



Nijmegen Institute for
Infection, Inflammation
& Immunity

Guidelines for antibiotic use

Development of Clinical Practice Guidelines
according to the AGREE II methodology

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Major objective of this presentation

- To familiarise members of the working groups with the AGREE methodology and its implications for the development of clinical practice guidelines.



“The profession has placed high value on developing the basic science of medicine; it has not emphasised the process by which the science is translated into practice.”

Guidelines

- Why?
- On which topic?
- For whom?
- Development method
- Are they known?
- Are they accepted?
- Are they adopted?
- What is the effect?

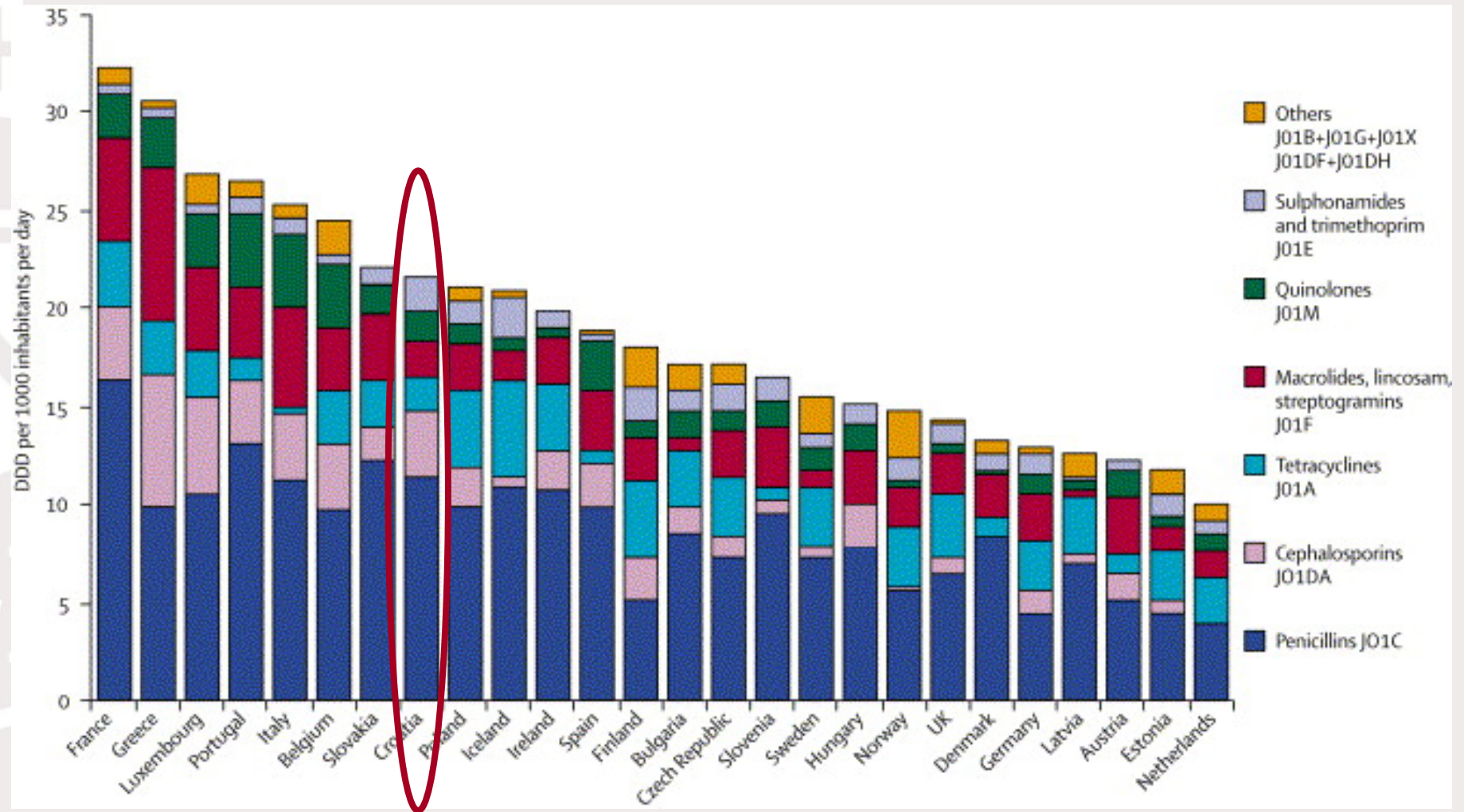


Why?

