

Resistance Trends: Case study *S. pneumoniae*

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- ❑ Definitions & stakeholders

 - ❑ Consensus principles versus and treatment guidelines.

 - ❑ SOAR study –methodology and objectives

 - ❑ Trends of antibiotic resistance : Case study *S. pneumoniae*

1. Appropriate antibiotic Prescribing

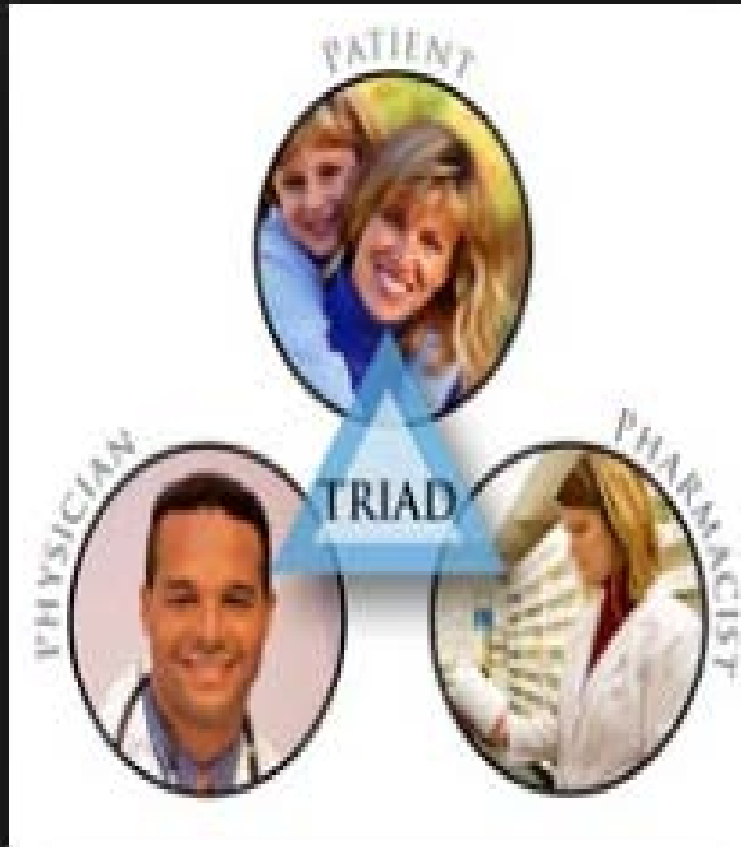
2. Antibiotic surveillance

AAP – Appropriate Antibiotic Prescribing

‘Optimal treatment’ means that patients are treated with the **right antibiotic** to treat their condition, the **right dose**, by the **right route**, at the **right time** and for the **right duration** based on accurate assessment and timely review’

J Antimicrob Chemother 2013; 68: 2428–2430

Stakeholders



CAUSES OF ANTIBIOTIC RESISTANCE



Antibiotic resistance happens when bacteria change and become resistant to the antibiotics used to treat the infections they cause.



Over-prescribing of antibiotics



Patients not finishing their treatment



Over-use of antibiotics in livestock and fish farming



Poor infection control in hospitals and clinics



Lack of hygiene and poor sanitation



Lack of new antibiotics being developed

www.who.int/drugresistance

#AntibioticResistance



*“Surveillance of antimicrobial resistance tracks changes in microbial populations, permits the early **detection of resistant strains of public health importance**, and supports the prompt notification and investigation of outbreaks”*

World Health Organisation

- **Use of WHO/CDC guidelines**
- **Antibiotic prescribing guidelines for HCPs (use of local antibiotic susceptibility data!)**
- **Following consensus principles**
- **Patient empowerment**
- **Public campaigns for HCPs, patients and pharmacists**
- **Training for HCPs, patients and pharmacists**

Godolphin W. *Healthcare Quarterly* 2009; 12:186-90

http://www.femeba.org.ar/fundacion/quienessomos/Novedades/medicamentosysalud/mysv3n3_oms_%20atb_%20resistencia.PD



WHY FOCUS ON ANTIBIOTIC STEWARDSHIP?

WHY the Emphasis on AAP?



Putting patients first

For GSK, how we do things is just as important as what we do. Our values based culture is designed to ensure we put patients and customers interests first

What is a guideline?



"Guidelines are recommendations intended to assist providers and recipients of health care and other stakeholders to make informed decisions. Recommendations may relate to clinical interventions, public health activities, or government policies."

How do we come up with guidelines?

Use of GRADE working group system



Definition of GRADE

GRADE Working Group Grades of Recommendation Assessment, Development and Evaluation

