

# Antibiotic Stewardship Conference: FROM EXPERT CONSENSUS TO EUROPE-WIDE ACTION AT THE POINT OF CARE

## Expert consensus on CRP POCT in children

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European Network  
for Antibiotic Stewardship  
at the Point of Care



ANTIBIOTIC STEWARDSHIP CONFERENCE:

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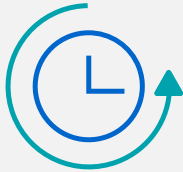
# EXPERT CONSENSUS ON CRP POCT TO GUIDE ANTIBIOTICS PRESCRIPTIONS FOR RESPIRATORY ILLNESS IN CHILDREN

*Effectiveness of CRP POCT in children*

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# Effect of point-of-care tests on antibiotic prescribing rate in children in primary care



**Serious infections are rare (<1%)  
but early detection  
is important**

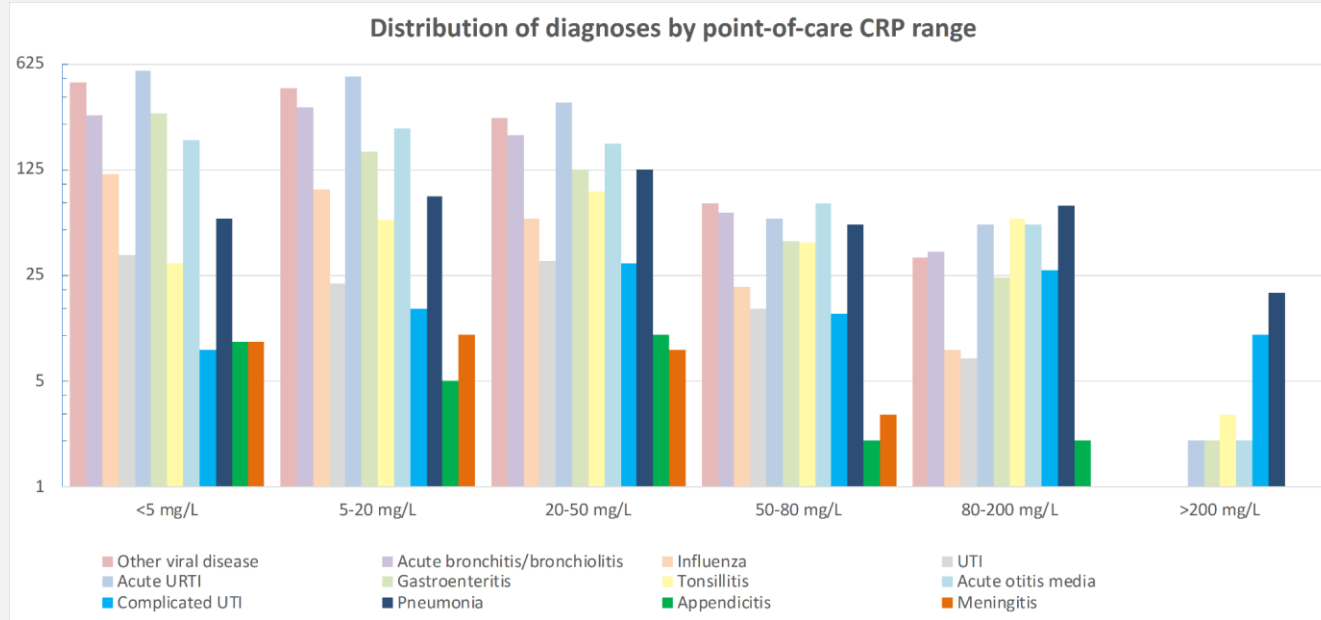


**High-risk for unnecessary  
antibiotic prescribing due  
to diagnostic uncertainty**



**In Belgium, almost every child  
receives one antibiotic  
prescription per year**

# Point-of-care CRP in children

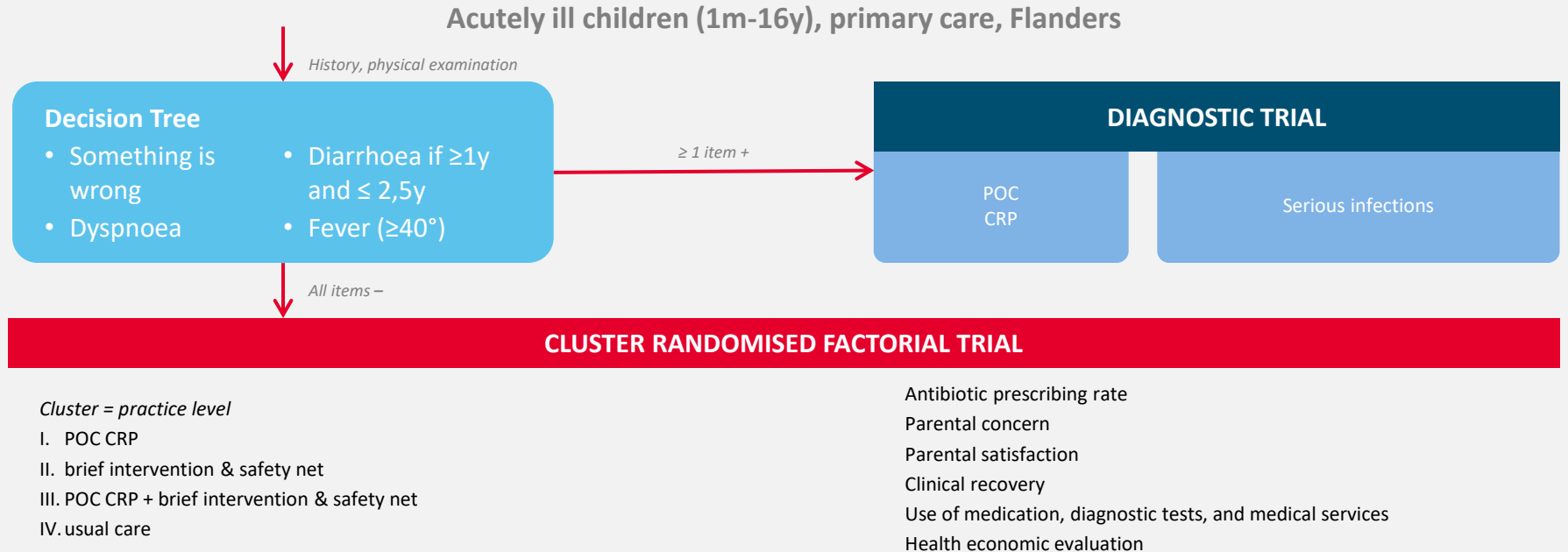


Distribution of frequency of diagnoses by point-of-care CRP range. X-axis displays 5 different point-of-care CRP ranges. Y-axis displays the frequency of the diagnoses on a logarithmic scale. CRP, C-reactive protein; URTI, upper respiratory tract infection; UTI, urinary tract infection

De Rop, L., *et al.* Point-of-care C-reactive protein test results in acute infections in children in primary care: an observational study.

