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Oxford Primary Care 2015

Cutting-edge research in the consulting room

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In partnership with:

NHS
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Postinfectious cough and pertussis

Dr Kay Wang, GP and Academic Clinical Lecturer

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Thank you

- 19 Beaumont Street Surgery
- Bampton Surgery
- Bicester Health Centre
- Broadshires Health Centre
- Burnham Health Centre
- Church Street Practice
- Denham Medical Centre
- Eynsham Medical Group
- Holyport Surgery
- Horsefair Surgery
- Langley Health Centre
- Malthouse Surgery
- Mill Stream Surgery
- Morland House Surgery
- Newbury Street Practice
- Red House Surgery
- Summertown Health Centre
- Temple Cowley Health Centre
- Thatcham Medical Practice
- Trinity Health
- Waterfield Surgery
- West Bar Surgery
- Westongrove Research Centre
- Woosehill Surgery

Objectives

- To consider the differential diagnosis of postinfectious cough
- To summarise the prognosis of postinfectious cough
- To examine the role of pertussis (whooping cough) in postinfectious cough

Case scenario 1

- 35-year-old teacher
- Persistent cough for 6/52
- Cough triggered by talking
- Ticklish sensation in throat leading to bouts of coughing
- Not helped by over the counter cough medication
- Never smoked, no known underlying medical conditions

Case scenario 1

- 35-year-old teacher
- Persistent cough for 6/52
- Cough triggered by talking
- Ticklish sensation in throat leading to bouts of coughing
- Not helped by over the counter cough medication
- Never smoked, no known underlying medical conditions

Differential diagnosis?

Classification of cough[1,2]

- Acute cough - less than 3 weeks
- Subacute cough - 3 to 8 weeks
- Chronic cough - More than 8 weeks

[1]Morice AH et al. Thorax 2006;61(Suppl I):i1–i24

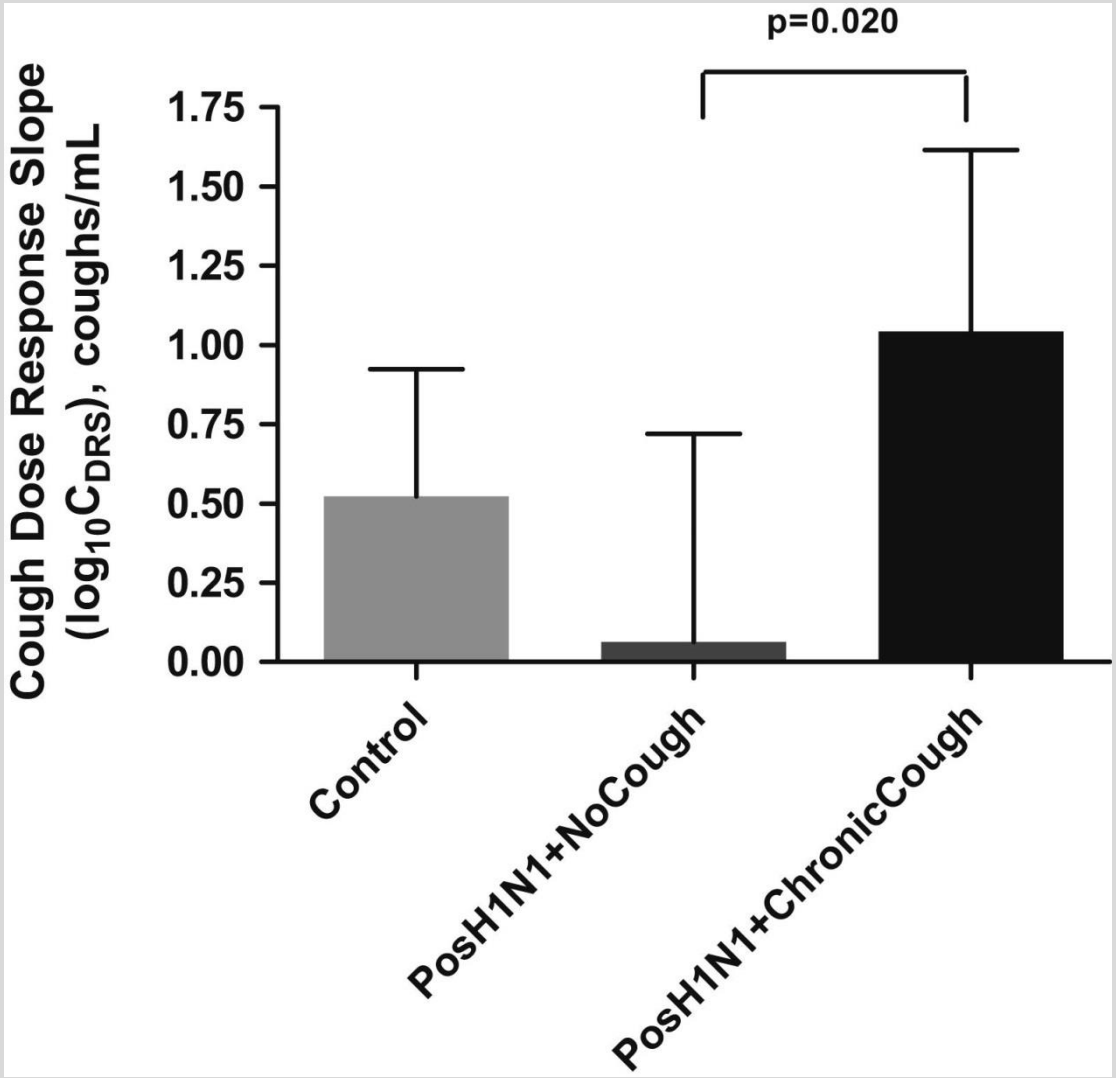
[2]Pratter MR et al. Chest 2006;129;222S-231S

Causes of subacute cough

Cause	Number of patients (%) (n=184)
Postinfectious	89 (48.4%)
Post nasal drip	61 (33.2%)
Cough-variant asthma	29 (15.8%)
Other (e.g. eosinophilic bronchitis)	5 (2.7%)