- To improve
- To support
- To deliver
- To Increase patient
- **More**

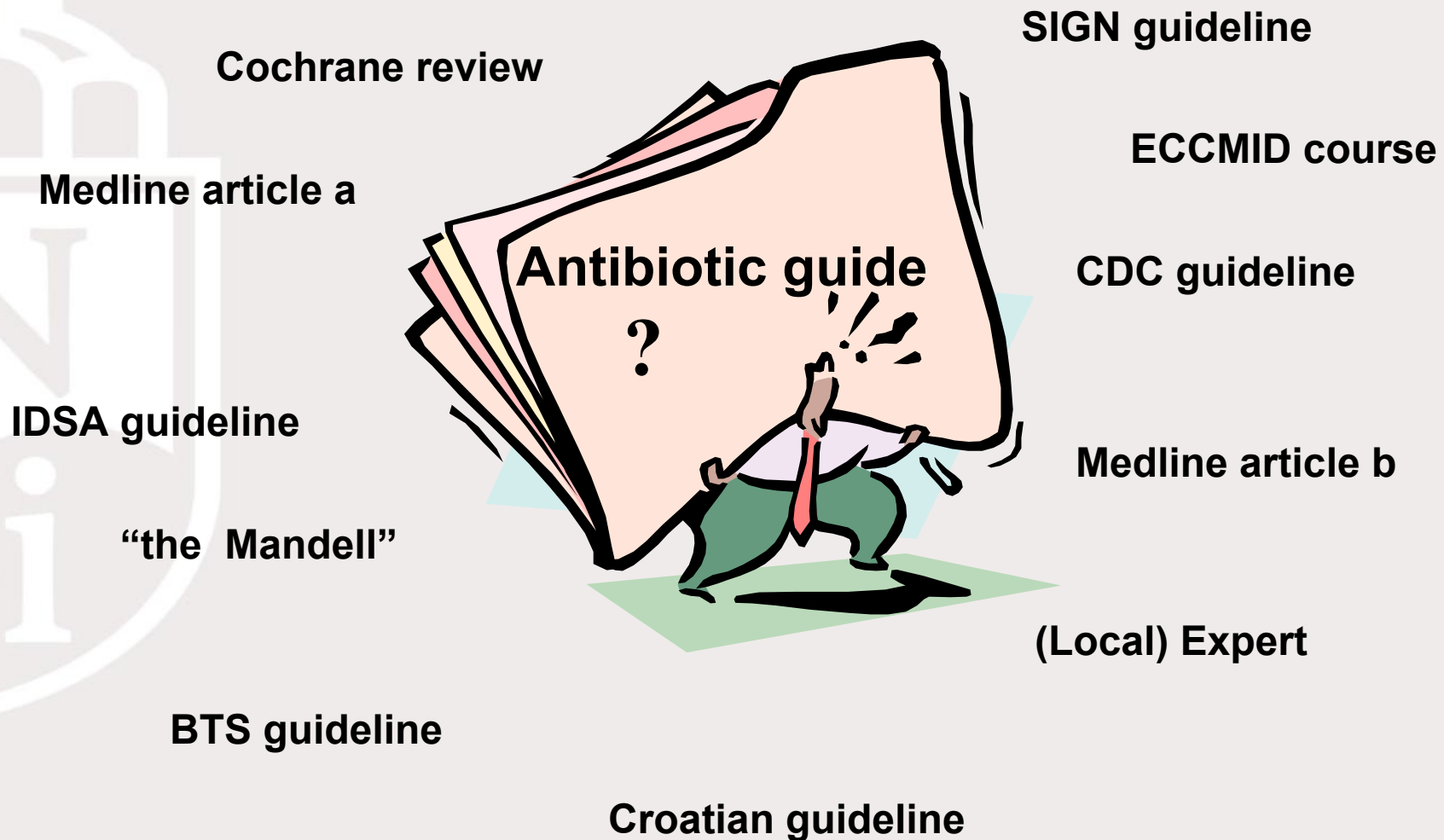
- To improve the quality of care
- To support clinical decisions
- To diminish unwanted diversity of practice
- To Increase transparency of care (for the doctor and the patient)
- More specific: to contain/limit resistance
to increase cost effectiveness

Outpatient antibiotic use in Europe




Lancet 2005; 365: 579-587

Antibiotic policy: Sources





Are there any barriers to guidelines?

- 
- Inquiry in The Netherlands: more than 75 percent of respondents does not have (any) objections towards clinical practice guidelines

Van Everdingen, Medisch Contact 2003;58: p. 12-21.

- Italian doctors consider guidelines as forced upon them and as an instrument for cost containment, more than a support for clinical practice.

Formoso et al. Arch Intern Med, 2001. 161: p. 2037-2042.

More this afternoon....



What do Croatians think about
guidelines?



On which topic?

Topics

- Most frequent diseases
- Less frequent diseases, but serious outcome
- Diseases for which there is an unwanted variation in treatment

Topics of infectious diseases guidelines

- Empirical therapy, Prophylaxis, Diagnostics
- Controversies about the best treatment
- Examples of SWAB guidelines:
 - CAP, sepsis, endocarditis, UTI, diarrhoea, meningitis....
 - But also selective bowel decontamination, MRSA carriage...

Consult with as large a group as possible !



How?



Method of Development of a guideline

- Design
- Distribution
- Implementation
- Independence

**APPRAISAL OF GUIDELINES
for RESEARCH & EVALUATION II**



AGREE II

INSTRUMENT

The AGREE Next Steps Consortium

May 2009



ii) Who can use the AGREE II?