*BMC Pediatr* **22**, 633 (2022). <https://doi.org/10.1186/s12887-022-03677-5>

# Point-of-care CRP in children



# Point-of-care CRP in children

SCANDINAVIAN JOURNAL OF PRIMARY HEALTH CARE  
2018, VOL. 36, NO. 4, 423–436  
<https://doi.org/10.1080/02813432.2018.1529900>



RESEARCH ARTICLE

OPEN ACCESS Check for updates

**Point-of-care CRP matters: normal CRP levels reduce immediate antibiotic prescribing for acutely ill children in primary care: a cluster randomized controlled trial**

Marieke B. Lemiengre<sup>a</sup>, Jan Y. Verbakel<sup>b,c</sup>, Roos Colman<sup>a</sup>, Kaatje Van Roy<sup>a</sup>, Tine De Burghgraeve<sup>c</sup>, Frank Buntinx<sup>c,d</sup>, Bert Aertgeerts<sup>c</sup>, Frans De Baets<sup>a</sup> and An De Sutter<sup>a</sup>



Future research should focus on whether POC CRP can effectively identify children that benefit from antibiotics more accurately, without increasing the risks of under-prescribing

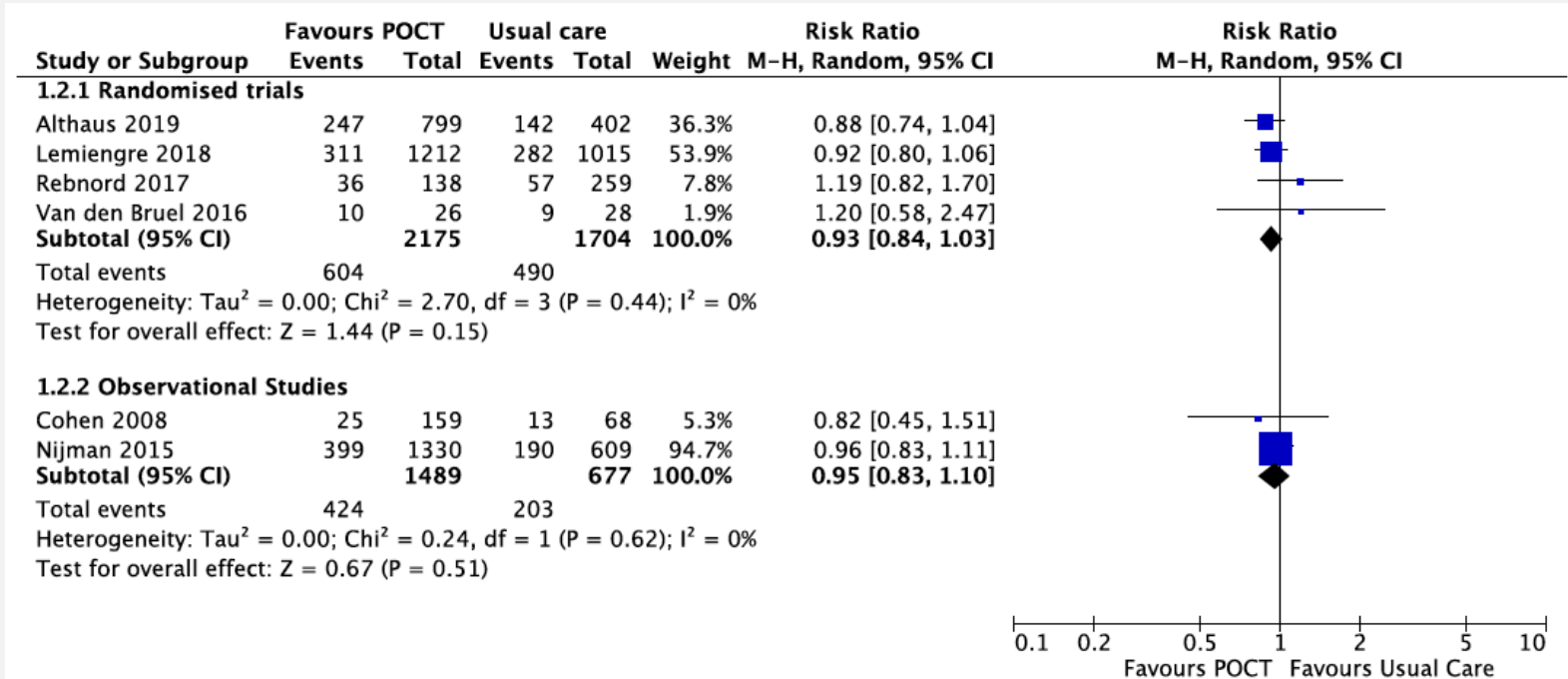


Normal CRP levels **discourage** immediate **antibiotic prescribing**, even when EBM practice guidelines advise differently.

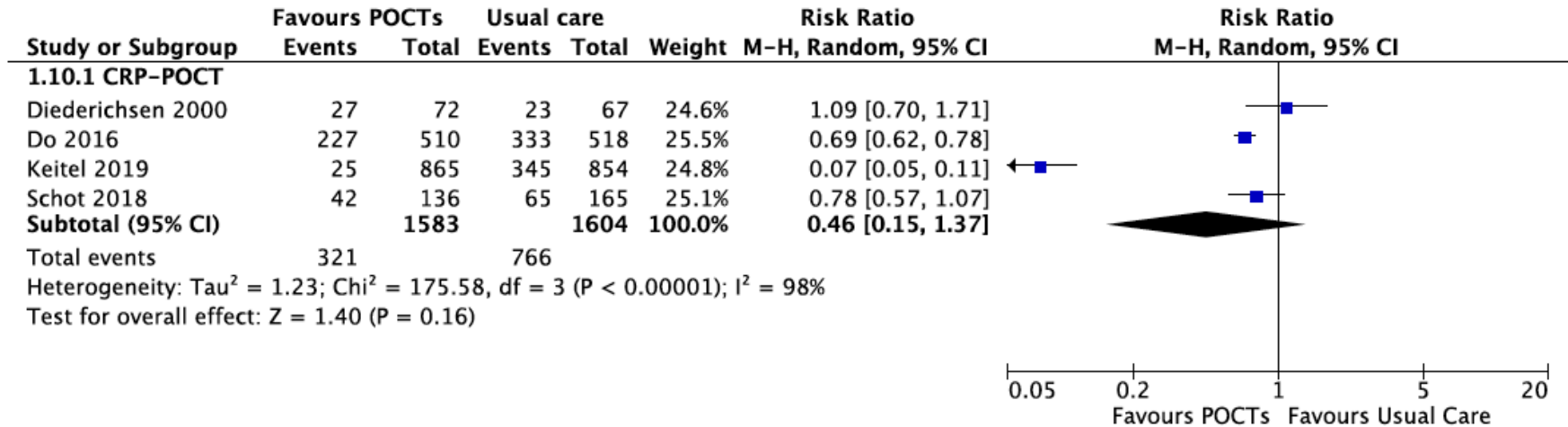


Most likely, a normal CRP convinces FPs to withhold antibiotics when guidelines go against their own gut feeling.