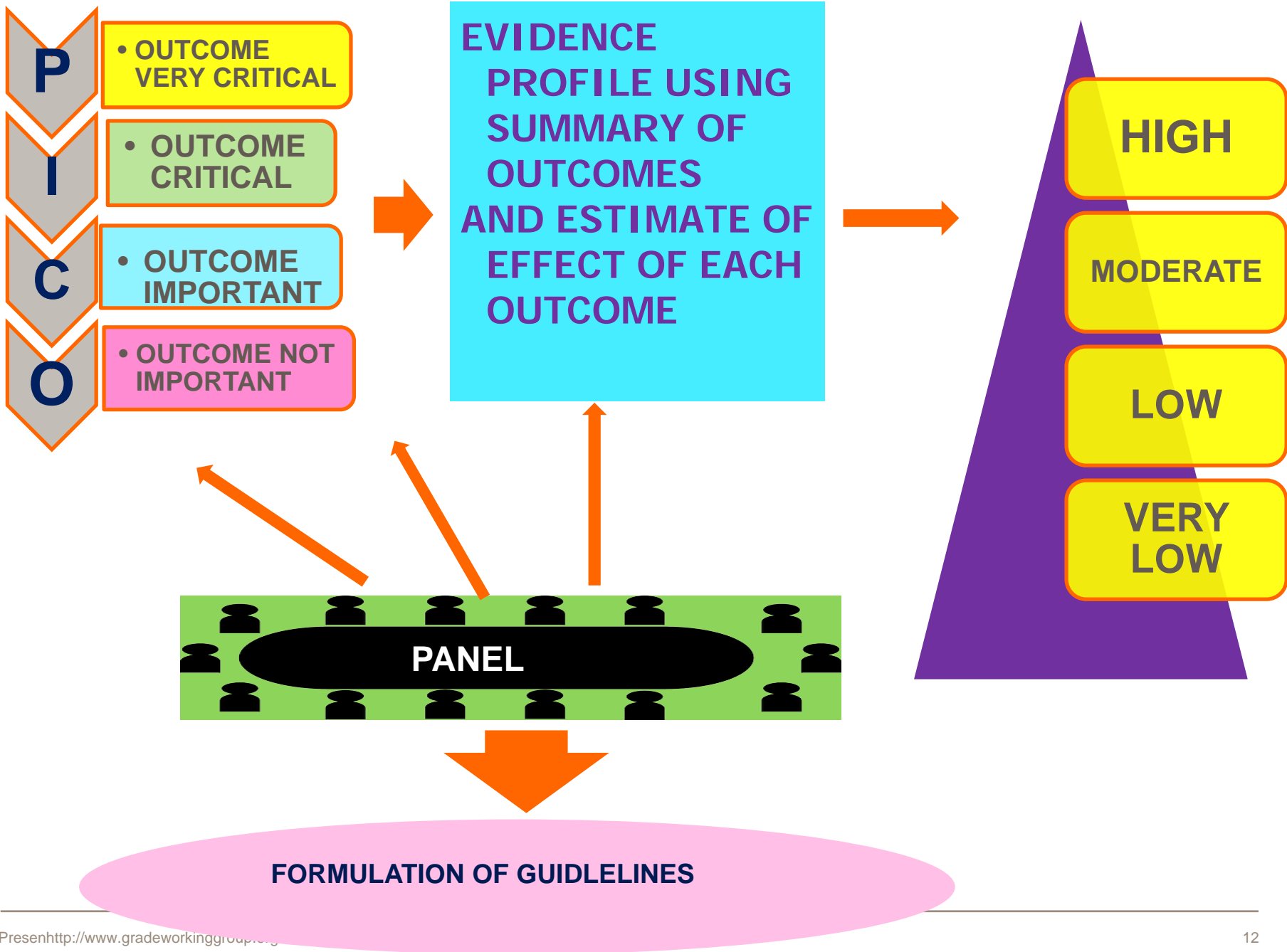
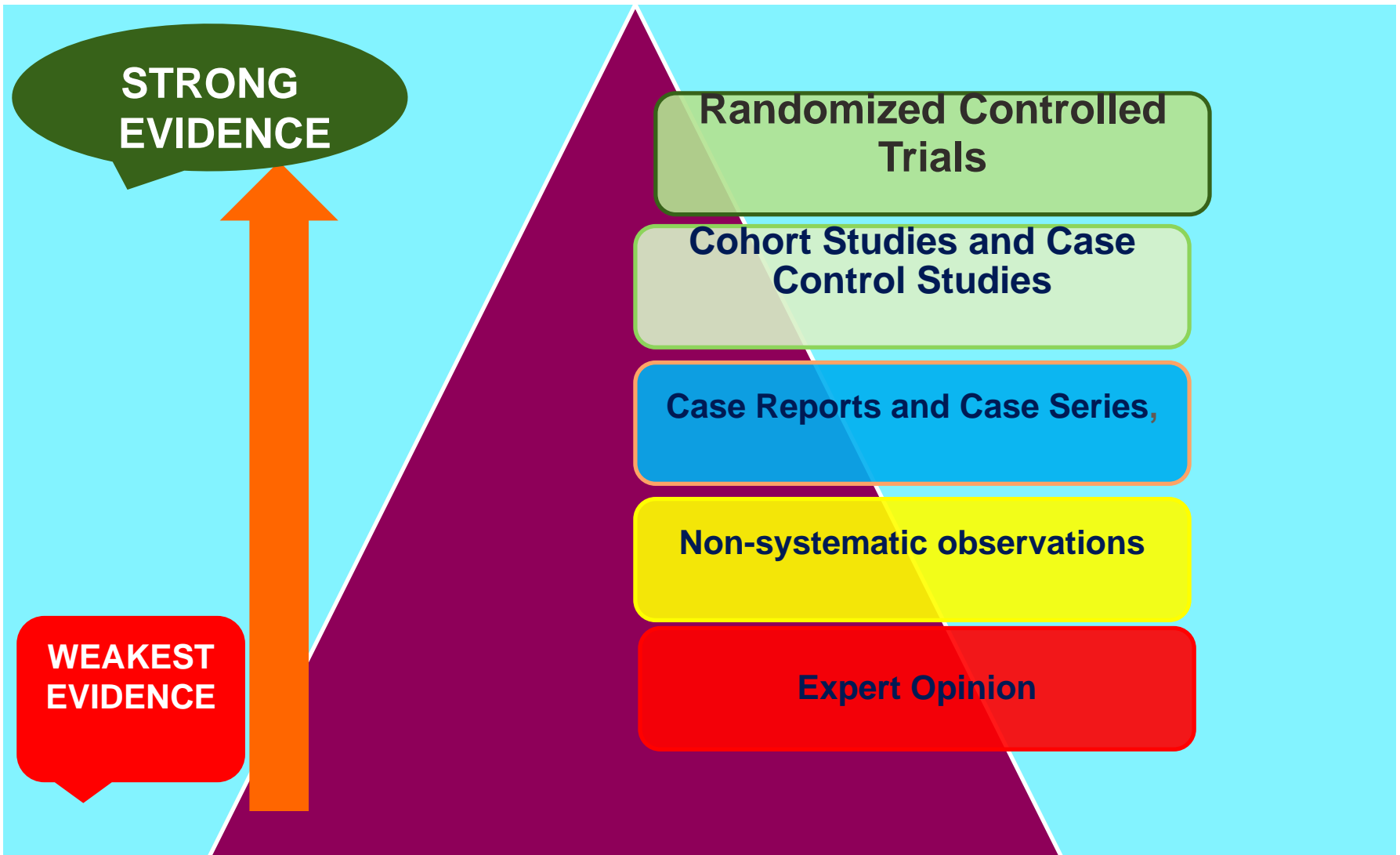