The AGREE II is intended to be used by the following stakeholder groups:

- by **health care providers** who wish to undertake their own assessment of a guideline before adopting its recommendations into their practice;
- by **guideline developers** to follow a structured and rigorous development methodology, to conduct an internal assessment to ensure that their guidelines are sound, or to evaluate guidelines from other groups for potential adaptation to their own context;
- by **policy makers** to help them decide which guidelines could be recommended for use in practice or to inform policy decisions; and
- by **educators** to help enhance critical appraisal skills amongst health professionals and to teach core competencies in guideline development and reporting.

site <http://www.agreetrust.org>

AGREE II Instrument

- ✓ 23 items
- ✓ 7-points-scale

**General
judgment**

Manual

Six Domains

1. Scope and purpose (3)
2. Stakeholder involvement (3)
3. Rigour of development (8)
4. Clarity of presentation (3)
5. Applicability (4)
6. Editorial independence (2)

II. Structure and Content of the AGREE II

The AGREE II consists of 23 key items organized within 6 domains followed by 2 global rating items ("Overall Assessment"). Each domain captures a unique dimension of guideline quality.

Domain 1. Scope and Purpose is concerned with the overall aim of the guideline, the specific health questions, and the target population (items 1-3).

Domain 2. Stakeholder Involvement focuses on the extent to which the guideline was developed by the appropriate stakeholders and represents the views of its intended users (items 4-6).

Domain 3. Rigour of Development relates to the process used to gather and synthesize the evidence, the methods to formulate the recommendations, and to update them (items 7-14).

Domain 4. Clarity of Presentation deals with the language, structure, and format of the guideline (items 15-17).

Domain 5. Applicability pertains to the likely barriers and facilitators to implementation, strategies to improve uptake, and resource implications of applying the guideline (items 18-21).

Domain 6. Editorial Independence is concerned with the formulation of recommendations not being unduly biased with competing interests (items 22-23).

Overall assessment includes the rating of the overall quality of the guideline and whether the guideline would be recommended for use in practice.



DOMAIN 1. SCOPE AND PURPOSE

1. The overall objective(s) of the guideline is (are) specifically described.
2. The health question(s) covered by the guideline is (are) specifically described.
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.

BTS Guidelines for the Management of Community Acquired Pneumonia in Adults

Thorax 2001;56;1-64
doi:10.1136/thorax.56.suppl_4.iv1

A large, light-colored, stylized lowercase letter 'i' is positioned on the left side of the slide, partially overlapping the text area. It has a circular dot above it and is set within a shield-like shape.

1.6 What patient populations are included and excluded?

Our guidelines address the management of unselected adults with CAP who are managed by their general practitioner or admitted to hospital as an emergency.

They are *not* aimed at the much larger group of adults with non-pneumonic lower respiratory tract infection, including illnesses labelled as acute bronchitis, acute exacerbations of chronic obstructive pulmonary disease (COPD), or “chest infections”.



STICHTING WERKGROEP ANTIBIOTICABELEID

SWAB guidelines for

Antibacterial therapy of adult patients with Sepsis

Dutch Working Party on Antibiotic Policy (SWAB)

Preparatory Committee

SWAB board, Chair

Coordinator

Dutch Society for Infectious Diseases (VIZ)

Dutch Society for Internal Medicine (NIV)

Dutch Society for Microbiology (NVMM)

Dutch Association of Hospital Pharmacists (NVZA)

Dutch Society for Surgery (NVH)

Dutch Society for Intensive Care (NVIC)

Dutch Society for Haematology (NVvH)

Prof. dr I.C. Gyssens

H.I. Bax

Dr E.F. Schippers, S. van Assen

Dr E.F. Schippers, S. van Assen

Dr C.W. Ang, Dr P. Sturm

Dr Y.G. van der Meer

Dr M.A. Boermeester

Dr J.A. Schouten, Dr P. Pickkers

Dr J.J.W.M. Janssen

Dr N. Blijlevens

DOMAIN 2. STAKEHOLDER INVOLVEMENT

4. The guideline development group includes individuals from all relevant professional groups.
5. The views and preferences of the target population (patients, public, etc.) have been sought.
6. The target users of the guideline are clearly defined.



STICHTING WERKGROEP ANTIBIOTICABELEID

SWAB guidelines for

Antibacterial therapy of adult patients with Sepsis

Scope of the guideline

This guideline concerns antimicrobial therapy in all adult patients with sepsis. The performed literature searches included studies on adult patients only. Therefore, this guideline can not indiscriminately be applied to children with sepsis.

In addition, this guideline does not cover the following:

- Other treatment components of sepsis such as volume resuscitation, inotropics, corticosteroids and activated protein C
- Antibiotic therapy of sepsis associated with indwelling intravascular devices which are not removed (tunnelled catheter or port-a-cath) and which need a different approach. A recent international guideline is available (2).
- Diagnostic measurements, such as the use of biomarkers

DOMAIN 3. RIGOUR OF DEVELOPMENT

7. Systematic methods were used to search for evidence.
8. The criteria for selecting the evidence are clearly described.
9. The strengths and limitations of the body of evidence are clearly described.
10. The methods for formulating the recommendations are clearly described.
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.
12. There is an explicit link between the recommendations and the supporting evidence.
13. The guideline has been externally reviewed by experts prior to its publication.
14. A procedure for updating the guideline is provided.