Kwon *et al.* Chest 2006;129;1142-1147

Post viral cough reflex hypersensitivity

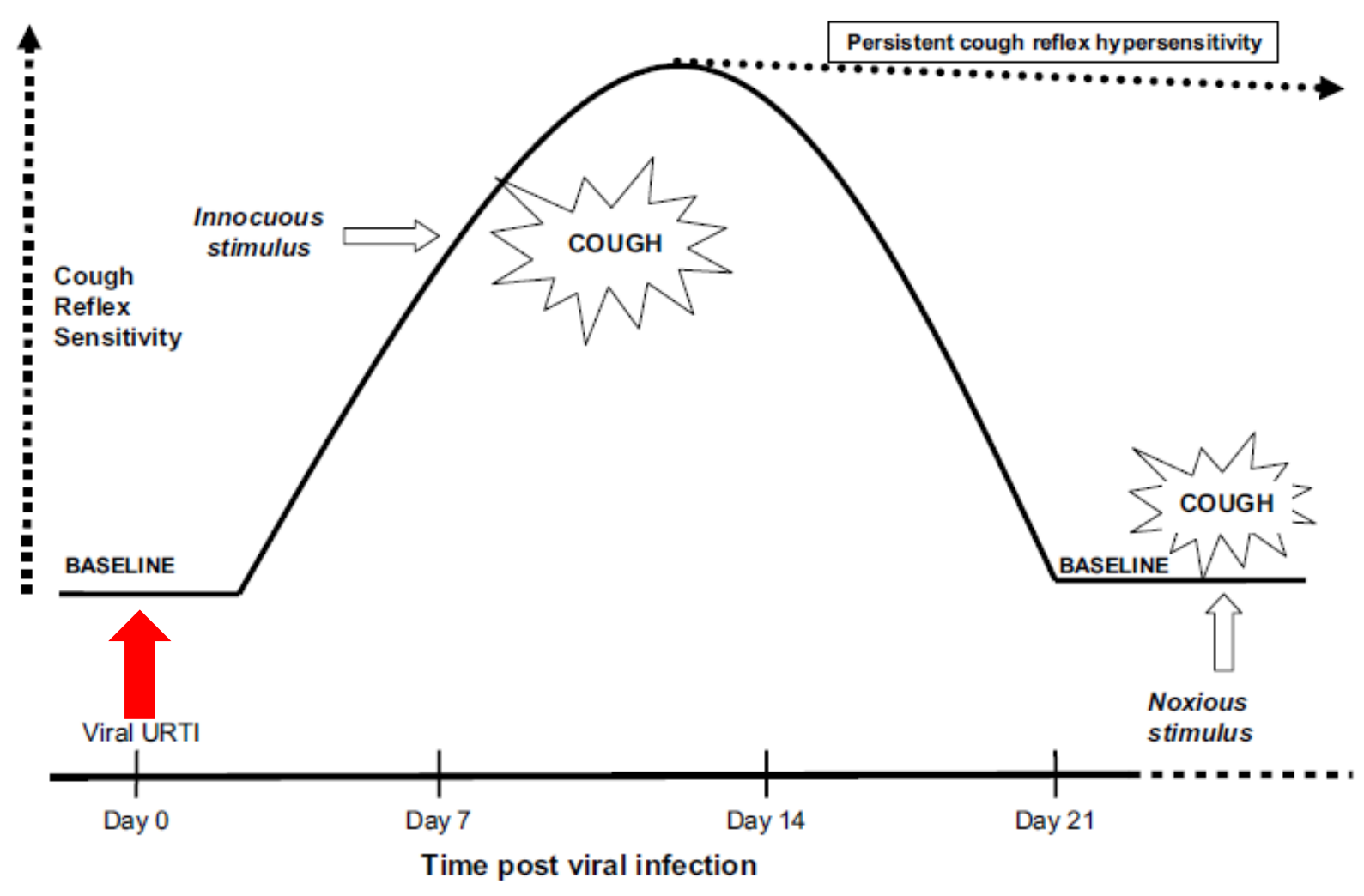


Ryan et al. Respir Med. 2012;106(1):138-144

Cough reflex hypersensitivity

- Cough triggered by ‘low threshold’ stimuli
  - Talking, laughing, scents/odours, changes in temperature
- Bouts of coughing
- Abnormal throat sensation
  - Itch, tickle, ‘urge to cough’, choking sensation

Post viral cough reflex hypersensitivity



McGarvey et al. Pulm Pharmacol Ther. 2009;22(2):59-64

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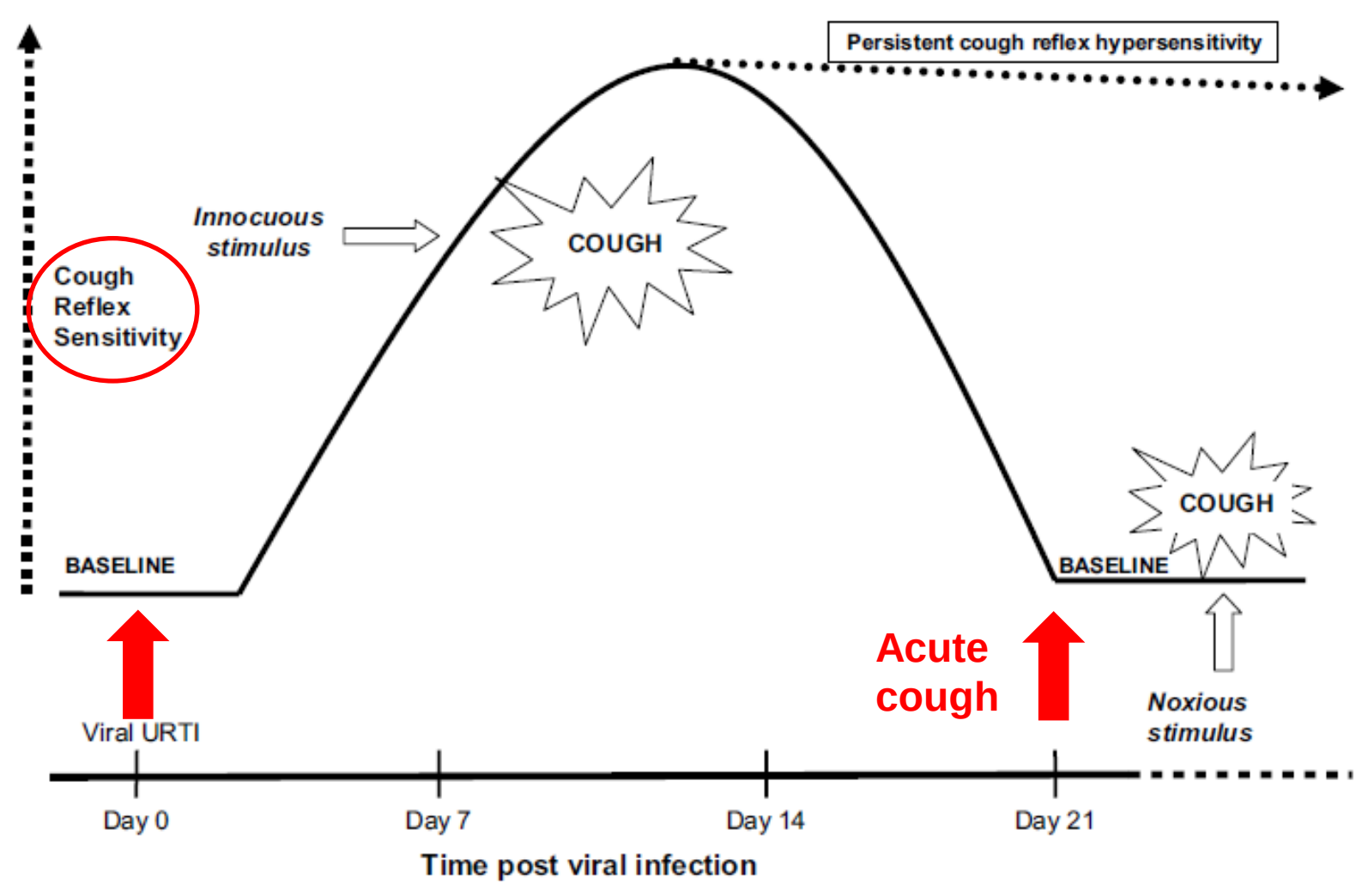