Figure 1. *Belief and confidence: a two-dimensional weather report. (Reprinted by permission from the Wall Street Journal).*

Hierarchy of evidence based on quality



- **Recommendations are judgments:**
 - Quality of evidence
 - Trade off between benefits and harms
 - Values and preferences
 - Resource use

- Judgments need to be based on the best available evidence and be transparent

Consensus Principles



Practice Guidelines Compared to Consensus Principles



Guidelines ^{1,2}	Consensus Principles ³
Goal: Improve care and outcomes	Goal: Improve care and outcomes
Specific infections	Specific antimicrobials, but General Principles
Based on evidence (but often not available)	Based on sound scientific rationale
Variance acceptable based on specific circumstances	Basic principles are generalisable

1. Committee to Advise the Public Health Service on Clinical Practice Guidelines, Institute of Medicine. *Clinical Practice Guidelines: Directions of a New Program*. Washington, DC: National Academy Press; 1990

2. Shideman A and Furberg C. *JAMA*. 2009;301:429–30;

3. Ball P et al. *J Antimicrob Chemother* . 2002;49:31–40

Consensus Principles

TREAT

Bacterial infection only

OPTIMISE

Diagnosis / severity assessment

MAXIMISE

Bacterial eradication (or load reduction)

RECOGNISE

(Local) resistance prevalence

UTILISE

PK/PD – effective choice of agent and dose

INTEGRATE

Local resistance, efficacy & cost-effectiveness

Appropriate prescribing conforms to these criteria

Principle 1:-TREAT- Bacterial infection only



Community acquired Pneumonia

Typical Organisms	Atypical Organisms
• <i>S pneumoniae</i>	<i>M pneumoniae</i>
• <i>H influenzae</i>	<i>Chlamydia spp</i>
• <i>Moraxella catarrhalis</i>	<i>Legionella spp</i>
• <i>S pyogenes</i>	Viruses

– **Viral causes identified in 41%-50%⁸**

Principle 1: TREAT bacterial infection only



-In almost one half of croup, influenza, common cold and in most non-specified ARIs an antibiotic was prescribed

-Consequences:

- ↑ economic costs
- Leads to development of resistance
- ↑ side effects and toxicity

-Routine antibacterial treatment is not recommended, regardless of duration of cough