Dimensions of 'evidence'

- | | |
|--------------|--|
| 1. Level | Study type (RCT, TS etc) |
| 2. Quality | Validity within the design |
| 3. Precision | Confidence interval
/ p value |
| 4. Size | Size of the effect and the clinical
relevance |
| 5. Relevance | Clinically relevant outcome
measure and follow-up |

Methodological quality of individual studies ⁽¹⁾

	Intervention	Aetiology, prognosis
A1	Systematic review of at least two independent A2-level studies	
A2	Randomised Controlled Trial (RCT) of sufficient methodological quality and power	Prospective cohort study with sufficient power and with adequate confounding corrections
B	Comparative Study lacking the same quality as mentioned at A2 (including patient-control and cohort studies)	Prospective cohort study lacking the same quality as mentioned at A2, retrospective cohort study or patient-control study
C	Non-comparative study	
D	Expert opinion	

Table 1b

Level of evidence of conclusions ⁽¹⁾

	Conclusions based on
1	Study of level A1 or at least two independent studies of level A2
2	One study of level A2 or at least two independent studies of level B
3	One study of level B or C
4	Expert opinion



STICHTING WERKGROEP ANTIBIOTICABELEID

SWAB guidelines for

Antibacterial therapy of adult patients with Sepsis

General Conclusions

<i>Level 1</i>	<ul style="list-style-type: none">· Ineffective antibacterial therapy in patients with bacteraemia/sepsis is associated with increased mortality. <p>A2 Ortega; Garnacho-Monero; Harbarth; Valles; Ibrahim; Leibovici^(51, 207, 210, 211, 213, 215)</p> <p>B Trecarichi; Micek; MacArthur; Kang; Harbarth; Kuikka; Maki^(24, 173, 206, 208, 209, 212, 214)</p>
<i>Level 2</i>	<ul style="list-style-type: none">· Ineffective empirical antibacterial therapy against <i>P.aeruginosa</i> and <i>E. coli/K. pneumoniae</i> was not associated with higher in-hospital mortality. <p>B Osih; Thom^(216, 217)</p>

*Table 1 Brief description of the generic levels of evidence and guideline statement grades used**

<i>Evidence level</i>	<i>Definition</i>	<i>Guideline statement grade</i>
Ia	A good recent systematic review of studies designed to answer the question of interest	A+
Ib	One or more rigorous studies designed to answer the question, but not formally combined	A–
II	One or more prospective clinical studies which illuminate, but do not rigorously answer, the question	B+
III	One or more retrospective clinical studies which illuminate, but do not rigorously answer, the question	B–
IVa	Formal combination of expert views	C
IVb	Other information	D

*A fuller description is given in section 1 and in appendices 1–4.

Search strategy



Antibiotics for exacerbation of COPD

Basic search strategy using Medline:

((("Pulmonary Disease, Chronic Obstructive"[MeSH]) OR (chronic bronchitis) OR (pulmonary emphysema) OR (chronic obstructive bronchitis*) OR (chronic airflow limitation*) OR (chronic airflow obstruction*) OR (obstructive airways disease*) OR (chronic obstructive lung disease*)))

AND

((("Anti-Bacterial Agents"[MeSH] OR "Anti-Bacterial Agents"[Pharmacological Action]) OR (antibiotic*))

AND

((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR "clinical trial"[tw] OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]))

AND

((mask*[tw] OR blind*[tw])) OR "latin square"[tw] OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR comparative study[mh] OR evaluation studies[mh] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR control*[tw] OR prospectiv*[tw] OR volunteer*[tw]) NOT (animal[mh] NOT human[mh])) Limits: English



Thorax 2001;**56** (suppl IV)

CAP in adults over 16 years. Initial searches were conducted on Medline (1966 onwards), Embase (1980 onwards), and the Cochrane Library in February 1998. These searches were repeated in May 1999 and again in January and September 2000 (on the latter occasions supplemented by a search of the National Library of Medicine PreMedline database featuring articles not yet fully indexed). A low yield of relevant references in sections on antibiotic management, non-antibiotic management, and complications led to a series of additional searches being conducted for these sections.



DOMAIN 4. CLARITY OF PRESENTATION

- 15. The recommendations are specific and unambiguous.
- 16. The different options for management of the condition or health issue are clearly presented.
- 17. Key recommendations are easily identifiable.

Synopsis of main recommendations

Investigations (section 5)

GENERAL INVESTIGATIONS FOR PATIENTS MANAGED IN THE COMMUNITY (SECTION 5.5)

- General investigations, including a chest radiograph, are not necessary for the majority of patients with suspected community acquired pneumonia (CAP) who are managed in the community [C].
- Out of hours and emergency general practitioner assessment centres should consider using pulse oximeters to allow for simple assessment of oxygenation [D].