# Immediate antibiotic prescribing for non-specific acute fever illnesses



# Immediate antibiotic prescribing for acute respiratory tract infections



PLoS One. 2020;15(7):e0235605.



## Point-of-care CRP in children

### PLOS ONE

RESEARCH ARTICLE

#### *In-vitro* diagnostic point-of-care tests in paediatric ambulatory care: A systematic review and meta-analysis

Oliver Van Hecke<sup>1\*</sup>, Meriel Raymond<sup>1</sup>, Joseph J. Lee<sup>1</sup>, Philip Turner<sup>1</sup>, Clare R. Goyder<sup>1</sup>, Jan Y. Verbakel<sup>2</sup>, Ann Van den Bruel<sup>2</sup>, Gail Hayward<sup>1</sup>

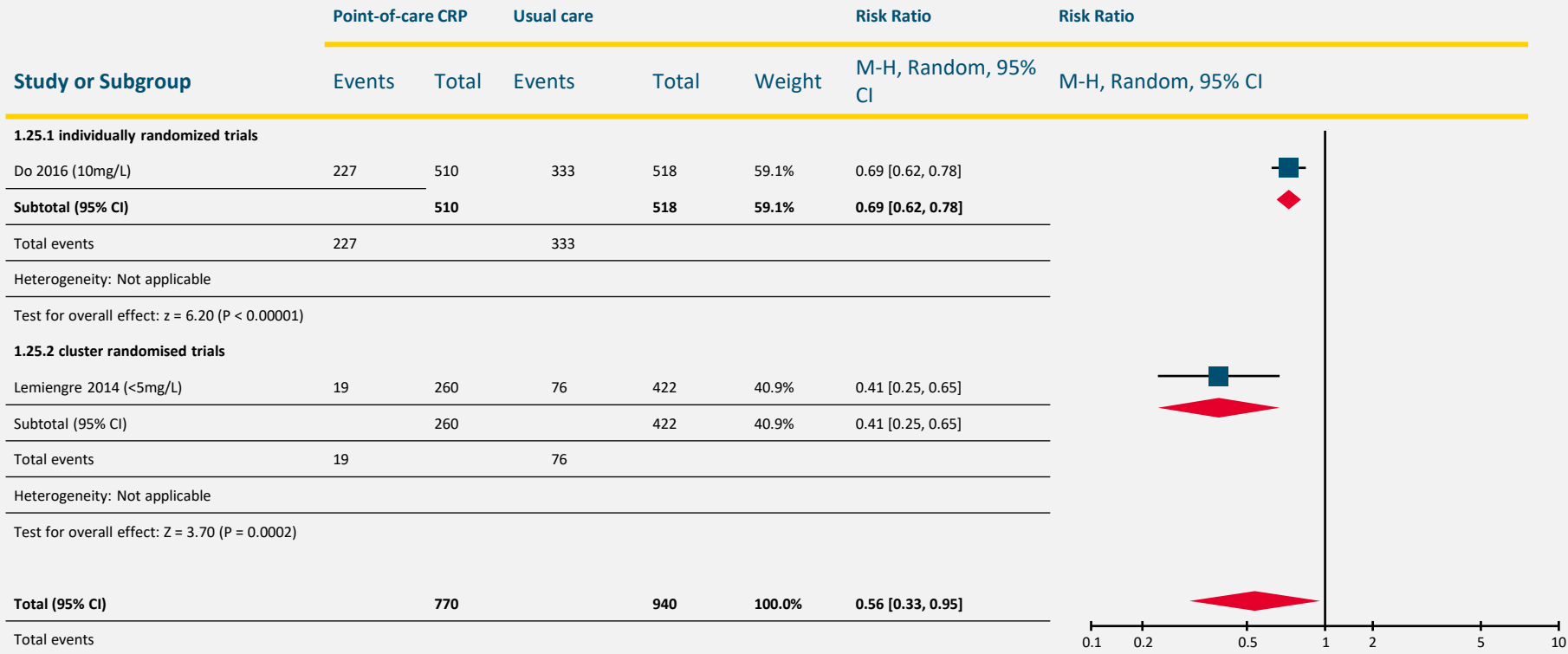


There is emerging evidence that POCT-CRP may better **target antibiotic prescribing** for children with acute RTIs



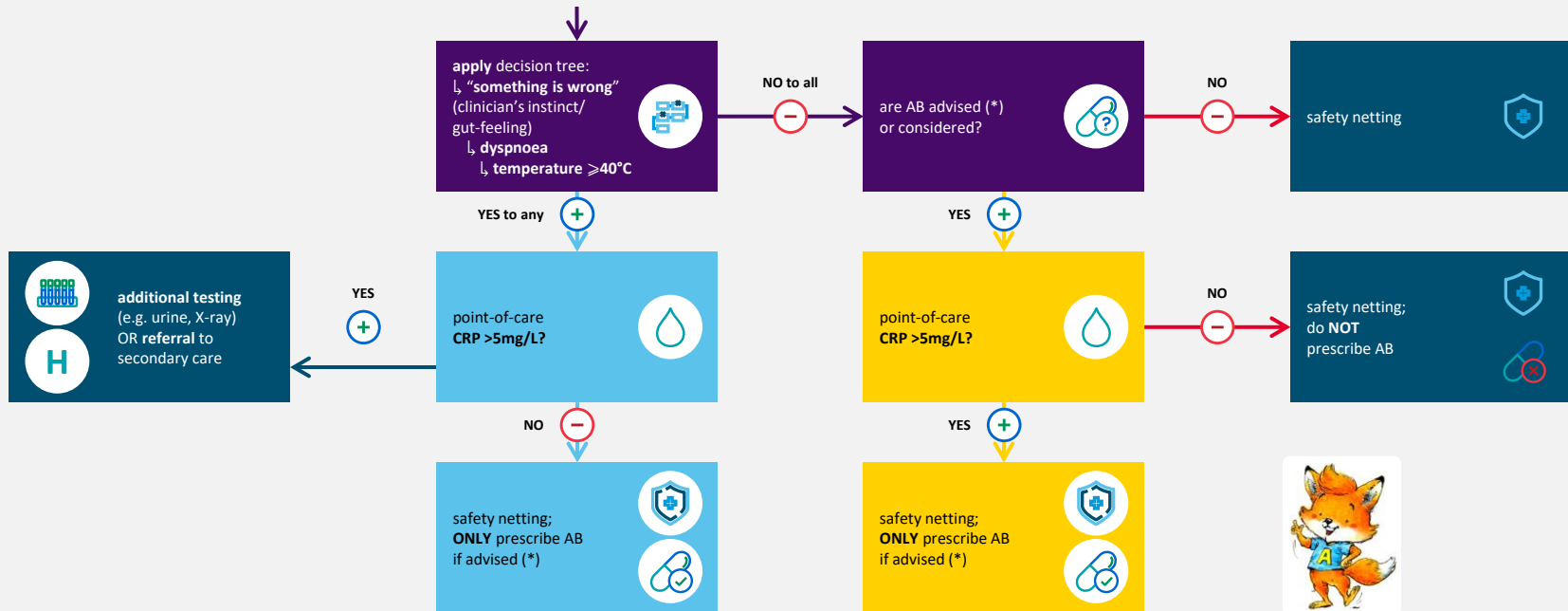
Research is **urgently needed** to understand where POCTs are likely to improve clinical outcomes in paediatric settings worldwide