Principle 2 : OPTIMIZE diagnosis

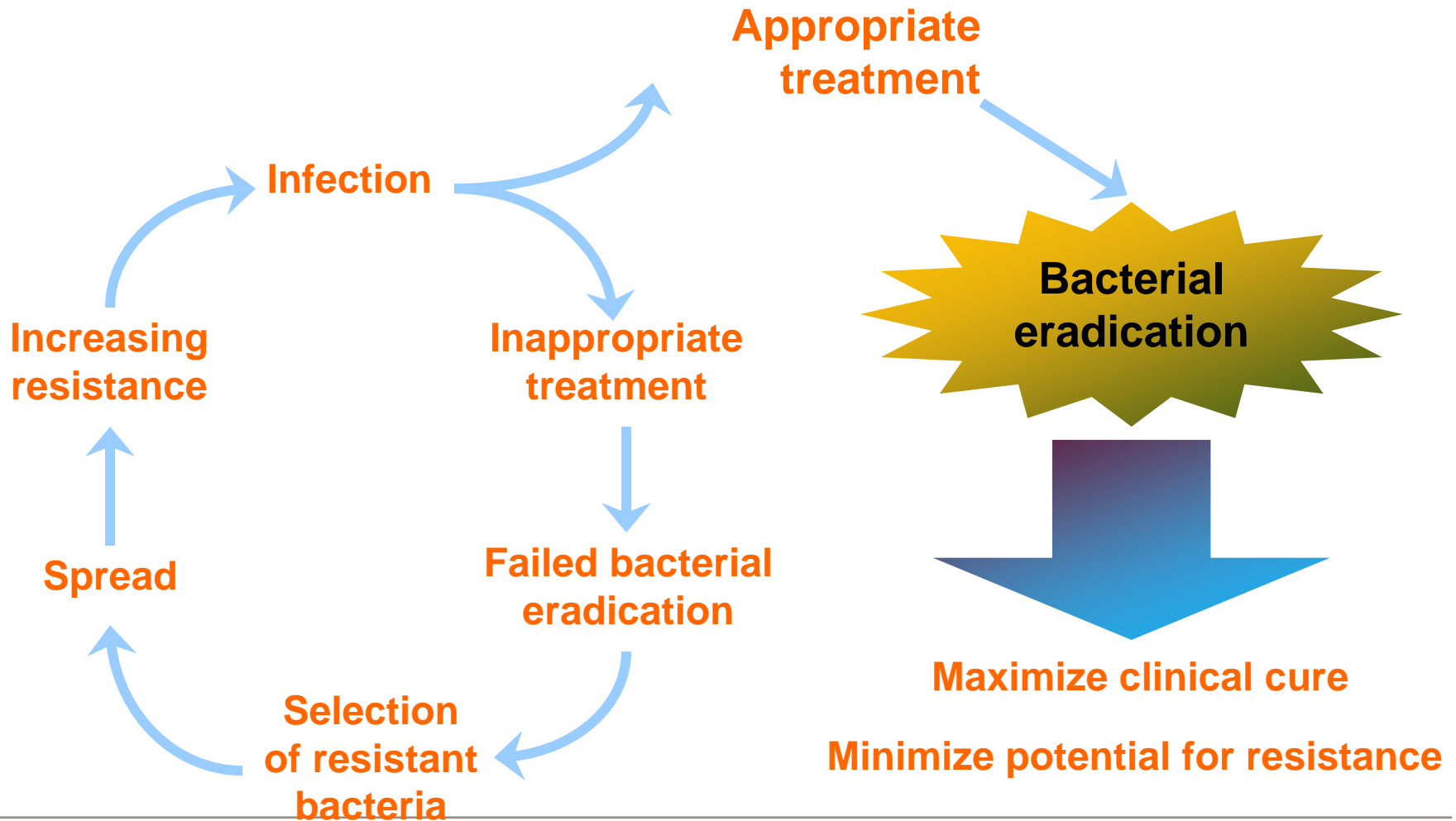
Clinical manifestations of A O M

Correlations with specific pathogens



Clinical data		<i>S. pneumoniae</i>	<i>H. influenzae</i>
Pain	Mild	38% (n = 31)*	42% (n = 25)
	Moderate	38% (n = 31)*	38% (n = 23)
	Severe	24% (n = 19)	20% (n = 12)
High temperature†		41% (n = 33)*	10% (n = 6)
TM appearance	Opacified, dull white or gray	32% (n = 27)*	58% (n = 35)
	Yellow	11% (n = 9)*	10% (n = 6)
	Red with total bulge	57% (n = 47)*	31% (n = 19)

Principle 3: MAXIMIZE bacterial eradication



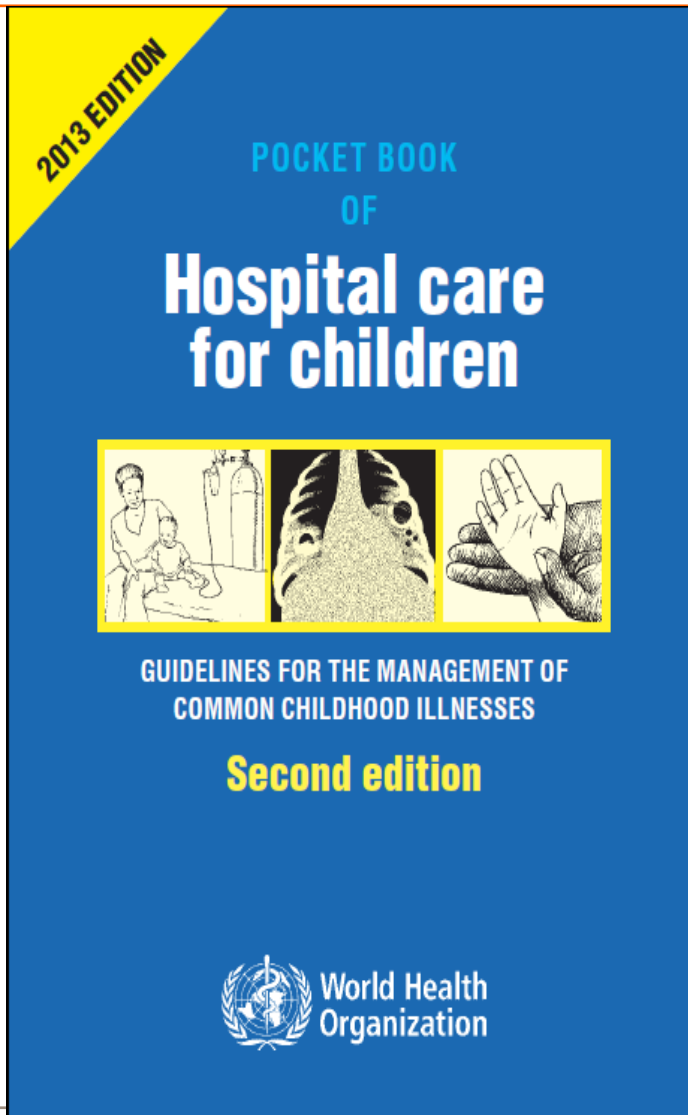
- Pneumococcal diagnostic tests performed on 281 Kenyan adults with pneumonia.
- Antimalarial use reported to be common