MICROBIOLOGICAL INVESTIGATIONS FOR PATIENTS MANAGED IN THE COMMUNITY (SECTION 5.8)

- Microbiological investigations are not recommended routinely [D].
- Examination of sputum should be considered for patients who do not respond to empirical antibiotic therapy [D].
- Examination of sputum for *Mycobacterium tuberculosis* should be considered for patients with a persistent productive cough, especially if malaise, weight loss or night sweats, or risk factors for tuberculosis (e.g. ethnic origin, social deprivation, the elderly) are present [D].
- Serological investigations may be considered during outbreaks (e.g. Legionnaires' disease) or epidemic
- Sputum cultures should also be performed for patients with severe CAP or those who fail to improve [D].
- Laboratories should offer a reliable Gram stain for patients with severe CAP or complications, as on occasions this can give immediate indication of likely pathogens. Routine performance or reporting of sputum Gram stain on all patients is unnecessary but can aid the laboratory interpretations of culture results [D].
- Laboratories performing sputum Gram stains should adhere to strict and locally agreed criteria for interpretation and reporting of results [B+].
- Paired serological tests should be performed for all patients with severe CAP, those who are unresponsive to β -lactam antibiotics, and for selected patients with particular epidemiological risk factors or in whom a specific microbiological diagnosis is important for public health measures (fig 6) [D].
- Serological tests should be extended to all patients admitted to hospital with CAP during outbreaks and when needed for the purposes of surveillance. The criteria for performing serological tests in these circumstances should be agreed locally between clinicians, laboratories, and public health officers [D].

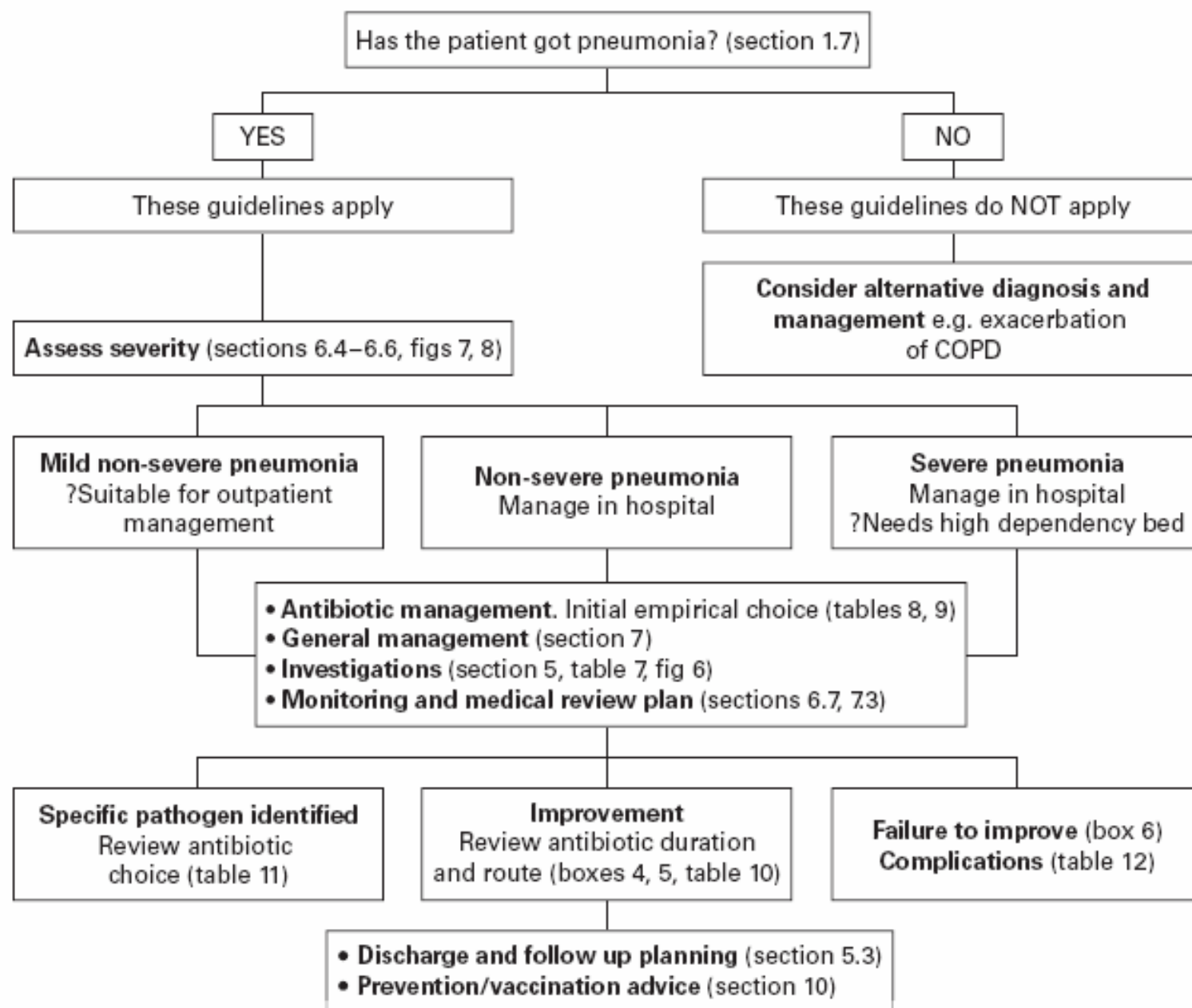



Figure 2 Synopsis of the management of adult patients seen in hospital with suspected CAP