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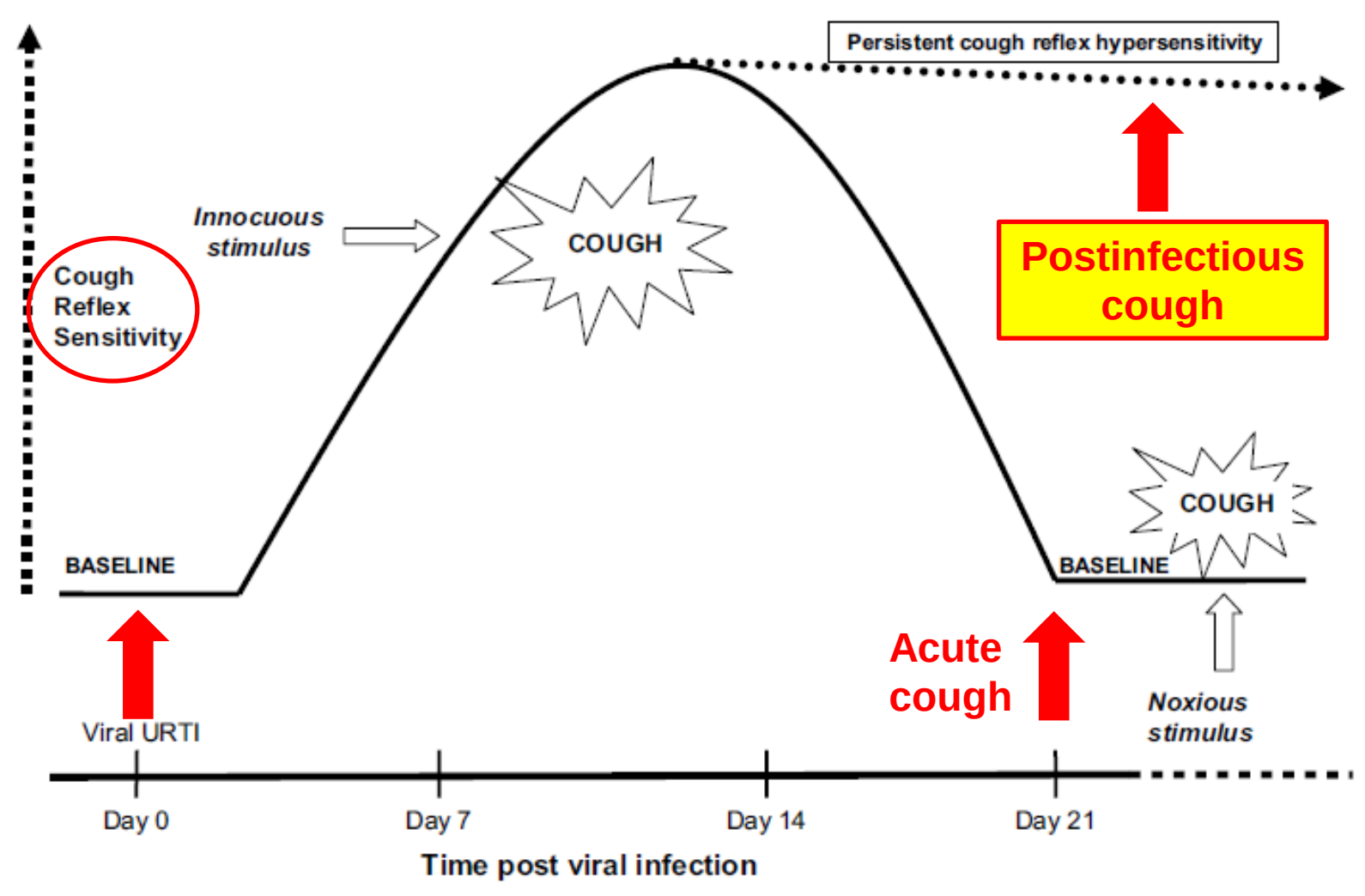
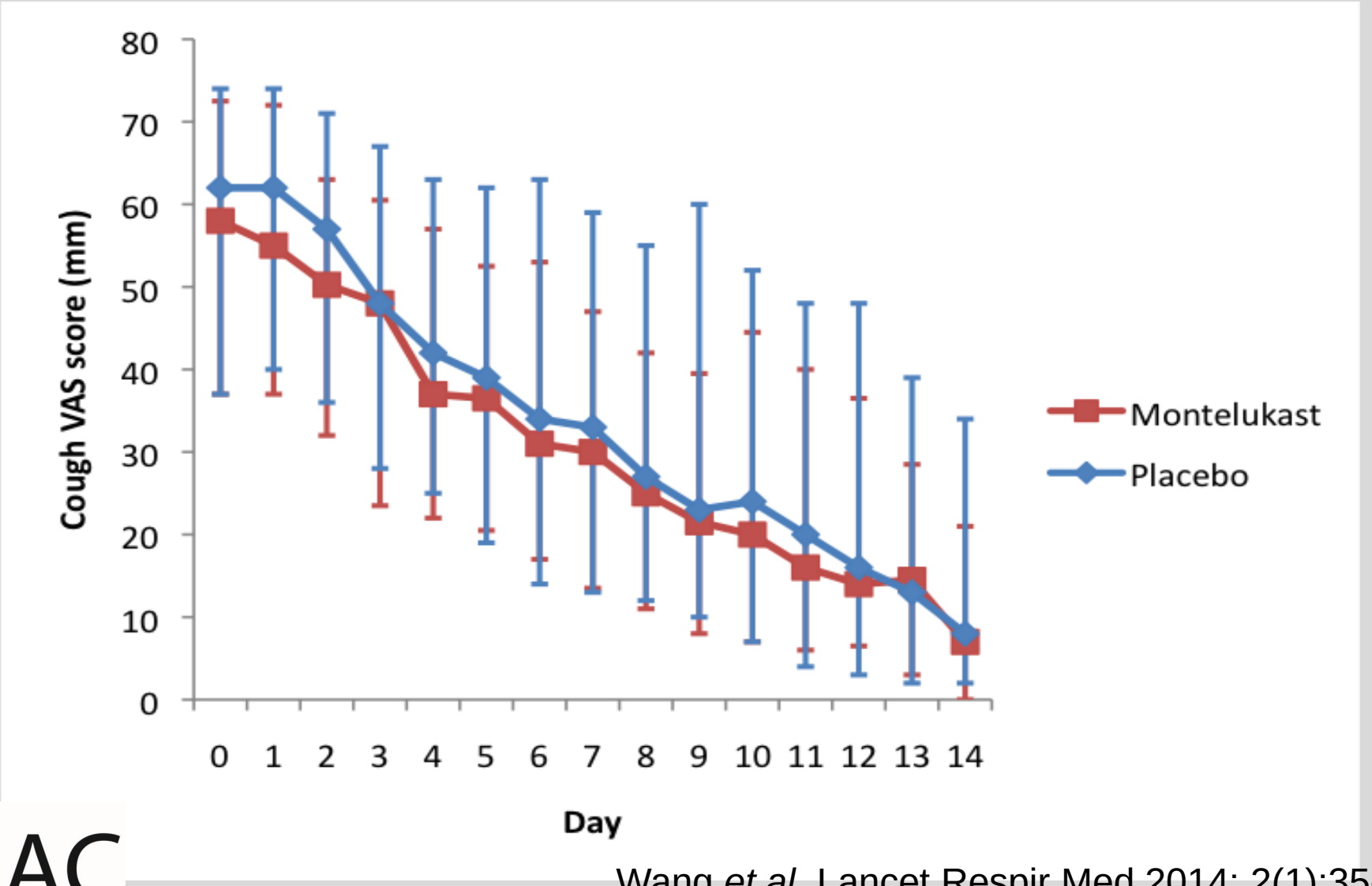