**46% attributed to
S.pneumococcal
bacteria**



**S. pneumonia
Susceptible to
Penicillin* -72%**

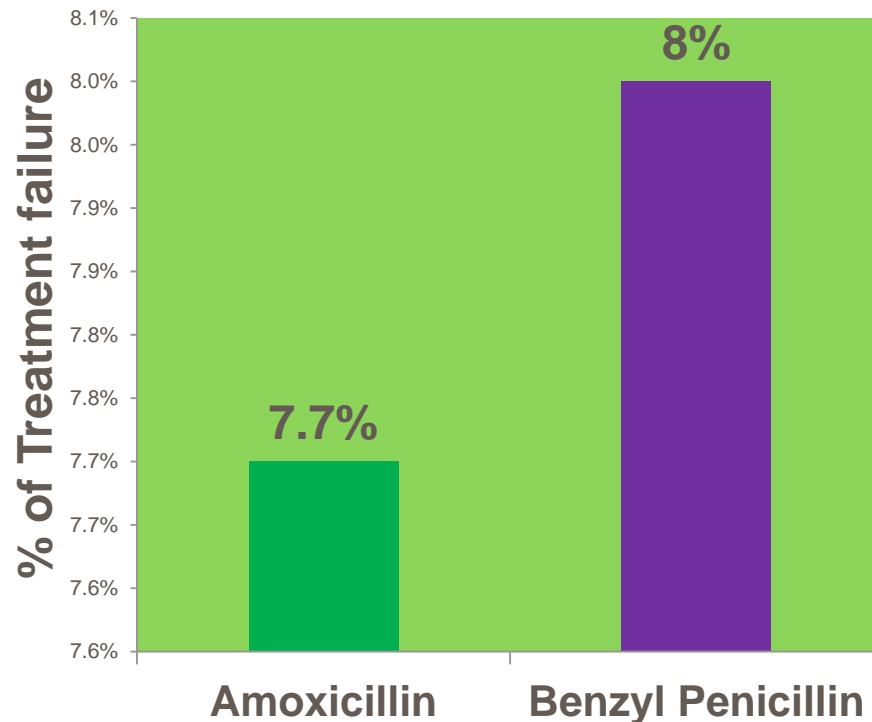
– * IV Penicillin breakpoints



*“Treat child as
outpatient...
...Give oral
amoxicillin –at
least 40mg/ kg per
dose twice a day
for 5 days”*

