhea? A pragmatic randomized double-blind controlled trial in family practice. *J Fam Pract* 2002;51:317-23.
- van Driel M, Christiaens T, De Maeseneer J. Evidence-based medicine and the patient's perspective [Editorial]. *Eur J Gen Pract* 2001;7:4-5.

Publications in national peer reviewed journals

- De Maeseneer J, van Driel M, Green L, van Weel C. Onderzoek in de eerste lijn. De nood aan medische, contextuele en beleidsgebonden evidentie. *Huisarts Nu* 2005;34:263-71.
- van Driel M, Chevalier P, Soenen K, Habraken H, Boudry D, Janssens I, Chapelle F, Verpooten GA, Bogaert M. Voorbereiding van consensusvergaderingen in België. *Huisarts Nu* 2004;33:619-22.
- Dirckx K, van Driel M, Habraken H, De Meyere M. Wat is de attitude van ouders ten opzichte van medicatiegebruik bij hun kind dat hoest? Een kwantitatief, beschrijvend onderzoek. *Huisarts Nu* 2003;32:171-9.
- De Sutter A, De Meyer M, Christiaens T, van Driel M, De Maeseneer J, Peersman W. Het effect van amoxicilline bij purulente rhinorree. Een pragmatische, gerandomiseerde, dubbelblinde en placebogecontroleerde studie in de huisartspraktijk. *Huisarts Nu* 2003;32:91-100.
- van Driel M, Boffin N, Verdonck P. Het basistakenpakket: wat vinden huisartsen ervan? Een verslag van drie bevragingen bij Vlaamse huisartsen. *Huisarts Nu* 2001;30:295-301.

Publications in Minerva,

Belgian journal for evidence-based medicine (www.minerva-ebm.be)

- Chevalier P, van Driel M. Hypolipemiërende middelen: verschil in effectiviteit tussen patiënten met of zonder diabetes? *Minerva* 2007;6(2):19-21.
- Chevalier P, van Driel M, Vermeire E. Systematische reviews en meta-analyses: een inleiding [Editoriaal]. *Minerva* 2007;6(2):18.
- Chevalier P, van Driel M. Coxibs, andere NSAID's en cardiovasculair risico. *Minerva* 2006;5(10):161-3.
- Chevalier P, van Driel M. De valkuilen van subgroepanalyses [Editoriaal]. *Minerva* 2006;5(10):154.
- Laekeman G, van Driel M. Door trouw aan placebo leef je langer [Editoriaal]. *Minerva* 2006;5(9):137.
- van Driel M, Christiaens T. Pioglitazon bij diabetes: ongefundeerd optimisme. *Minerva* 2006;5(5):74-6.

- Numans ME, van Driel M. Behandeling van H. pylori-negatieve dyspepsie. *Minerva* 2006;5(6):87-9.
- Lemiengre M, van Driel M. Marketing van primaire en secundaire eindpunten [Editoriaal]. *Minerva* 2006;5(5):69.
- Coenen S, van Driel M. Antibiotica bij acute lage luchtweginfecties: onmiddellijk, later of niet voorschrijven? *Minerva* 2006;5(4):63-6.
- Lapeere H, van Driel M. Hoofdluis mechanisch of chemisch bestrijden? *Minerva* 2006;5(4):61-3.
- van Driel M. Intra-articulair hyaluronzuur bij gonartrose. *Minerva* 2006;5(3):44-6.
- van Driel M en Chevalier P. Evaluatie van nieuwe geneesmiddelen: 'superieur', 'equivalent' of 'niet-inferieur'? [Editoriaal] *Minerva* 2005;4(10):154.
- van Driel M. "Bijna helemaal waar": het verhaal van de coxibs [Editoriaal]. *Minerva* 2003;2(8):120-1.
- van Driel M. Coxibs versus paracetamol bij gonartrose. *Minerva* 2003;2(8):122-3.
- van Driel M, Chevalier P, Janssens I. Cox-2-selectieve NSAIDs: evaluatie na vijf jaar. *Minerva* 2003;2(8):126-9.
- van Driel M. Preventie van trombo-embolie bij immobilisatie van een been. *Minerva* 2003;2(3):42-3.
- van Driel M. Heeft antibiotische profylaxe zin na een tekenbeet? *Huisarts Nu (Minerva)* 2002;31(4):213-4.
- van Driel M, Lemiengre M, Christiaens T. Hypercholesterolemie: 'state of the art'. *Huisarts Nu (Minerva)* 2002;31(2):101-4.
- van Driel M. *Minerva*: stap voor stap van wetenschap naar praktijk [Editoriaal]. *Minerva* 2002;1(2):18-20.
- Lemiengre M, van Driel M. Vaccineren tegen influenza en pneumokokken bij 65-plussers? *Huisarts Nu (Minerva)* 2001;30(8):383-4.
- van Driel M. Hoe veilig zijn de nieuwe COX-2-selectieve NSAID's? *Huisarts Nu (Minerva)* 2001;30(6):263-8.
- van Driel M. Borstkanker en gezondheidsbeleid [Editoriaal]. *Huisarts Nu (Minerva)* 2001;30(4):168-9.
- van Driel M, Vermeire E. Is borstkankerscreening verantwoord? *Huisarts Nu (Minerva)* 2001;30(4):170-3.
- van Driel M. Is borstkankerscreening minder gevoelig bij hormonale substitutie? *Huisarts Nu (Minerva)* 2001;30(4):182-3.