# RCTs, children if cut-off guidance applied, immediate AB prescribing rate



# The ARON trial: recruitment ongoing

## 1. Intervention group (diagnostic algorithm)



# Ambulatory care

Effect of point-of-care C-reactive protein testing on antibiotic prescription in febrile patients attending primary care in Thailand and Myanmar: an open-label, randomised, controlled trial

- A multicentre, open-label, randomised, controlled trial
- 2410 enrolled patients, of whom 1200 children <12 years

**Clinical characteristics and self-reported symptoms**

Documented fever (>37.5°C)	200 (50%)	155 (38%)	203 (51%)	143 (35.5%)	223 (56%)	148 (37%)
Neurological symptoms†	62 (15%)	148 (37%)	39 (10%)	156 (39%)	40 (10%)	155 (39%)
Respiratory symptoms‡	326 (81%)	323 (80%)	315 (79%)	315 (78%)	327 (82%)	299 (75%)
Gastrointestinal tract symptoms§	104 (26%)	95 (23%)	124 (31%)	83 (21%)	109 (27%)	68 (17%)
Other symptoms¶	9 (2%)	25 (6%)	41 (10%)	37 (9%)	30 (8%)	43 (11%)

**GROUP A**

20 mg/L CRP  
POCT CUT-OFF

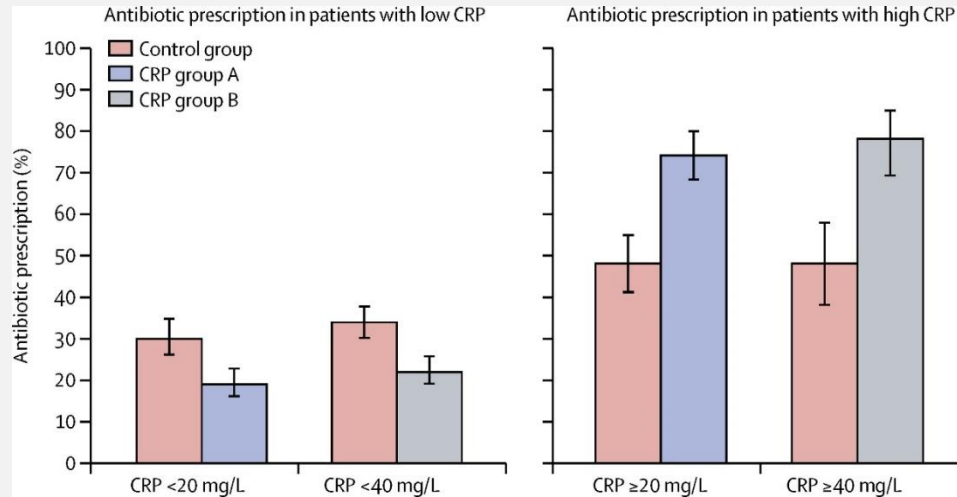
**GROUP B**

40 mg/L CRP  
POCT CUT-OFF

**GROUP C**

NO CRP POCT

# Primary outcome



- A significant difference of antibiotic prescription from day 0 up to day 5 between the control group (318 [39%] of 807) and patients in group B was observed (275 [34%] of 800), with a risk difference of – 5.0 percentage points (95% CI –9.7 to –0.3) and an adjusted odds ratio (aOR) of 0.80 (95% CI 0.65 to 0.98)

## Emergency setting

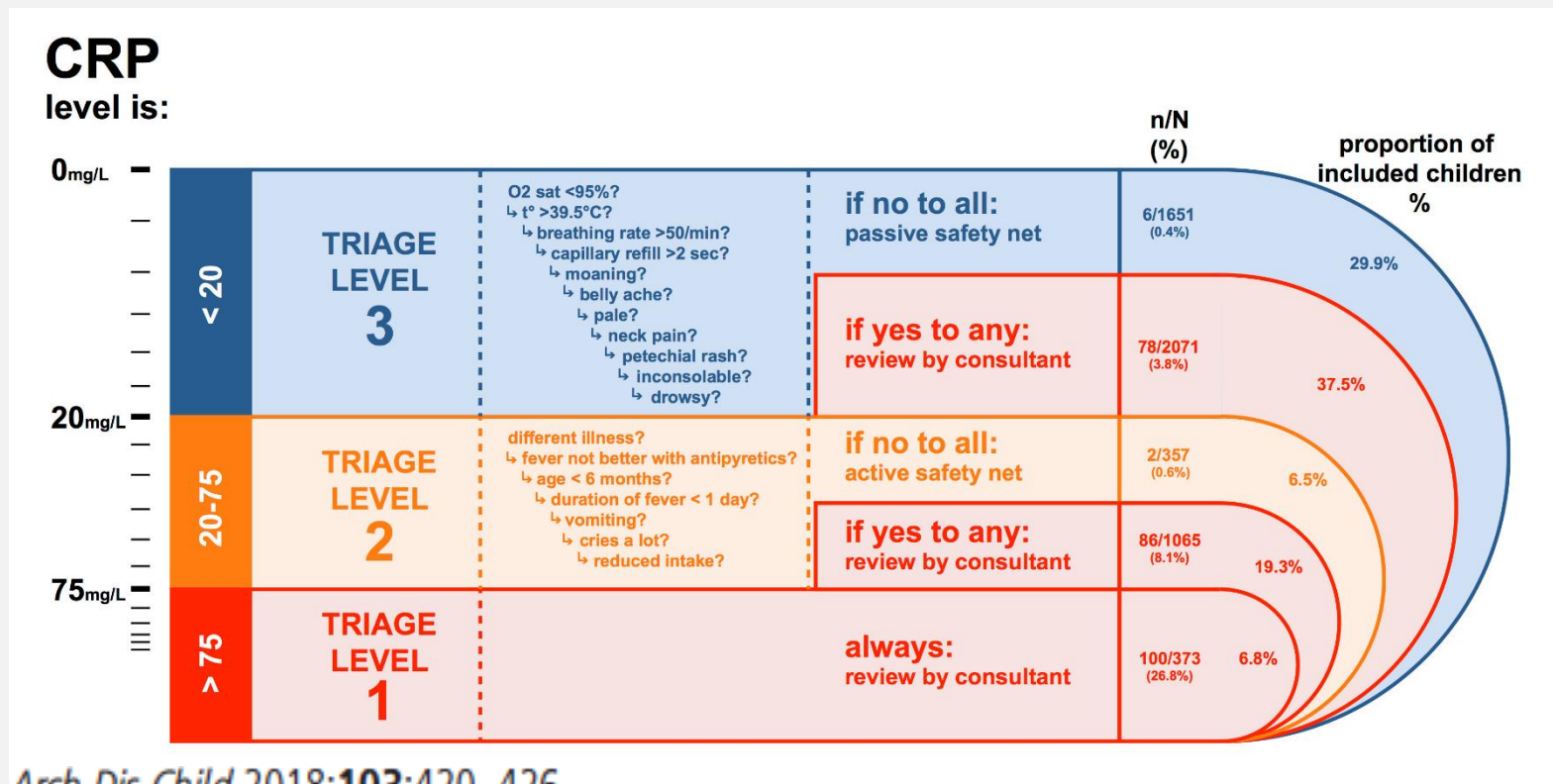
Point-of-care C reactive protein to identify serious infection in acutely ill children presenting to hospital: prospective cohort study