Other considerations
are also important:

in particular for antibiotic guidelines

Local epidemiology

Local resistance percentages

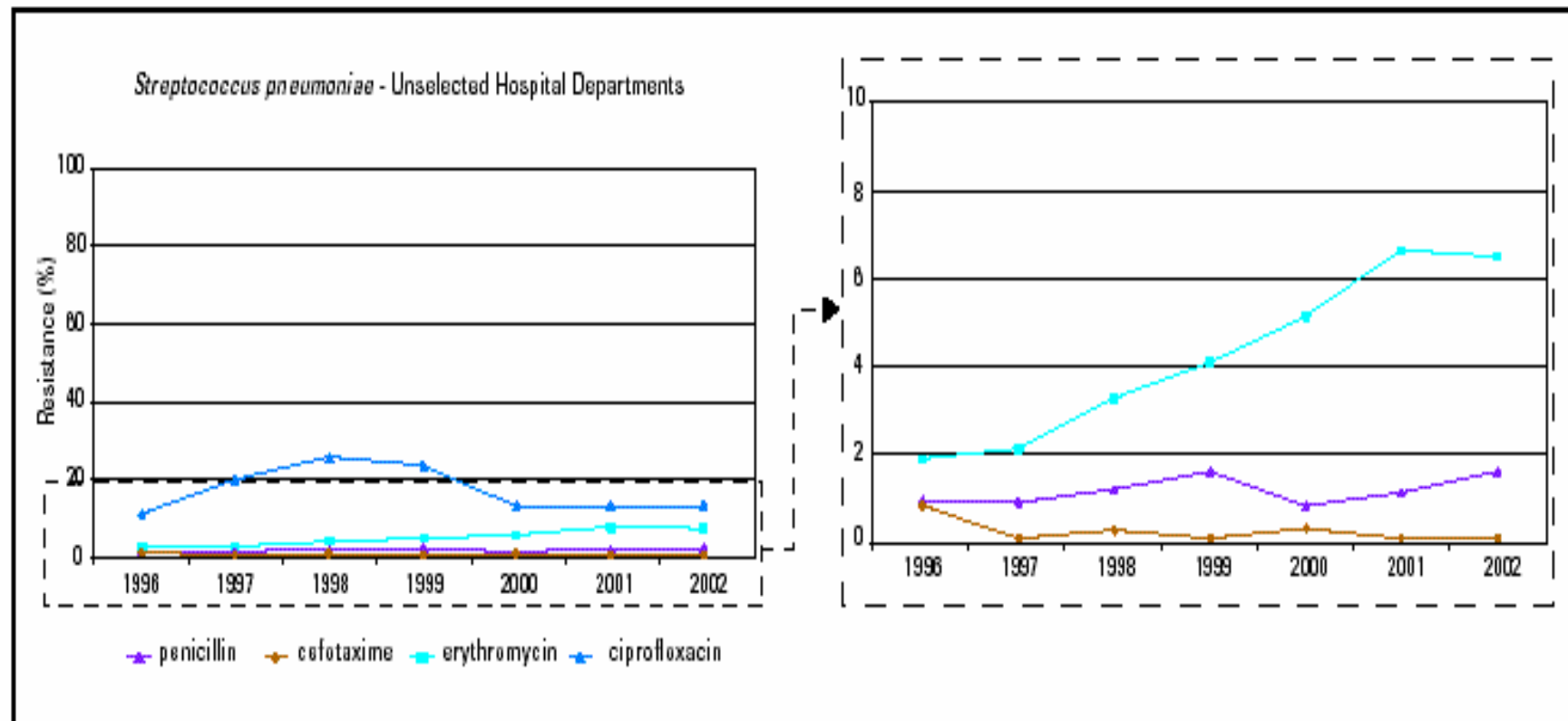
Example:
Surveillance report
www.swab.nl

- < 1 % MRSA
- E. coli in the community:
< 2 % resistant to cephalosporins



Sensitivity of pneumococci

NETHMAP 2004





Uw richtlijnen

De volgende richtlijnen zijn aan u voorgelegd:

Review Community acquired pneumonie



In stadium: **1H 2 2H 3 3H 4 5**

Een uitleg van de verscheidene fasen:



Deze richtlijn bevindt zich in stadium:

Klik **hier** voor informatie over stadia

DOMAIN 5. APPLICABILITY

- 18. The guideline describes facilitators and barriers to its application.
- 19. The guideline provides advice and/or tools on how the recommendations can be put into practice.
- 20. The potential resource implications of applying the recommendations have been considered.
- 21. The guideline presents monitoring and/or auditing criteria.



DOMAIN 6. EDITORIAL INDEPENDENCE

- 22. The views of the funding body have not influenced the content of the guideline.
- 23. Competing interests of guideline development group members have been recorded and addressed.

British Pharmacology Society.