McGarvey et al. Pulm Pharmacol Ther. 2009;22(2):59-64

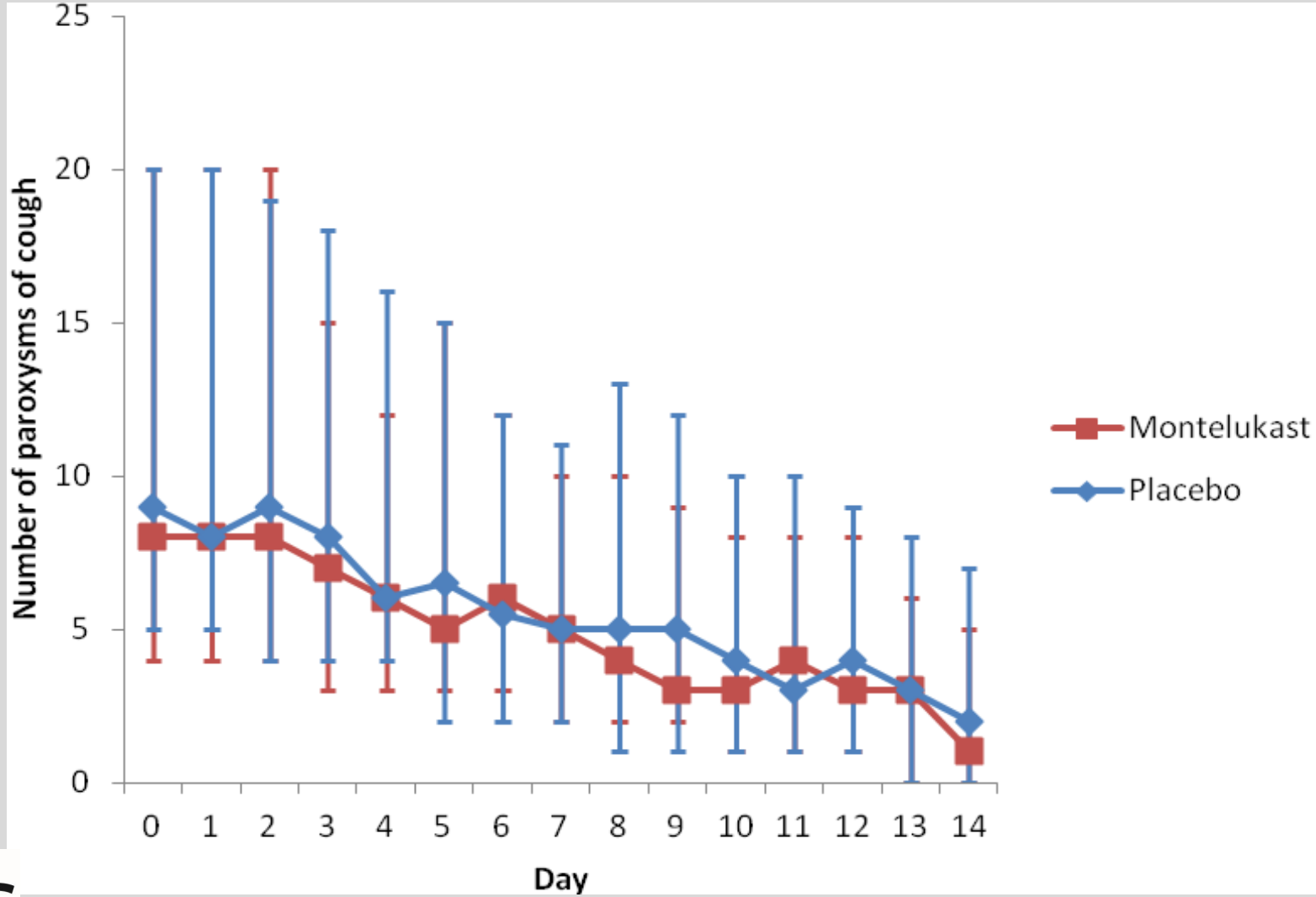
Cough Visual Analogue Scale Scores



Wang *et al.* Lancet Respir Med 2014; 2(1):35-43

MAC
Montelukast & Persistent Cough

Number of paroxysms of cough



Wang *et al.* Lancet Respir Med 2014; 2(1):35-43

MAC
Montelukast & Persistent Cough

- Inhaled ipratropium bromide (Holmes *et al.* Respir Med 1992)
  - Improvement in cough severity after 3 weeks (n=14)
  - used unvalidated patient-reported cough outcome

- Nociceptin opioid 1 (NOP1) agonist (Woodcock *et al.* Lung 2010)
  - No improvement in cough severity scores
  - Difficulties with recruitment

- Inhaled corticosteroids (El-Gohary *et al.* Fam Pract 2013)
  - 2/4 trials reported improvement in cough

- Montelukast (Wang *et al.* Lancet Respir Med 2014)
  - No improvement in cough-specific quality of life

Managing postinfectious cough

- Explain mechanism
  - Transient increase in cough reflex sensitivity
- Explain prognosis
  - Virtually resolves around 2 weeks after initial presentation in around 50% of patients.
- No proven effective treatments

Case scenario 2

- 11-year-old boy
- Persistent cough for 5/52
- Bouts of coughing
- SOB and vomiting after bouts of coughing
- All vaccinations up to date

Case scenario 2

- 11-year-old boy
- Persistent cough for 5/52
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- SOB and vomiting after bouts of coughing
- All vaccinations up to date

Diagnosis?

WHO clinical case definition of whooping cough (pertussis)

- Cough lasting ≥2 weeks, **plus** at least one of:
  - Paroxysms of coughing
  - Inspiratory whooping
  - Post-tussive vomiting

- http://www.whoopingcough.net/

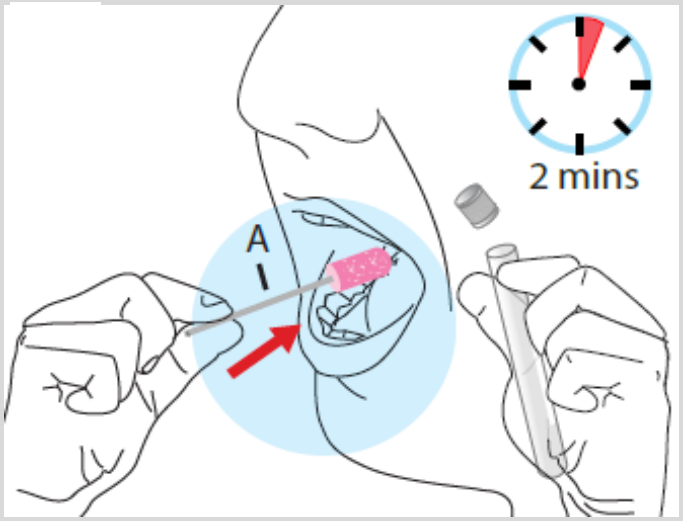
Whooping cough (pertussis)

- One of commonest vaccine preventable diseases

- UK pertussis vaccinations:
  - Primary course at 2, 3 and 4 months
  - Pre-school booster at 3 years 4 months (introduced in October 2001)

Oral fluid test for pertussis

Anti-pertussis toxin IgG



>= 70 arbitrary units (aU): pertussis positive

60-69 aU: borderline; <60 aU: pertussis negative

Laboratory-confirmed pertussis

- Total cohort
  - 56/279 (20%, 95% CI 16% to 25%)

- Fully vaccinated* children
  - 39/215 (18%, 95% CI 13% to 24%)

*Three doses of primary pertussis vaccine + pre-school pertussis booster vaccination

CAPS

The Children And Persistent cough Study

Wang et al. BMJ 2014;348:g3668

Laboratory-confirmed pertussis

	Montelukast (n=137)	Placebo (n=139)
Pertussis positive	31 (23%)	39 (28%)
Vaccinated*	52 (38%)	58 (42%)