- Lemiengre M, van Driel M. Voorkomt risedronaat fracturen bij vrouwen met wervelfracturen? Huisarts Nu (Minerva) 2001;30(2):72-6.
- van Driel M. Verhoogd risico op kanker na IVF? Huisarts Nu (Minerva) 2001;30(1):45-6.
- van Driel M. Toegevoegde waarde van tamoxifen bij borstkanker? Huisarts Nu (Minerva) 2001;30(1):41-2.
- van Driel M. Evidence-based medicine: het perspectief van de patiënt [Editoriaal]. Huisarts Nu (Minerva) 2000;29(9):412-3.
- van Driel M. Pneumokokkenvaccinatie. Huisarts Nu (Minerva) 2000;29(8):366-9.
- van Driel M. Marketingstrategieën: een tip van de sluier opgelicht [Editoriaal]. Huisarts Nu (Minerva) 2000;29(5):222-4.
- van Driel M, Art B, Soenen K. De nieuwe COX-2 selectieven: een aanwinst? Huisarts Nu (Minerva) 2000;29(5):225-9.
- van Driel M. Mirena®: een alternatief voor hysterectomie? Minerva Kort. Huisarts Nu (Minerva) 2000;29(1):68-9.
- Lemiengre M, Christiaens T, van Driel M. Hypercholesterolemie, vissen in troebel serum. Huisarts Nu (Minerva) 1999;28(9):397-401.
- van Driel M. 'Evidence': niet altijd 'evident' [Editoriaal]. Huisarts Nu (Minerva) 1999;28(6):242-3.
- van Driel M. Minerva Kort. Huisarts Nu (Minerva) 1999;28(6):256.
- Wens J, Vermeire E, van Driel M. The United Kingdom Prospective Diabetes Study: onderzoeksopzet. Huisarts Nu (Minerva) 1999;28(3):122-4.
- van Driel M. MINERVA stap voor stap [Editoriaal]. Huisarts Nu (Minerva) 1999;28(2):74-6.
- van Driel M. De meta-analyse mammografisch doorgelicht [Editoriaal]. Huisarts Nu (Minerva) 1998;27(8):268-9.

Books

- van Driel M. Minerva Glossaire des termes utilisés en Evidence-Based Medicine. Gent: Minerva, 2004. ISBN 90-80856-21-5.
- van Driel M. Minerva Verklarende woordenlijst voor Evidence-Based Medicine (2^e gewijzigde druk). Gent: Minerva, 2003. ISBN 90-76023-06-5.

- van Driel M, Provoost S, van Paepegem T, De Meyere M. Op wetenschappelijke evidentie gebaseerde zorg: van theorie naar praktijk: een tweevoudige strategie. Gent: Academia Press, 2003.
 - Van Driel M. Evidence-based medicine. In: De Welzijnsgids. Mechelen: Kluwer, September 2003.
 - Lemiengre M, van Driel M. Van vermeende zekerheid naar zekere waarschijnlijkheid. Evidence-based medicine in historisch en praktisch perspectief. In: François L en De Maeseneer J (red.). Omzien naar de toekomst. Huisartsgeneeskunde op de drempel van de 21e eeuw. Gent: Vakgroep Huisartsgeneeskunde en Eerstelijnsgezondheidszorg, 2000; pp 111-122.
 - van Driel M. Hoofdstuk 21. De apotheek: overzicht van medicijnen. In: Coene EH (eindredactie). Depressie Zelfzorgboek. Amsterdam: Stichting September, 1999.
 - Protocol Lyme ziekte. In opdracht van Landelijke Coördinatiestructuur Infectieziekten (LCI). Ministerie van VWS. Rijswijk, Nederland, 1998.
 - van Driel M. Hoofdstuk 2. Behandeling. In: Coene EH (eindredactie). Multiple Sclerose Zorgmap. Amsterdam: Stichting Augustus, 1997.
 - van Driel M, Greber E, Hamelynck A, Werkman J. Is dit nog wel hulp? Seksisties gedrag en seksueel geweld door hulpverleners. Handleiding bij de opvang van vrouwen. Utrecht: Vrouwegezondheidscentrum, 1986.
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