A summary of declarations of interests for the life time of the committee is given below:

TB has received research funding from Eisai Ltd, lecture fees from Aventis and support for attending conferences from Wyeth; GD has received research funding from SmithKline Beecham and Astra, lecture fees from Allen and Hanburys and support for attending conferences from Allen and Hanburys and 3M; RGF has received consultancy fees from Glaxo Wellcome, Nexstar, Bristol Myers Squibb, SmithKline Beecham, AstraZeneca, Pharmacia, Parke Davis and Pantherix, research funding from GlaxoWellcome and Pharmacia, and support for attending conferences from Glaxo Wellcome, Aventis, Wyeth, and Biomerieux; WFH has received consultancy fees from GlaxoWellcome, Schering Plough, Boehringer Ingelheim, Hoechst Marion Roussel, Astra, 3M, Zeneca and Rhone Poulenc Rorer, research funding from 3M and Rhone Poulenc Rorer, and support for attending conferences or courses from GlaxoWellcome, Schering Plough, Zeneca and 3M; DH has received consultancy fees from Bayer, GlaxoWellcome, SmithKline Beecham, Pfizer, Abbott and Bristol Myers Squibb, research funding from Hoechst Marion Roussel, SmithKline Beecham, Pharmacia/Upjohn, Grunenthal and



How to score guidelines?

III. Rating Scale and User's Manual Sections

Each of the AGREE II items and the two global rating items are rated on a 7-point scale (1–strongly disagree to 7–strongly agree). The User's Manual provides guidance on how to rate each item using the rating scale and also includes 3 additional sections to further facilitate the user's assessment. The sections include User's Manual Description, Where to Look, and How to Rate.

i) Rating Scale

All AGREE II items are rated on the following 7-point scale:

1	2	3	4	5	6	7
Strongly Disagree						Strongly Agree

IV. Scoring the AGREE II

A quality score is calculated for each of the six AGREE II domains. The six domain scores are independent and should not be aggregated into a single quality score.

i) Calculating Domain Scores

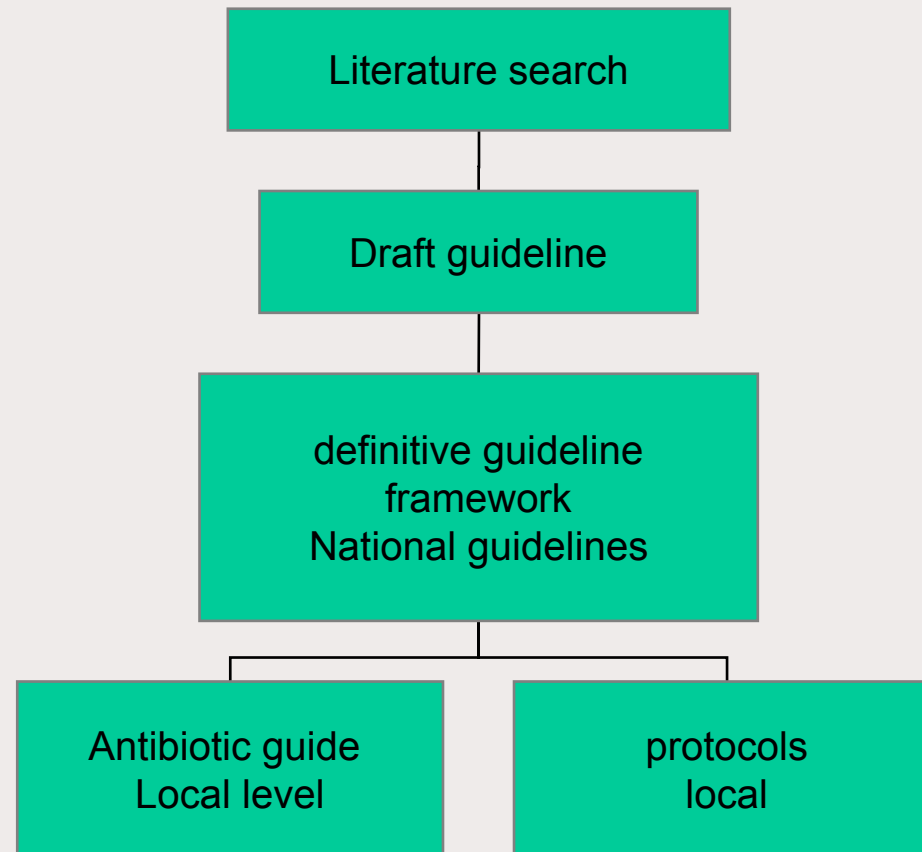
Domain scores are calculated by summing up all the scores of the individual items in a domain and by scaling the total as a percentage of the maximum possible score for that domain.

Example:

If 4 appraisers give the following scores for Domain 1 (Scope & Purpose):

	Item 1	Item 2	Item 3	Total
Appraiser 1	5	6	6	17
Appraiser 2	6	6	7	19
Appraiser 3	2	4	3	9
Appraiser 4	3	3	2	8
Total	16	19	18	53

From national guidelines to a local guideline for antimicrobial therapy



Distribution of guidelines


As extensive as possible!