Paediatric Severe Pneumonia study

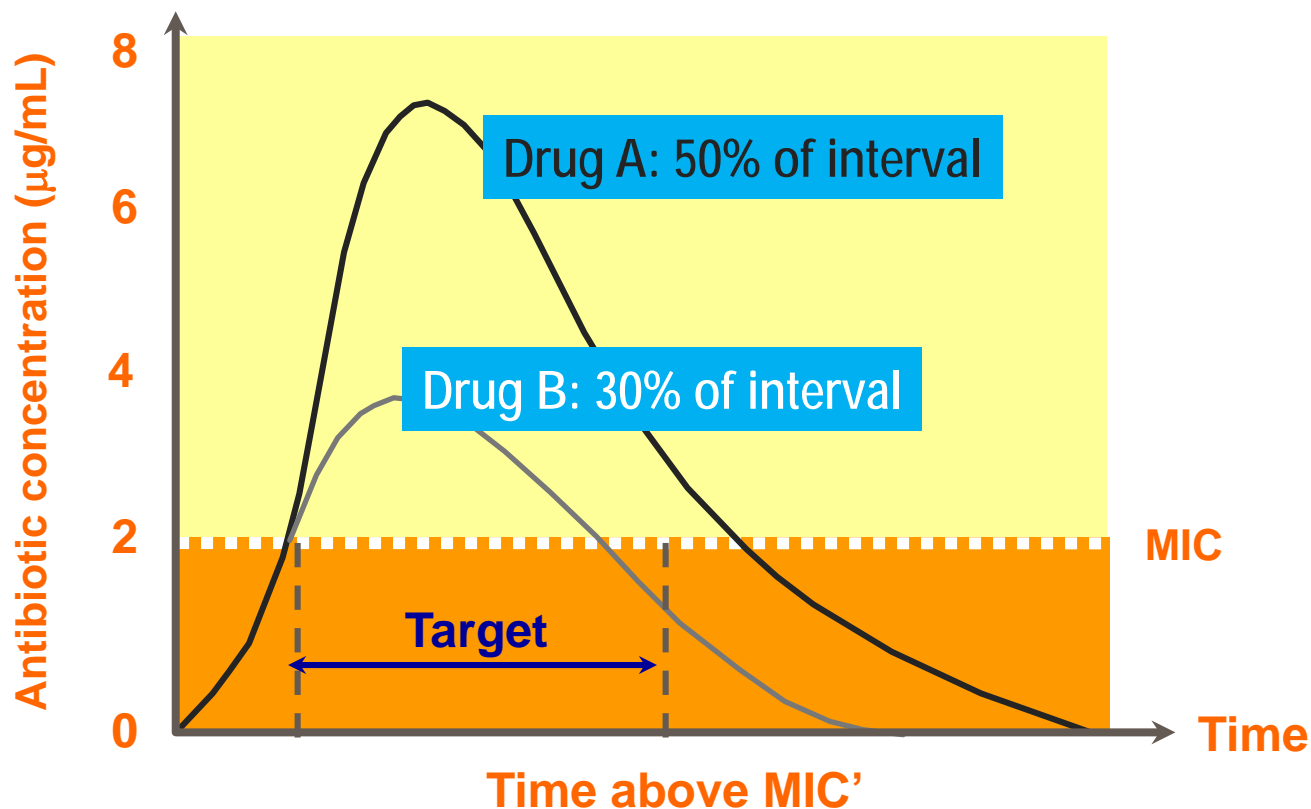
Severe Pneumonia Study Outcomes



- Recruited 527 children
- Non-inferiority trial was conducted at 6 Kenyan hospitals.
- Treatment failure was observed in 20 of 260 (7.7%) and 21 of 261 (8.0%) of patients in the amoxicillin and benzyl penicillin arms, respectively

Principle 5: UTILIZE PD for effective therapy

Target for β -lactams = 'Time above MIC'



Time above MIC' > 40% correlates with clinical and bacteriological outcome
Drug B does not achieve this pharma codynamic target

Summary :Consensus Principles

TREAT

Bacterial infection only

OPTIMISE

Diagnosis / severity assessment

MAXIMISE

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RECOGNISE

(Local) resistance prevalence

UTILISE

PK/PD – effective choice of agent and dose

INTEGRATE

Local resistance, efficacy & cost-effectiveness

Appropriate prescribing conforms to these criteria

Local resistance data and antibiotic resistance surveillance

Question time



What threshold of % R indicates “This antibiotic should be used with caution”?

- a) 50%
- b) 15-20%
- c) 90%
- d) 5%
- e) Have no idea

Question time



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The need for appropriate prescribing



- Principles required for appropriate prescribing and effective (locally compliant) guidelines:

TREAT - bacterial infection only

OPTIMISE - diagnosis/severity assessment

MAXIMISE - eradication of bacterial pathogens

RECOGNISE - (local) resistance prevalence

UTILISE - pharmacodynamics to choose most effective agents and dosage

INTEGRATE - local resistance, efficacy and maximise cost-effectiveness

Pharmaceutical industry-led surveillance studies

Institution-led surveillance studies

Some surveillance studies (1)



STUDY	FUNDING	ORGANISM	ANT. AGENT	COMMENTS
ALEXANDER PROJECT¹	SmithKline Beecham/ GlaxoSmithKline	Key pathogens from LRTI	22 agents	Central testing MIC Wide range of countries
MYSTIC²	Astra Zeneca	ICU	9 agents	MIC 46 centres worldwide
PROTEKT³	Sanofi-Aventis	CA-RTI	18 agents	MIC many centres worldwide
SENTRY⁴	Bristol-Myers Squibb	Wide range	Many	MIC 70 centres from 30 countries

LRTI: Lower respiratory tract infection, ICU: Intensive care unit; CA-RTI: Community-acquired respiratory tract infection MIC: Minimum inhibitory concentration

SOAR



**SURVEY
OF
ANTIBIOTIC
RESISTANCE**

Evolution of SOAR studies...



2002–2004

- Kenya
- South Africa
- Tunisia
- Egypt
- Jordan
- Kuwait
- Lebanon
- Saudi Arabia
- Turkey
- UAE
- Pakistan

2004–2006

- Cote d'Ivoire
- Senegal
- Nigeria

- Tunisia
- Kuwait
- Lebanon
- Morocco
- Turkey
- UAE
- Pakistan

2007–2009

- Cote d'Ivoire
- Senegal
- Kenya
- Algeria
- Morocco
- Pakistan
- Egypt
- UAE
- Qatar

- Kuwait
- Nigeria
- Turkey
- Thailand
- Saudi Arabia
- Lebanon

Survey of Antibiotic Resistance (SOAR) studies



Main focus is collecting/testing the community-acquired respiratory tract infection (CA-RTI) related pathogens such as *S. pneumoniae* and *H. influenzae*

- Aim is to collect from each centre at least 100 *Streptococcus pneumoniae* + 100 *Haemophilus influenzae*
- Multinational and longitudinal programme (since 2002)
- Internationally recognised and standardised methodology (CLSI)
- Not a clinical study/it is an *in vitro* antibiotic surveillance study