**Table 2** Accuracy of POC CRP at different thresholds to diagnose serious infection

POC CRP threshold	Sensitivity (95% CI)	Specificity (95% CI)	Likelihood ratio (95% CI)		Predictive value (95% CI)	
			negative	positive	negative	positive
≥5 mg/L	90.8 (86.6 to 94.0)	33.4 (32.0 to 34.7)	0.3 (0.2 to 0.4)	1.4 (1.3 to 1.4)	98.5 (97.7 to 99.0)	7.1 (6.3 to 8.0)
≥20 mg/L	73.1 (67.2 to 78.4)	63.9 (62.5 to 65.2)	0.4 (0.3 to 0.5)	2.0 (1.9 to 2.2)	97.7 (97.1 to 98.2)	10.2 (8.9 to 11.7)
≥80 mg/L	35.0 (29.2 to 41.1)	94.8 (94.1 to 95.4)	0.7 (0.6 to 0.8)	6.7 (5.5 to 8.2)	96.3 (95.7 to 96.8)	27.3 (22.6 to 32.5)
≥200 mg/L	9.6 (6.3 to 13.9)	99.7 (99.5 to 99.9)	0.9 (0.9 to 0.9)	37.1 (18.9 to 37.1)	95.2 (94.5 to 95.7)	67.6 (50.2 to 82.0)

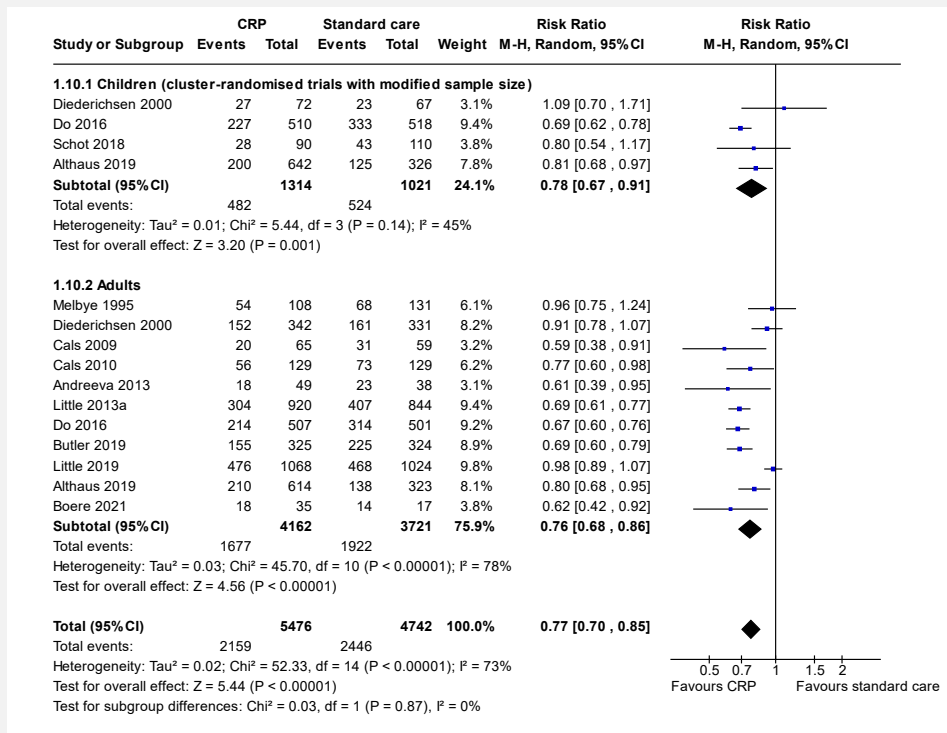
*Arch Dis Child* 2018;**103**:420–426.

# Emergency setting



Arch Dis Child 2018;103:420–426.

# Cochrane update 2022





## CONSENSUS STATEMENT #6

In the ambulatory care of febrile children presenting with symptoms of respiratory illness, CRP POCT can be useful to guide decisions regarding antibiotic prescribing and hospital referrals

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# EXPERT CONSENSUS ON CRP POCT TO GUIDE ANTIBIOTICS PRESCRIPTIONS FOR RESPIRATORY ILLNESS IN CHILDREN

*How and when to use CRP POCT*

PROF. A. STAIANO  
UNIVERSITY OF NAPLES



# Table of Contents

- Clinical scenario
- Antibiotics' burden in children
- Efficacy of CRP POCT in different paediatric settings
- How to improve CP RPOCT in children

# HOW AND WHEN TO USE CRP POCT TO GUIDE ANTIBIOTIC PRESCRIPTION IN CHILDREN?

## Clinical Scenario

# CLINICAL SCENARIO

- A child aged 8 months is admitted in the ambulatory of a General Pediatrician
- The parents refer the onset of fever started three days ago with frequent cough episodes and sneezes
- The temperature is very high reaching even  $39^{\circ}\text{C}$  and it normalizes after the administration of paracetamol
- The parents look very anxious



# CLINICAL EXAMINATION

- Non contributory clinical history. Well being child with excellent growth
- At the clinical examination the child appears febrile, but reactive and with no signs of dehydration
- At the pulmonary auscultation no signs of lower RTI
- Dipstick for urinalysis negative



# WHAT WOULD YOU CONSIDER THE BEST PRACTICE IN THE MANAGEMENT OF THIS CASE?

- A. I would consider antibiotics' prescription
- B. I would prescribe a complete blood work to rule out the infection etiology
- C. I would wait and revisit the child after 24 hours
- D. I would use CRP POC if available and revisit the child after 24 hours



# ACTUAL MANAGEMENT

- Taking into account the duration of the febrile episode and the concern of the family, the GP advise a cycle of Amoxicillin at the dose of 60 mg/kg/day for 7 days
- After 24 hours no more fever, but the parents report the appearance of this rash
- Diagnosis: Viral infection, most probably Roseola infantum, caused by Herpes virus type 6







HOW AND WHEN TO USE CRP POCT TO GUIDE ANTIBIOTIC PRESCRIPTION  
IN CHILDREN?