Publication on paper

Several journals: NTVG (national medical journal), Neth J Med (national medical journal in English), specialist journal

Websites

- Downloadable (pdf)



Features of guidelines that may improve physician adherence

- Simplicity
- Feasibility/applicability
- Flexibility (allowing for personal judgement)
- Testing (shown to improve outcomes)
- Intended to improve quality of care
- Not intended to reduce costs
- Not used in litigation or disciplinary actions

Adapted from Finch & Low Clin Microbiol Infect 2002;8 suppl 2:69-91; Christakis et al. Pediatrics 1998, Flores et al. Pediatrics 2000

Conclusion:

Good guideline programs

- ✓ systematic literature search
- ✓ 'evidence' and consensus important
- ✓ should we involve patients?
- ✓ ample distribution
- ✓ several implementation strategies
- ✓ revision and evaluation

Implementation of guidelines

- Good preparation and planning
- Creating support/acceptance by stakeholders
- Development of realistic goals for improvement
- Practical tools for support
- Analysis of barriers to implementation
- Plan for interventions
- Development of indicators for monitoring

Grol & Grimshaw. Lancet 2003 362;1225-1230



Example: Surgical prophylaxis

Uniformity facilitates follow-up

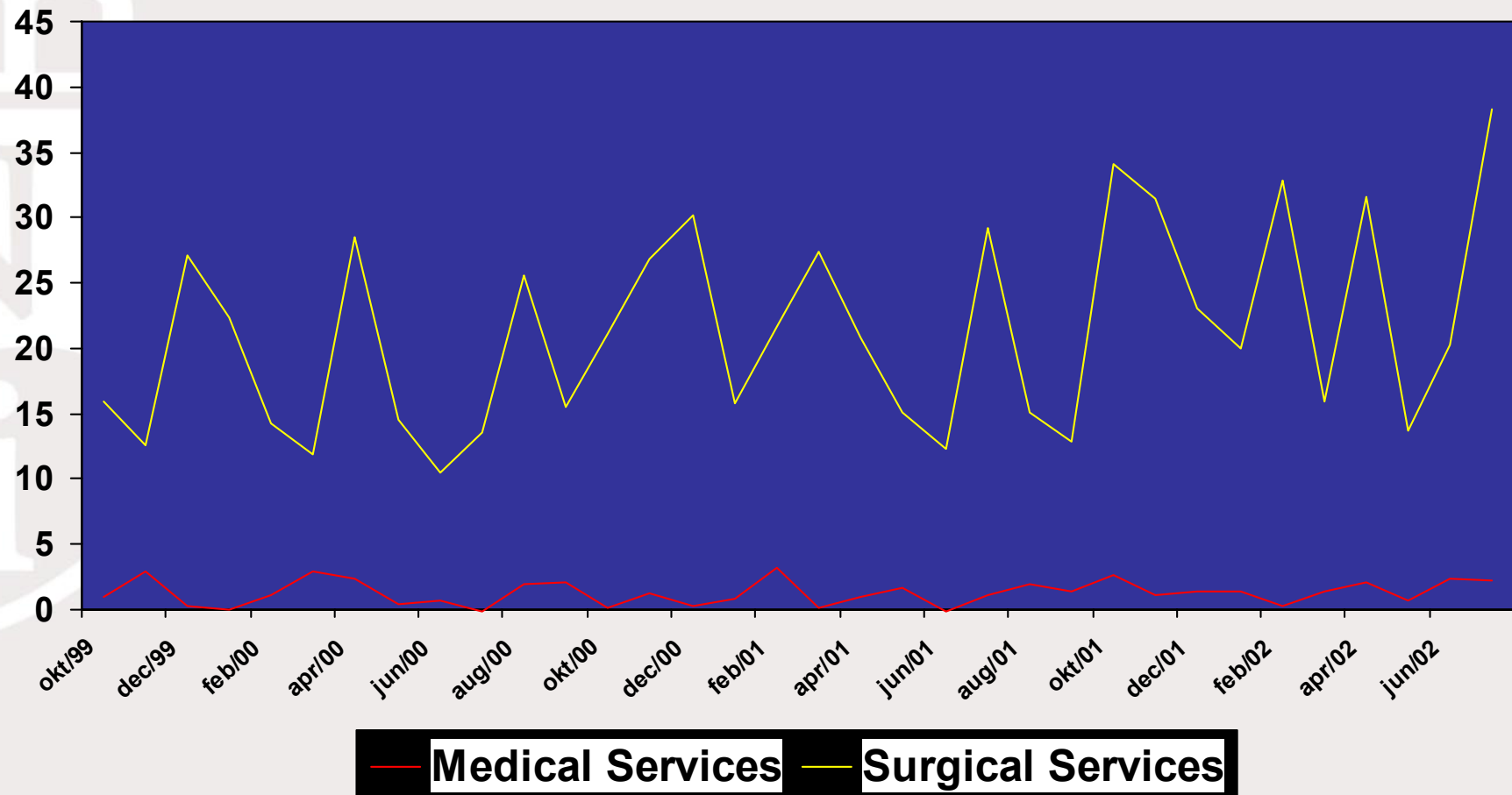
Quantitative surveillance as a Quality marker

Example : Monitoring the indication for cefazolin at Erasmus MC
Rotterdam (2001):

cefazolin is confined to surgical prophylaxis

department	cefazolin (g)	%
operating theatres	4266	64
ICUs	1507	23
surgical wards	716	10
medical wards	208	3
total	6697	100

Use of First Generation Cephalosporins DDD/100 patient days Erasmus MC, 2000-2002



Filius, Endtz & Gyssens, unpublished 2002

Use of cephalosporins in surgical departments, Erasmus MC

DDD/100 patient days