* 3 doses of pertussis vaccine documented in medical records

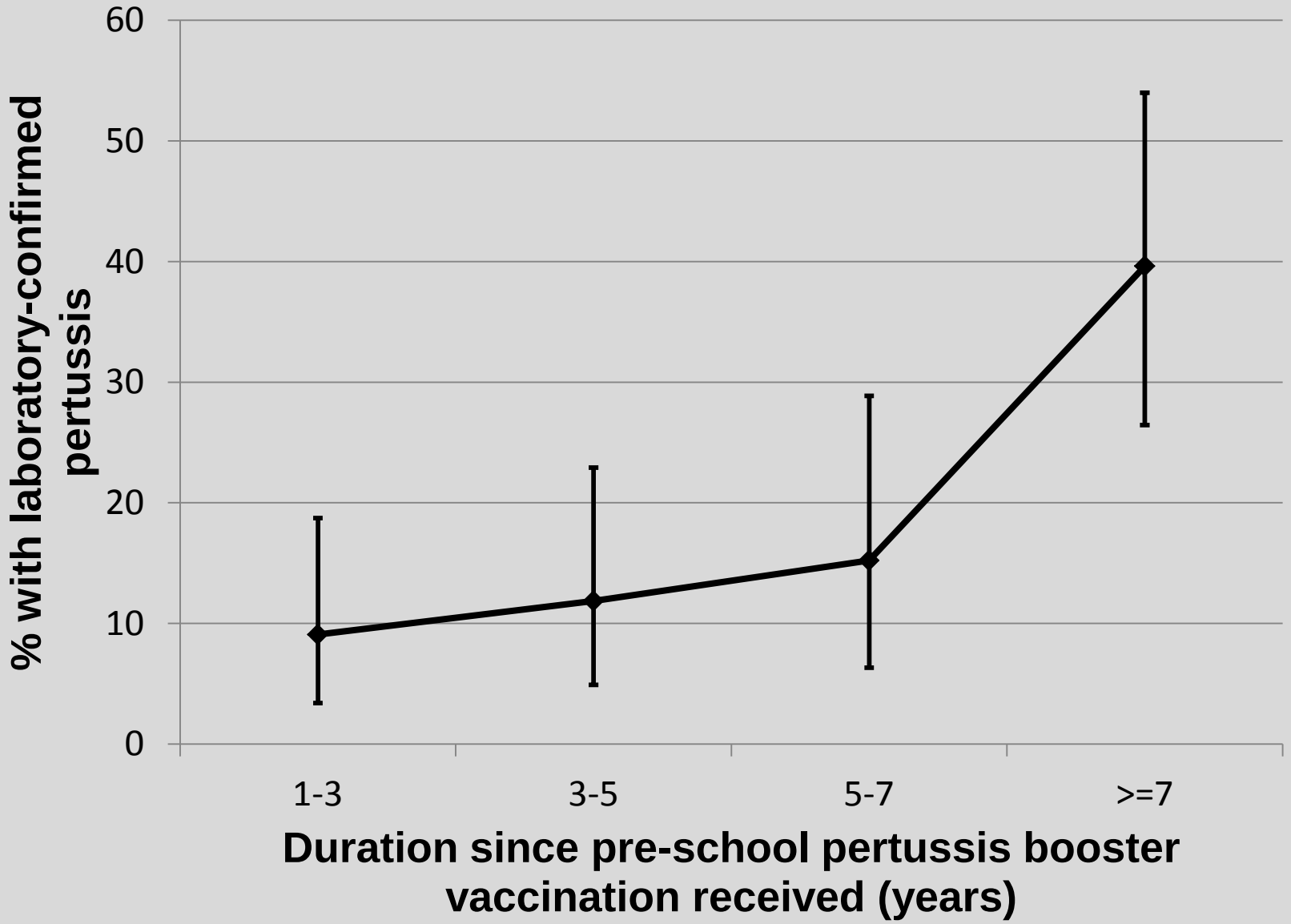
MAC
Montelukast & Persistent Cough

Montelukast for Adults with persistent Cough

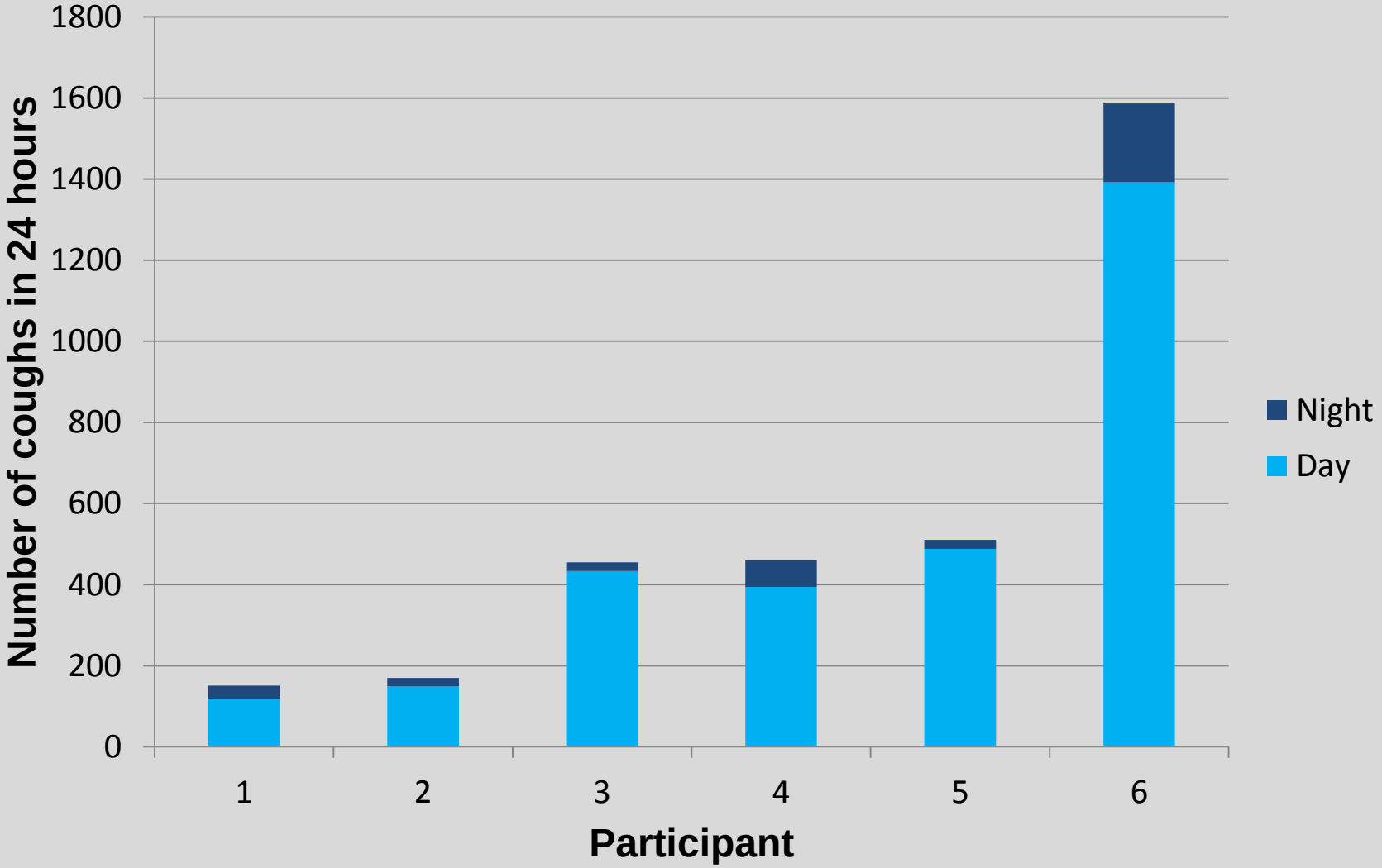
Wang et al. Lancet Respir Med 2014; 2(1):35-43