# Antibiotics' burden in children

# Antibiotics' prescription in the pre-pandemic years

- **About 4 out of 10 children** received at least one antibiotic prescription in 2018 and, on average, each child was prescribed only one package during the year, for a total of **8.9 million prescriptions**

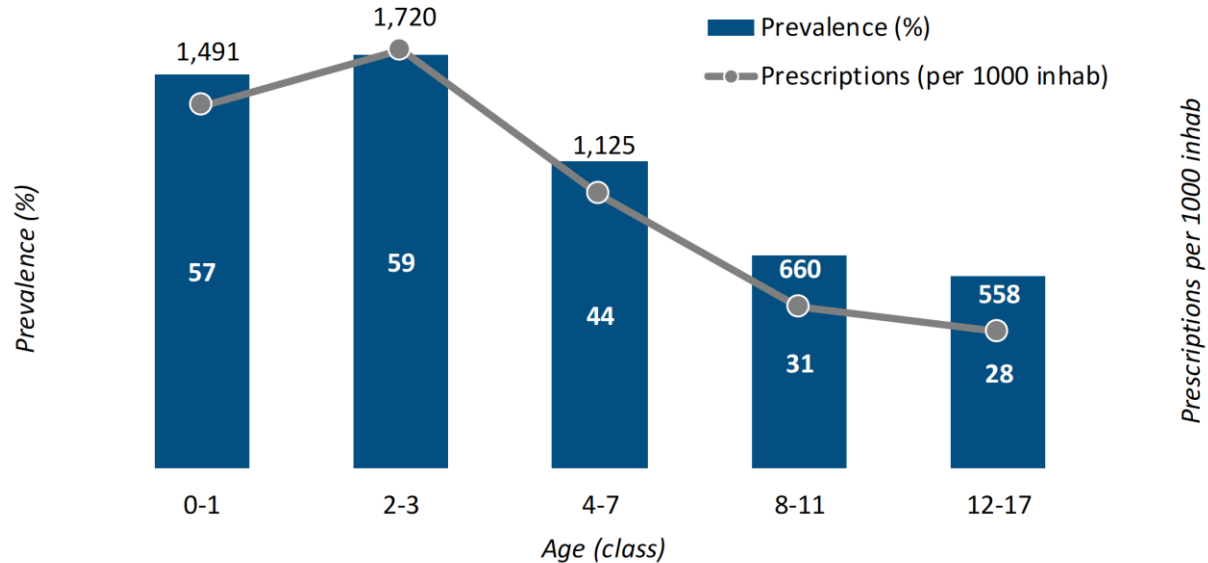
National Report  
on Medicines  
use in Italy  
Year 2018

**Table 2.1.8.** Prescription of antibiotics in the pediatric population (2018)

	<b>Total</b>
Prescriptions	8,943,269
Per 1000 children	912.0
Δ % 18-17	1.1
% share of overall consumption	45.1
Packages	9,269,047
Per prescription	1.0
Users	3,712,358
Prevalence (%)	37.9

# Antibiotics' prescription in the pre-pandemic years

**Figure 2.1.7.** Trend of antibiotics prescription by age group (2018)



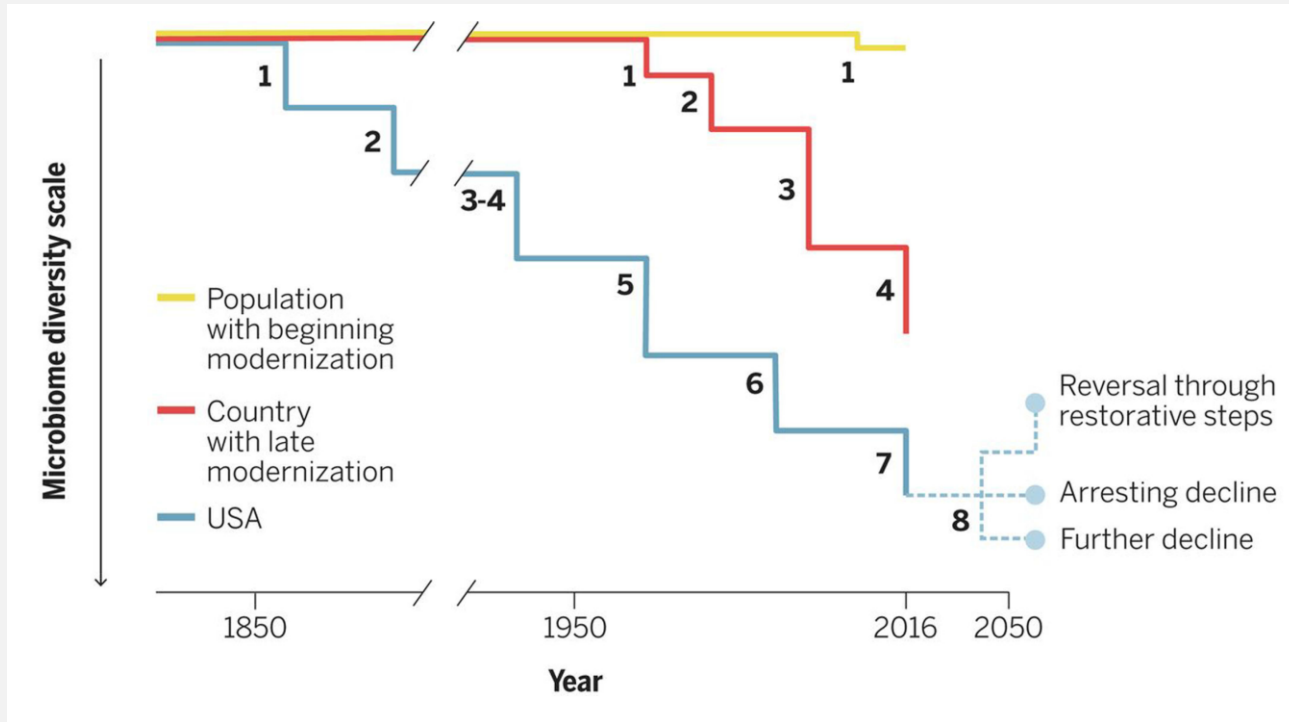
National Report  
on Medicines  
use in Italy  
Year 2018

# Antibiotics' prescription in the pre-pandemic years

**Table 2.1.9.** Prescription of antibiotics in the pediatric population by therapeutic category and substance (2018)

Categories and substances	Prevalence (%)	Prescriptions (per 1000 inhab.)	Δ % 18-17
penicillin associations (including beta lactamase inhibitors)	19.9	356.8	-3.8
macrolides and lincosamides	11.3	177.7	-3.4
oral cephalosporins	10.2	175.6	-3.8
broad-spectrum penicillins and penicillins sensitive to beta lactamases	7.6	143.1	3.1
cephalosporine im/ev iii-iv gen	0.5	31.0	-2.1
tetracyclines	0.3	8.4	1.6
other antibiotics	0.7	8.2	-4.4
quinolones	0.4	7.5	-3.4
cephalosporins im/ev ii gen	0.2	4.3	-7.7
sulfonamides and trimetropim	0.2	3.9	-3.6
aminoglycosides	<0.05	3.3	-16.1
cephalosporins im/ev i gen	<0.05	0.3	-15.6

# Antibiotics' consequences on microbiome health



*Science*. 2016 April 29; 352(6285): 544–545.

## Antibiotics' use and children's health

Antibiotic use and inflammatory bowel diseases in childhood

*Gut* 2011;**60**:49–54.