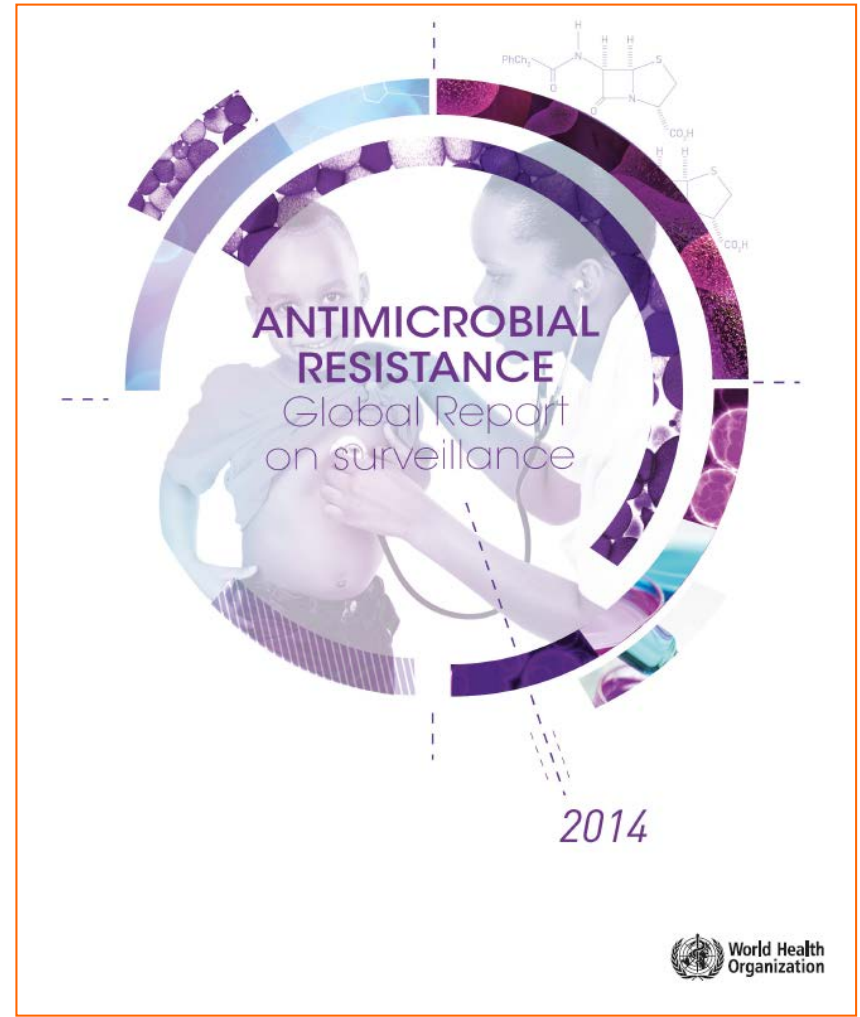
- Respiratory infections remain the leading infectious cause of death^{1,2}
- Antimicrobial resistance continues to evolve in these pathogens²
- Beta-lactams are frequently used treatments for respiratory infections³

WHO Global Report on surveillance (2014)



World Health Organization. Antimicrobial Resistance. Global report on surveillance, 2014 accessed 20 July, 2015.

- Regional report (Africa, Americas, Eastern Mediterranean, European, South-East Asia, Western Pacific)
- Data for:
 - *Escherichia coli*
 - *Klebsiella pneumoniae*
 - *Staphylococcus aureus*
 - ***Streptococcus pneumoniae***
 - Non-typhoidal Salmonella
 - *Shigella spp*
 - *Neisseria gonorrhoeae*
 - Tuberculosis
 - Malaria
 - HIV
 - Influenzae



-
- Penicillin (for *S.pneumoniae* only)
 - Ampicillin (for *H.influenzae* only)
 - Amoxicillin + clavulanic acid
 - Cefuroxime
 - Second/third generation of cephalosporin
 - Erythromycin
 - Azithromycin
 - Clarithromycin
 - Ofloxacin
 - Moxifloxacin
 - Levofloxacin

METHODOLOGY FOR ANTIBIOTIC SUSCEPTIBILITY TESTING (based on CLSI guidelines)



-Disk diffusion (Kirby Bauer)

-Broth micro-dilution MIC (CLSI reference method)

-E-test (bio-Merieux)

-Quality Control :- using the ATCC strains

Breakpoints used:

CLSI

EUCAST

PK/PD

DATA INTERPRETATION

Algeria, Cote d'Ivoire, Egypt, Kenya, Morocco, Qatar, Pakistan, Senegal & UAE:



S. Pneumoniae Overall pattern (2007-2009)

	N	S%	R%	Mg/L
Penicillin*	929	61.5	5.6	1
Amoxicillin	202	99.5	0	0.5
Amoxicillin/clavulanate	929	99	0.1	0.5
Cefuroxime	928	87.7	4.5	2
Cefaclor	806	77.9	17	12
Ceftriaxone	189	99.5	0.5	0.25
Erythromycin ^a	928	76.4	20.2	–
Azithromycin	804	73.1	22.3	>256
Clarithromycin	715	75.9	22.9	>256

- ❑ Overall, 61.5% (571/929) of *S. pneumoniae* were penicillin susceptible (PSSP), 32.9% (306/929) intermediate (PISP) and 5.6% (52/929) were penicillin resistant (PRSP)
- ❑ The highest prevalence of PNSP was highest in Kenya (66.7%) and UAE 60.0%.
- ❑ All PISP strains were susceptible to amoxicillin, amoxicillin- clavulanate _____