Age	Clinical symptoms	
	≤ 2 weeks cough	> 2 weeks cough*
≤ 1 yr Hospitalised	NPA/NPS/PNS for PCR (RVPBRU) **or** NPS/PNS for culture (local laboratory)[1]	NPA/NPS/PNS for PCR (RVPBRU) **or** NPS/PNS for culture (local laboratory)[1]
≤ 1 yr[2] Community	NPS/PNS for culture (local laboratory)[1]	Serum for serology (RVPBRU)
> 1 yr to 6 yrs[2]		
> 6yrs[3]		

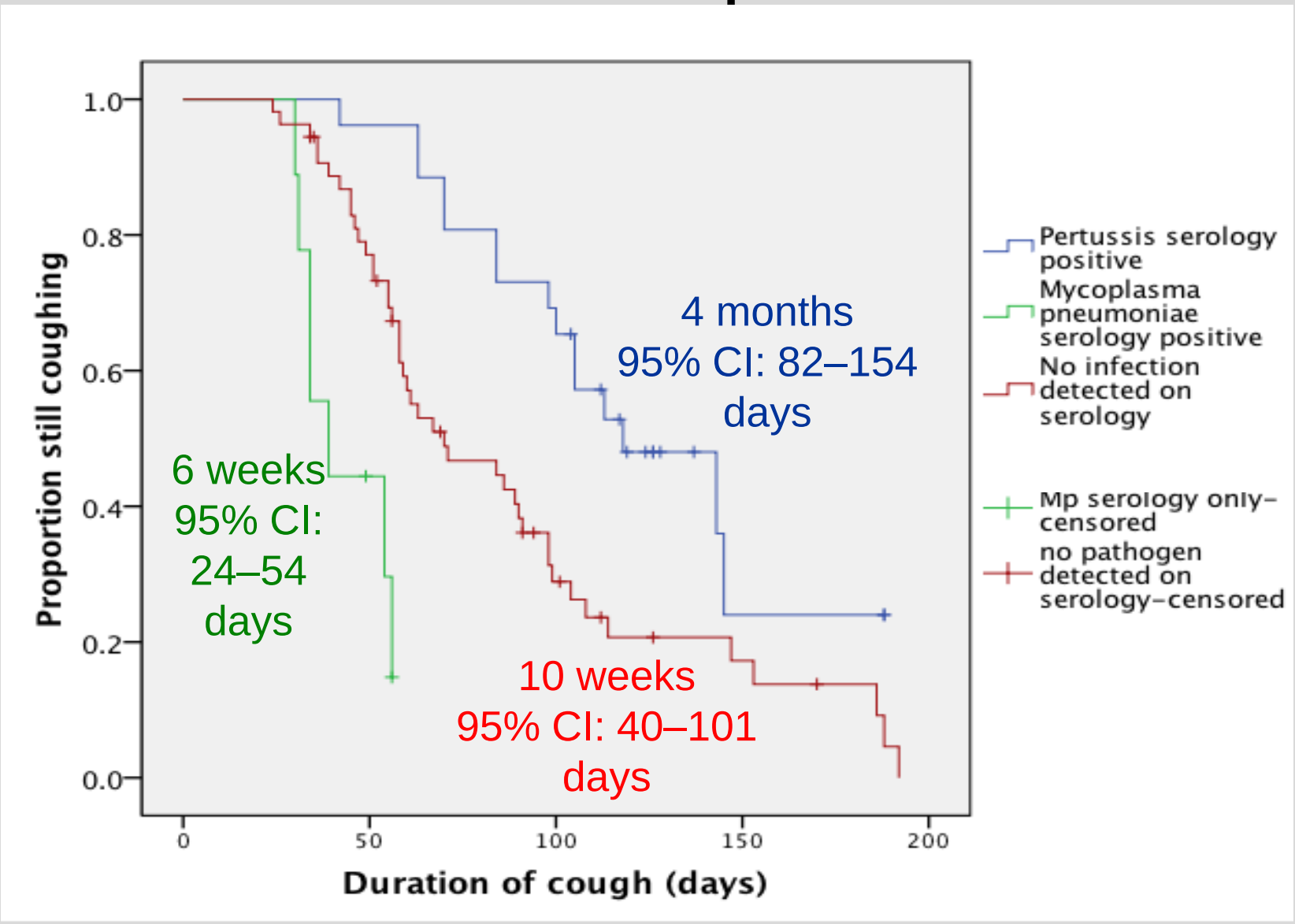
HPA guidelines for the Public Health Management of Pertussis (updated Oct 2012)


60
50
40
30
20
10
0
% with laboratory-confirmed pertussis
1-3
3-5
5-7
>=7
Duration since pre-school pertussis booster vaccination received (years)

Cough frequency in pertussis



Duration of pertussis-induced



Wang *et al.* Pediatr Infect Dis J. 2011; 30:1047-51

Role of macrolides

Mycoplasma pneumoniae

- Recommended for the treatment of suspected *M. pneumoniae* infections
- Insufficient evidence to demonstrate efficacy of macrolide antibiotics in the treatment of laboratory-confirmed *M. pneumoniae*[1]

[1]Gardiner et al. Cochrane Database Syst Rev. 2015 Jan 8;1:CD004875

Whooping cough

- Start within 3 weeks of onset of cough
- Recommended to reduce risk of ongoing pertussis transmission[2]
- Have not been shown to reduce duration or severity of cough[2]

[2] Altunaiji et al. Cochrane Database Syst Rev. 2007 Jul 18;(3):CD004404

Treatments for cough due to pertussis

Treatment (versus placebo)	Mean difference (95% confidence interval)
Diphenhydramine*	1.90 (-4.66 to 8.46)
Salbutamol*	-0.22 (-4.13 to 3.69)
Pertussis immunoglobulin**	-0.07 (-0.42 to 0.27)

*Number of paroxysms of cough per 24 hours

** Mean paroxysmal coughs per hour

Wang et al. Cochrane Database Syst Rev. 2014

Montelukast for pertussis

	Montelukast (n=31)	Placebo (n=39)	Between group difference (unadjusted)	Between group difference (adjusted)
Change in LCQ total score (baseline to 2 weeks)	2.2 (1.0 to 3.3)	3.1 (2.1 to 4.1)	-0.9 (-2.4 to 0.6) p=0.2	-0.8 (-2.3 to 0.7) p=0.3
Change in LCQ total score (baseline to 4 weeks)	4.5 (3.1 to 6.0)	5.6 (4.5 to 6.8)	-1.1 (-2.9 to 0.7) p=0.2	-1.0 (-2.8 to 0.8) p=0.3
Overall cough severity	550.8 (452.1 to 649.6)	623.0 (529.4 to 716.5)	-72.1 (-207.9 to 63.5) p=0.3	-110.3 (-208.6 to -11.9) p=0.03
Paroxysmal cough severity	138.6 (92.2 to 185.0)	162.4 (101.6 to 223.3)	-23.9 (-104.2 to 56.5) p=0.6	-9.1 (-27.4 to 45.6) p=0.6