Antibiotic-induced changes in the human gut microbiota for the most commonly prescribed antibiotics in primary care in the UK: a systematic review

*BMJ Open* 2020;**10**:e035677.

Antibiotic Use and Vaccine Antibody Levels

PEDIATRICS Volume 149, number 5, May 2022:e2021052061

# Which children need to be targeted to reduce Ab prescriptions?

## MAIN INDICATIONS FOR ANTIBIOTICS' USE IN CHILDREN

Multilevel mixed-effects logistic regression model for potential determinants of antibiotic prescription without indication.

Variable	OR	95% CI	P-value
<i>Model 1. Outcome: Antibiotic prescription without indication Log-likelihood, -165.63; Wald <math>\chi^2</math>, 75.56; P &lt; 0.0001; No. of obs. = 367</i>			
<b>Clinical diagnosis</b>			
Pharyngotonsillitis*	1.00		
Influenza	0.09	0.03–0.30	< 0.001
Bronchitis	21.60	6.67–70	< 0.001
AOM	15.87	4.09–61.64	< 0.001
Laryngotracheitis	0.30	0.10–0.84	0.022
Sinusitis	0.35	0.07–1.86	0.22
<b>Presence of fever</b>			
No*	1.00		
Yes	3.62	1.83–7.15	< 0.001

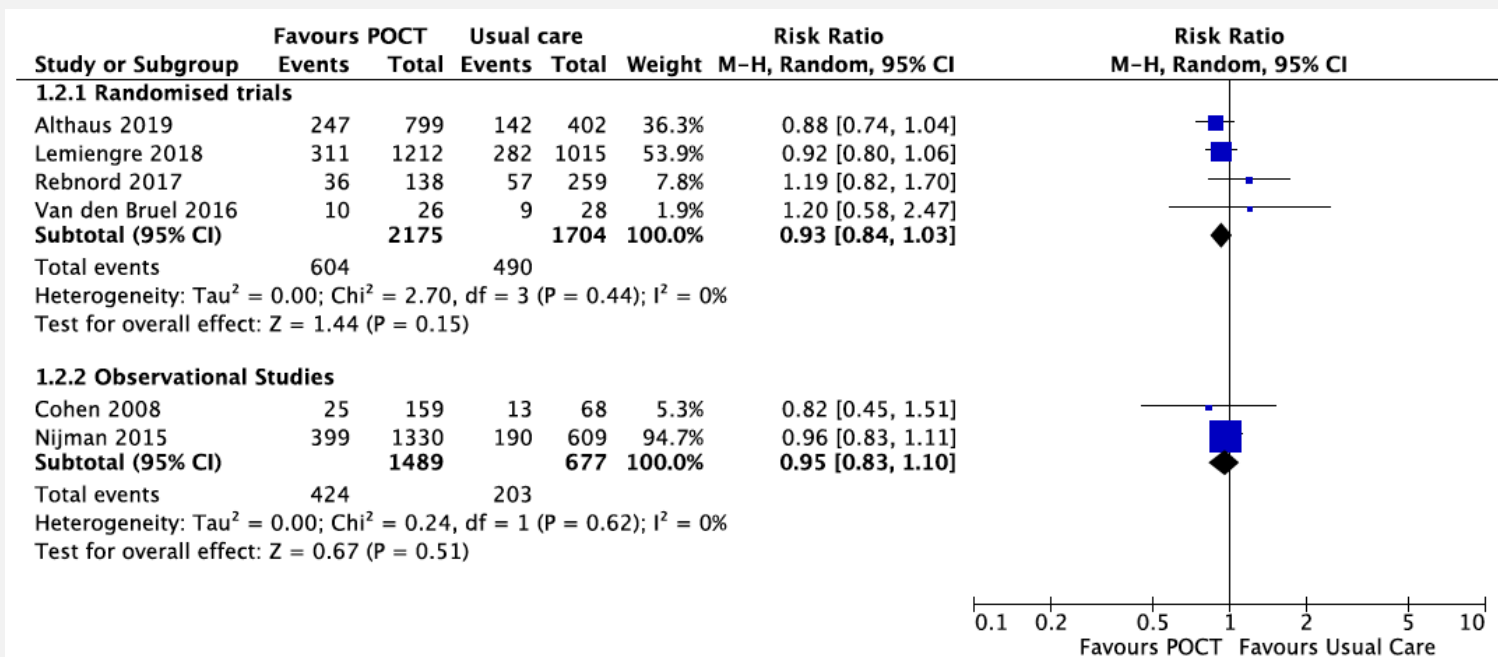


HOW AND WHEN TO USE CRP POCT TO GUIDE ANTIBIOTIC PRESCRIPTION  
IN CHILDREN?