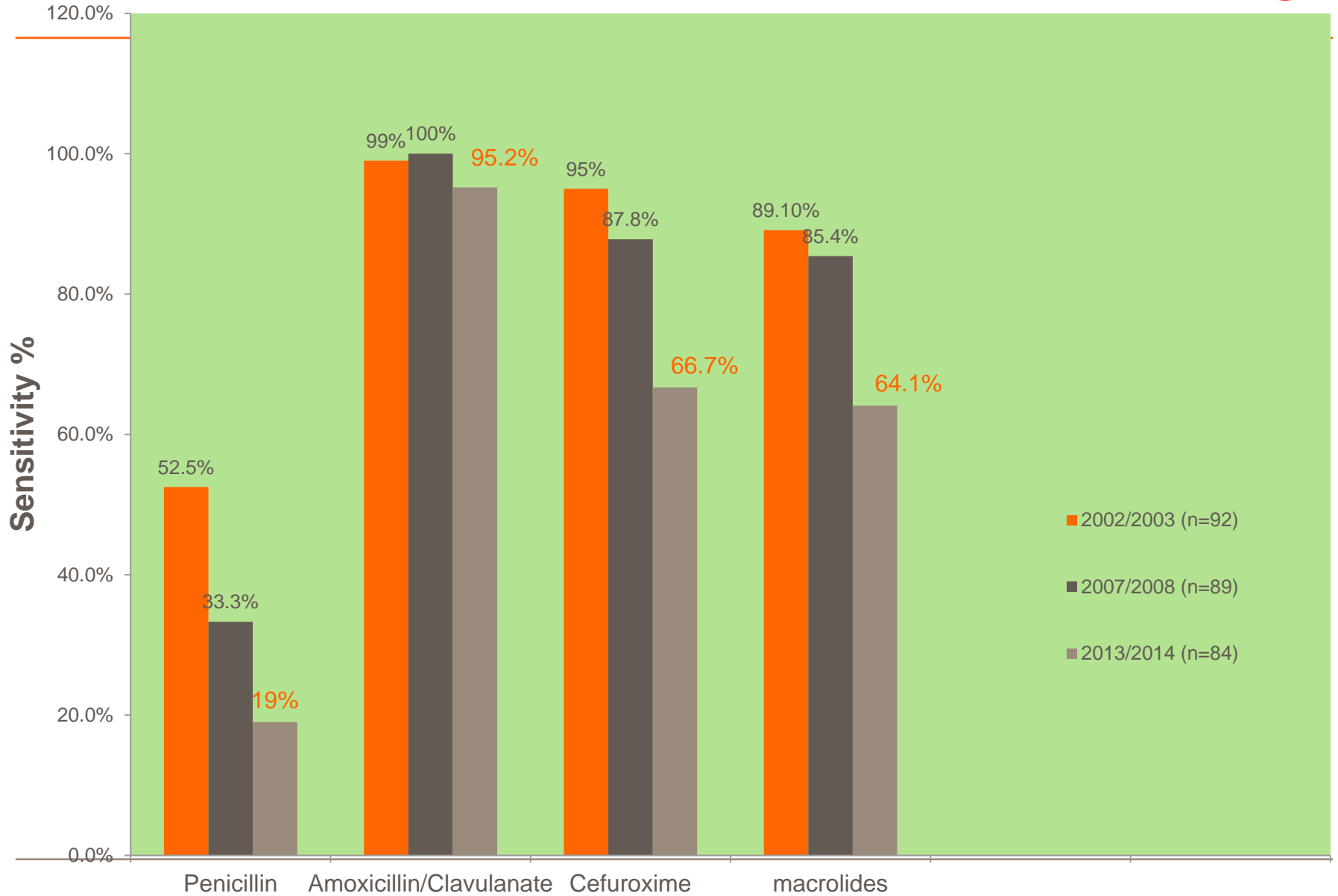
Kenya: Susceptibility of *S. pneumoniae* isolates




Antimicrobial (n=123)	CLSI		MIC ₉₀
	S%	R%	Mg/L
Penicillin*	33.3	4.1	1
Amoxicillin/clavulanate	100	0	0.5
Cefuroxime	87.8	3.3	2
Cefaclor	—	—	—
Cefpodoxime	—	—	—
Erythromycin ^a	85.4	12.2	—
Azithromycin	—	—	—
Clarithromycin	—	—	—

*CLSI 2008 breakpoints/CLSI 2009 breakpoints for oral penicillin V; ^adisk susceptibility

S. Pneumoniae Resistance trend patterns





 New guidelines support higher doses of amoxicillin (+/- clavulanate) as one option when *S. pneumoniae* with reduced susceptibility to penicillin is suspected

New ATS -Acute Bacterial Rhinosinusitis (ABRS) guidelines



Recommendation: Amoxicillin-clavulanate rather than amoxicillin alone is recommended as empiric antimicrobial therapy for ABRS in children

Recommendation: Amoxicillin-clavulanate rather than amoxicillin alone is recommended as empiric antimicrobial therapy for ABRS in adults

Question time



How long can we rely on a generated antibiotic surveillance data?

- a) 10 years
- b) 2 years
- c) 5 years**
- d) 15 years
- e) No limit

-
- *S. pneumoniae* resistant strains are on the increase
 - Amoxicillin and amoxicillin clavulanate exhibit susceptibility to PSSP and PISP
 - Macrolides show increasing resistance over the past decade
 - Current WHO Treatment guidelines are aligned with evidenced – surveillance results and clinical trials

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THANK YOU!!