Wang *et al.* Lancet Respir Med 2014; 2(1):35-43

Managing pertussis

- Consider pertussis as potential diagnosis in patients with persistent cough, even if previously vaccinated
- Start macrolides if within first 21 days of onset of cough
- Role of macrolides is to prevent transmission

Summary

- Postinfectious cough accounts for nearly 50% of subacute coughs and is predominantly caused by cough reflex hypersensitivity
- Most subacute cough resolves within 2 weeks of clinical presentation, but duration of cough varies according to type of infection
- Pertussis should still be considered in adults and fully vaccinated individuals

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Thank you for listening

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C-reactive protein and other point-of-care tests in primary care

Dr Ann Van den Bruel
Associate Professor
Director NIHR Diagnostic Evidence Co-operative

C-reactive protein

- Plasma protein
- Produced in the liver
- Inflammatory marker:
  - Levels increase during inflammation and after tissue damage

- Used for:
  - Diagnosis
  - Prediction
  - Management decisions

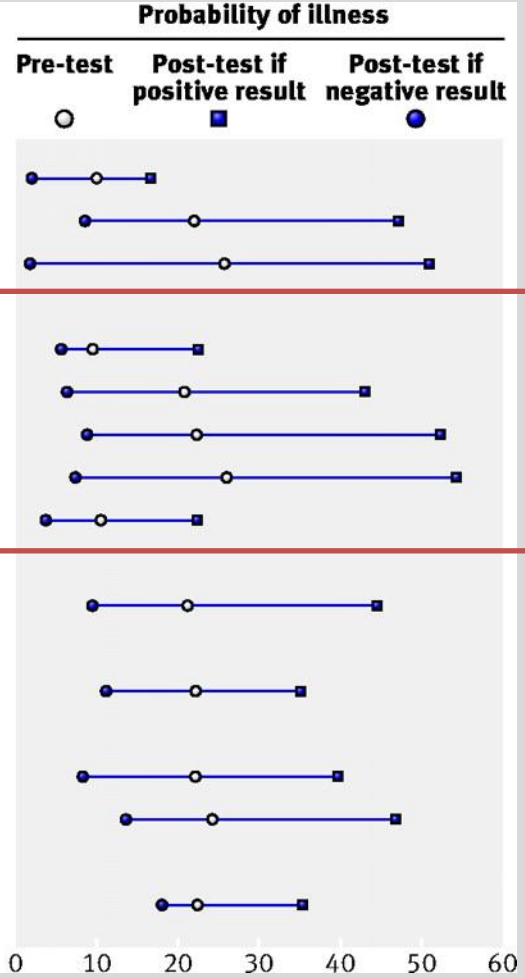
CRP for the diagnosis of …

- Serious infections in children

- Pneumonia
- Complicated urinary tract infection
- Sepsis and meningitis
- Osteomyelitis, cellulitis

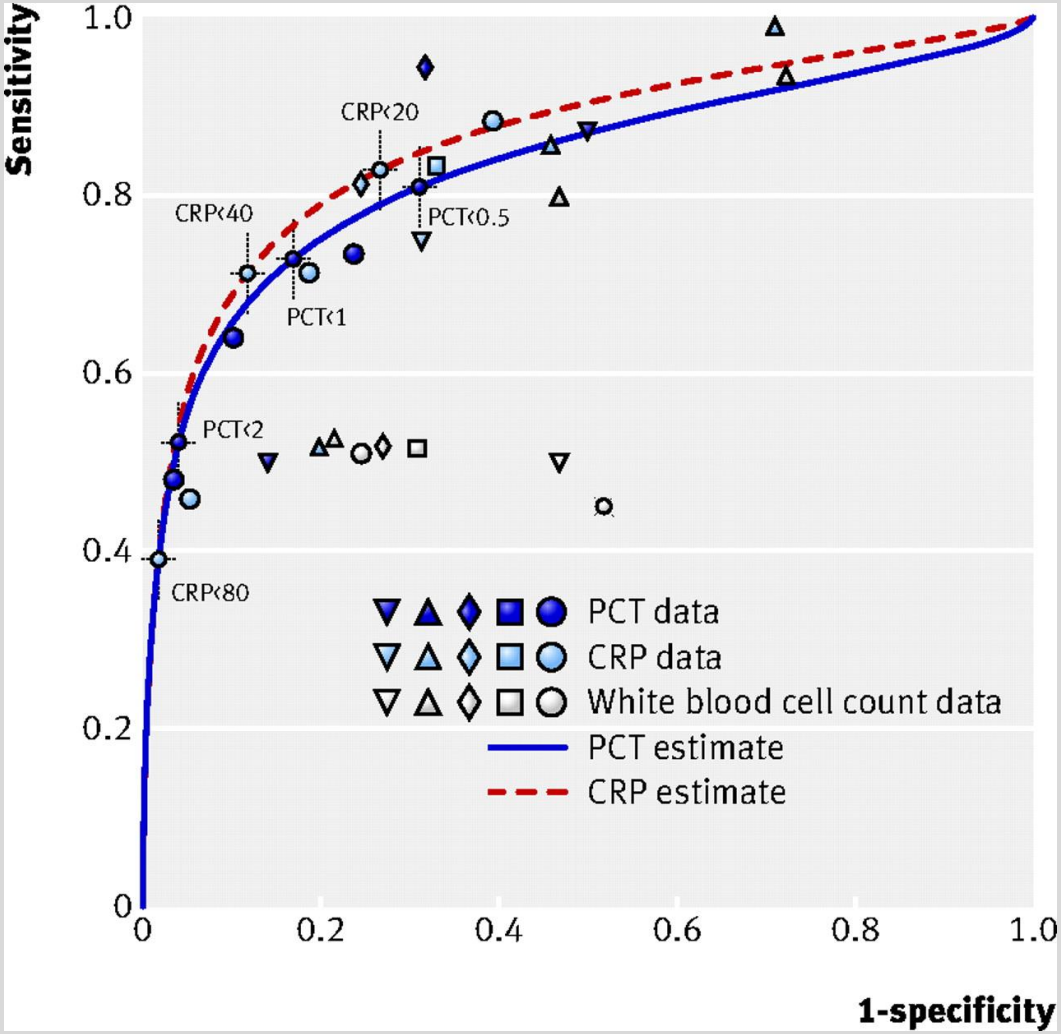
Diagnostic value of inflammatory markers for serious infection in febrile children.

Study	Prevalence setting	Cut-off value	Likelihood ratio (95% CI) Positive	Likelihood ratio (95% CI) Negative
Procalcitonin (ng/mL)				
Thayyil[14]	Intermediate	>0.5	1.75 (1.22 to 2.50)	0.25 (0.04 to 1.59)
Andreola[16]	High	>0.5	3.11 (2.47 to 3.93)	0.35 (0.25 to 0.49)
Galetto-Lacour[21]	High	>0.5	2.96 (2.33 to 3.80)	0.08 (0.03 to 0.25)
C reactive protein (mg/L)				
Hsiao[22]	Intermediate	>9.8	2.61 (1.81 to 3.76)	0.61 (0.44 to 0.83)
Berger[39]	High	>20	2.53 (1.82 to 3.50)	0.25 (0.11 to 0.56)
Andreola[16]	High	>40	3.79 (2.92 to 4.94)	0.35 (0.26 to 0.49)
Galetto-Lacour[21]	High	>40	3.35 (2.45 to 4.57)	0.25 (0.14 to 0.43)
Thayyil[14]	Intermediate	>50	2.40 (1.40 to 4.12)	0.36 (0.11 to 1.22)
Erythrocyte sedimentation rate (mm/h)				
Berger[39]	High	>50	2.49 (1.73 to 3.59)	0.34 (0.17 to 0.65)
Interleukin 1 receptor antagonist (pg/L)				
Galetto-Lacour[19]	High	>9500	1.90 (1.34 to 2.70)	0.46 (0.25 to 0.84)
Interleukin 6 (pg/L)				
Galetto-Lacour[19]	High	>50	2.29 (1.63 to 3.20)	0.33 (0.16 to 0.67)
Galetto-Lacour[20]	Intermediate	≥100	2.74 (1.33 to 5.61)	0.50 (0.24 to 1.01)
Interleukin 8 (pg/L)				
Galetto-Lacour[19]	High	≥70	1.89 (1.03 to 3.45)	0.77 (0.56 to 1.05)



Ann Van den Bruel et al. BMJ 2011;342:bmj.d3082

Summary receiver operating characteristic curves for C reactive protein (CRP) and procalcitonin (PCT) levels for serious infection.