# Efficacy of CRP POC in paediatrics

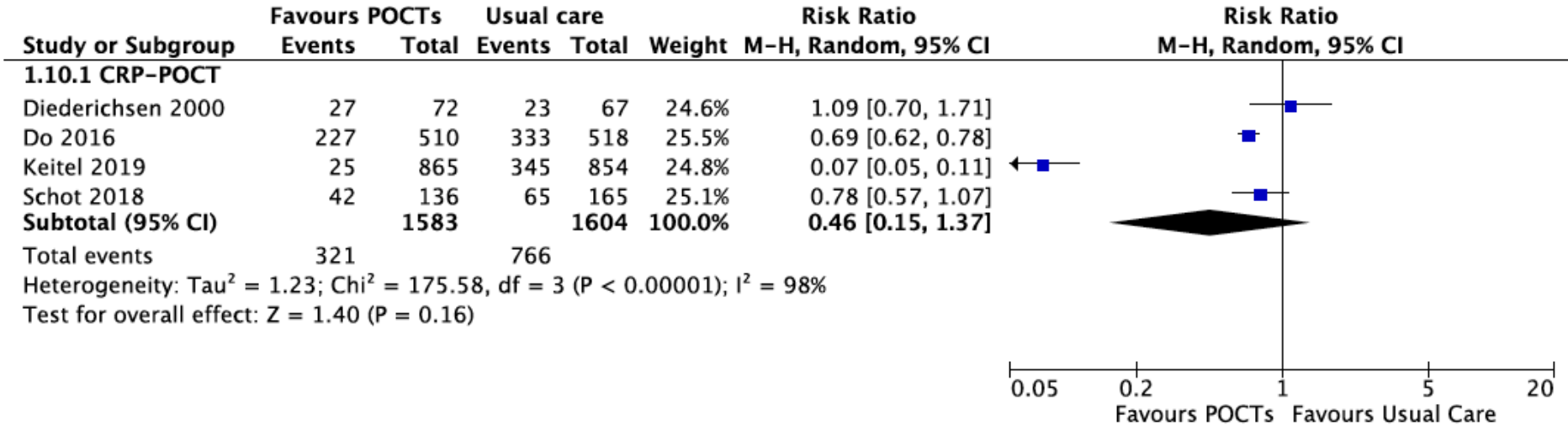


# Immediate antibiotic prescribing for non specific acute fever illnesses



*PLoS One. 2020;15(7):e0235605.*

# Immediate antibiotic prescribing for acute respiratory tract infections



## CONSENSUS STATEMENT #6

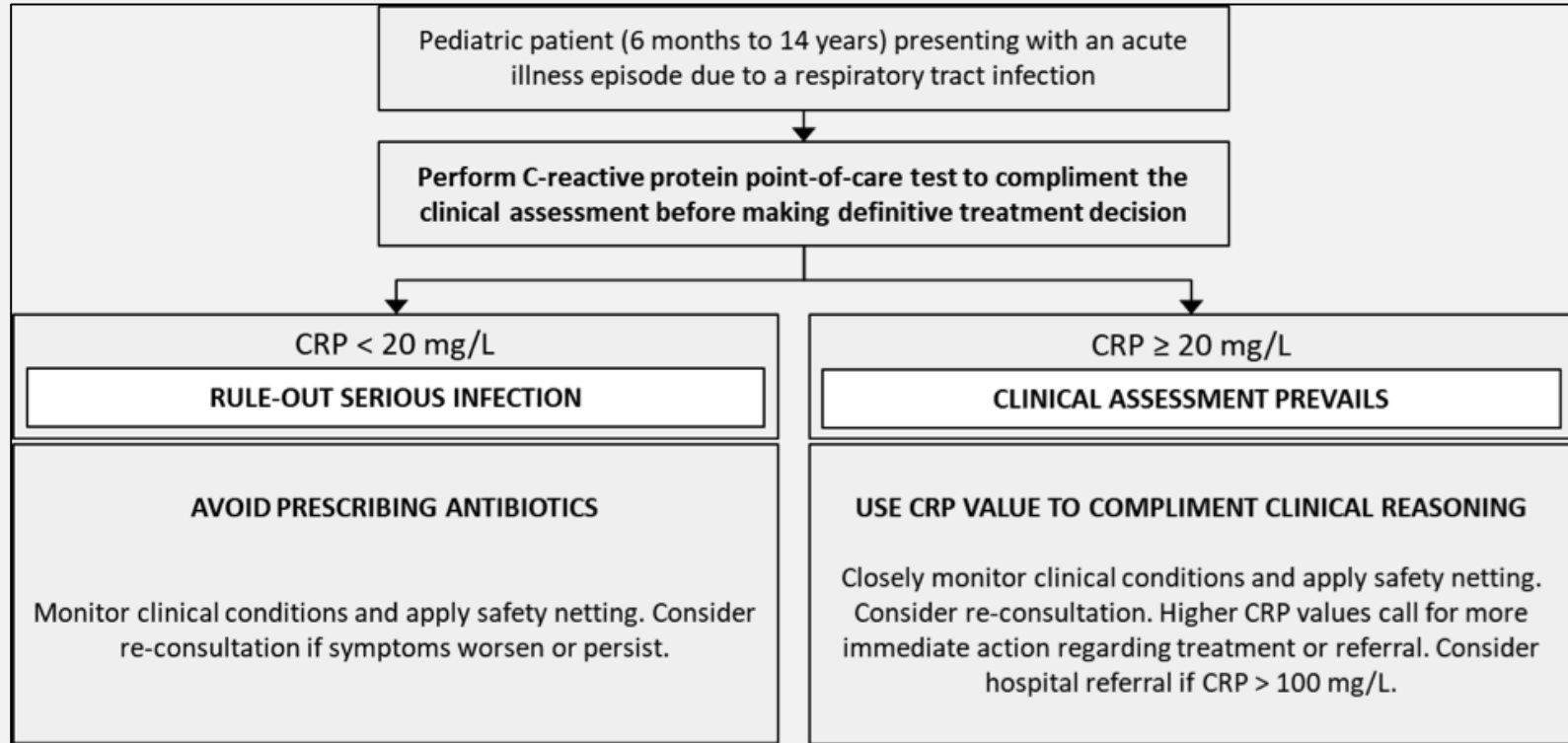
In the ambulatory care of febrile children presenting with symptoms of respiratory illness, CRP POCT can be useful to guide decisions regarding antibiotic prescribing and hospital referrals



HOW AND WHEN TO USE CRP POCT TO GUIDE ANTIBIOTIC PRESCRIPTION  
IN CHILDREN?

# How to improve CRP POC in children?

# Our proposed algorithm



# Guidance on CRP POCT cut-off values

CRP < 20 mg/L

**RULE-OUT SERIOUS INFECTION**

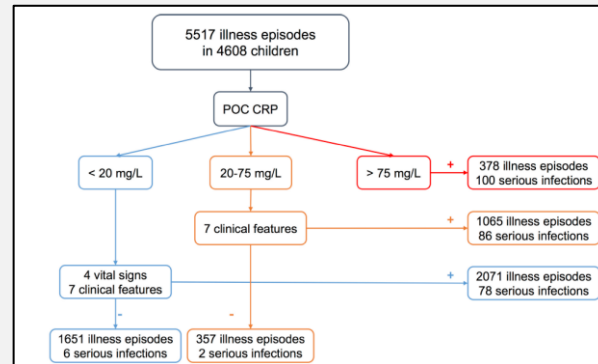
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**AVOID PRESCRIBING ANTIBIOTICS**

Monitor clinical conditions and apply safety netting. Consider re-consultation if symptoms worsen or persist.

- CRP < 20 mg had a negative predictive value of 99.6%
- 6 infections were missed of whom UTI and bronchopneumonia

- Very high negative predictive value
- No antibiotics' prescription
- Careful monitoring of clinical conditions, particularly if the consultation occurs in the first 24-48 hours of infection



# The importance of clinical assessment

CRP $\geq$ 20 mg/L
<b>CLINICAL ASSESSMENT PREVAILS</b>
<b>USE CRP VALUE TO COMPLIMENT CLINICAL REASONING</b> Closely monitor clinical conditions and apply safety netting. Consider re-consultation. Higher CRP values call for more immediate action regarding treatment or referral. Consider hospital referral if CRP > 100 mg/L.

In this scenario the clinical assessment of the patient prevails, and CRP values can be used to complement clinical reasoning using the following parameters:

1. The timing of the CRP measurement
2. The degree of elevation of CRP values
3. The suspected type of infection plays an important role when making a therapy decision.

## CONSENSUS STATEMENT #5

An effective implementation combining CRP POCT together with evidence-based complementary strategies, can increase the contribution to more appropriate antibiotic prescribing

- **Communication skills training to clinicians/physicians**
- **Safety netting advice**
- **Delayed prescribing techniques**
- **Decision Aids**



# TAKE HOME MESSAGES

- Widespread antibiotics' use and consequent antibiotic resistance are a significant threat also for the pediatric population
- Evidence clearly demonstrates inappropriate use of antibiotics in young children, which are not only useless, but may have significant consequences on their health
- Although not conclusive as in adults, evidence suggests the potential efficacy of CRP POC in order to decrease inappropriate antibiotics' prescription in children
- Our proposed algorithm together with the suggested complimentary strategies may represent a promising strategy in order to decrease Ab overprescription

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