Ann Van den Bruel et al. BMJ 2011;342:bmj.d3082

NICE guideline feverish illness in children <5 years

- May 2013
- Blood tests only by paediatric specialist
- Full blood count, blood culture and CRP
- Infants <3 months with fever
- Children >3 months with 1 or more red features

Traffic light system for identifying risk of serious illness*

	Green – low risk	Amber – intermediate risk	Red – high risk
Colour (of skin, lips or tongue)	• Normal colour	• Pallor reported by parent/carer	• Pale/mottled/ashen/ blue
Activity	• Responds normally to social cues • Content/smiles • Stays awake or awakens quickly • Strong normal cry/not crying	• Not responding normally to social cues • No smile • Wakes only with prolonged stimulation • Decreased activity	• No response to social cues • Appears ill to a healthcare professional • Does not wake or if roused does not stay awake • Weak, high-pitched or continuous cry
Respiratory		• Nasal flaring • Tachypnoea: – RR >50 breaths/ minute, age 6–12 months – RR >40 breaths/ minute, age >12 months • Oxygen saturation ≤95% in air • Crackles in the chest	• Grunting • Tachypnoea: RR >60 breaths/minute • Moderate or severe chest indrawing
Circulation and hydration	• Normal skin and eyes • Moist mucous membranes	• Tachycardia: – >160 beats/minute, age <12 months – >150 beats/minute, age 12–24 months – >140 beats/minute, age 2–5 years • CRT ≥3 seconds • Dry mucous membranes • Poor feeding in infants • Reduced urine output	• Reduced skin turgor
Other	• None of the amber or red symptoms or signs	• Age 3–6 months, temperature ≥39°C • Fever for ≥5 days • Rigors • Swelling of a limb or joint • Non-weight bearing limb/not using an extremity	• Age <3 months, temperature ≥38°C • Non-blanching rash • Bulging fontanelle • Neck stiffness • Status epilepticus • Focal neurological signs • Focal seizures

CRT, capillary refill time; RR, respiratory rate

This traffic light table should be used in conjunction with the recommendations in the guideline on investigations and initial management in children with fever. See http://guidance.nice.org.uk/CG160 (update of NICE clinical guideline 47).

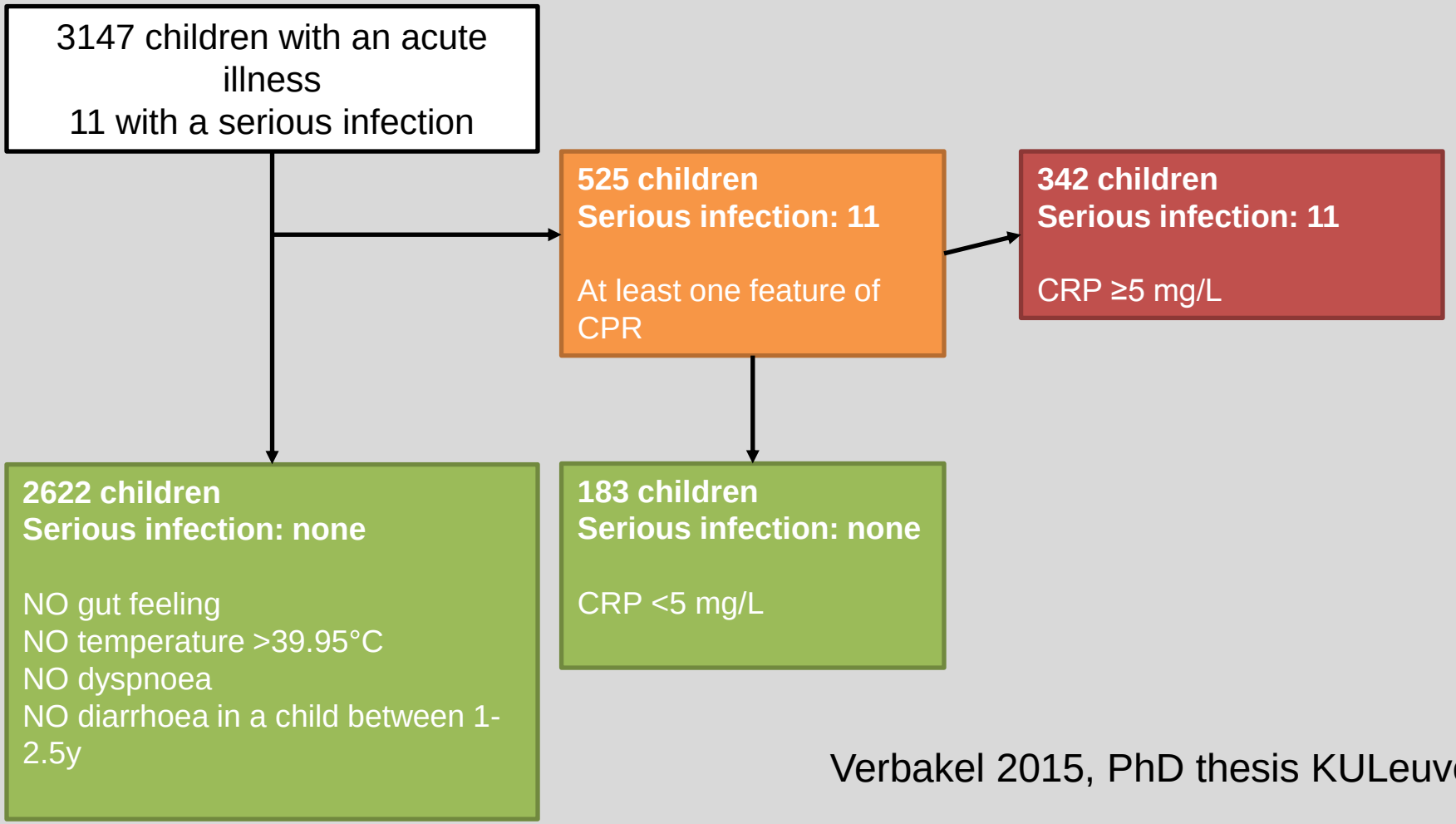
CRP as a point-of-care test

- Result available in 4 minutes
- Pilot study in Oxfordshire out-of-hours services
  - Recruitment rate
  - Planning larger study
  - Finger prick test feasible and acceptable to clinicians and patients/parents

CRP as a point-of-care test

- Prospective study in Flanders in daytime general practice
- Children 1 month-16 years, with an acute illness of a maximum of 5 days
- Outcome = serious infection requiring hospital admission for at least 24h
- Incremental value CRP over and above clinical features

CRP as a point-of-care test



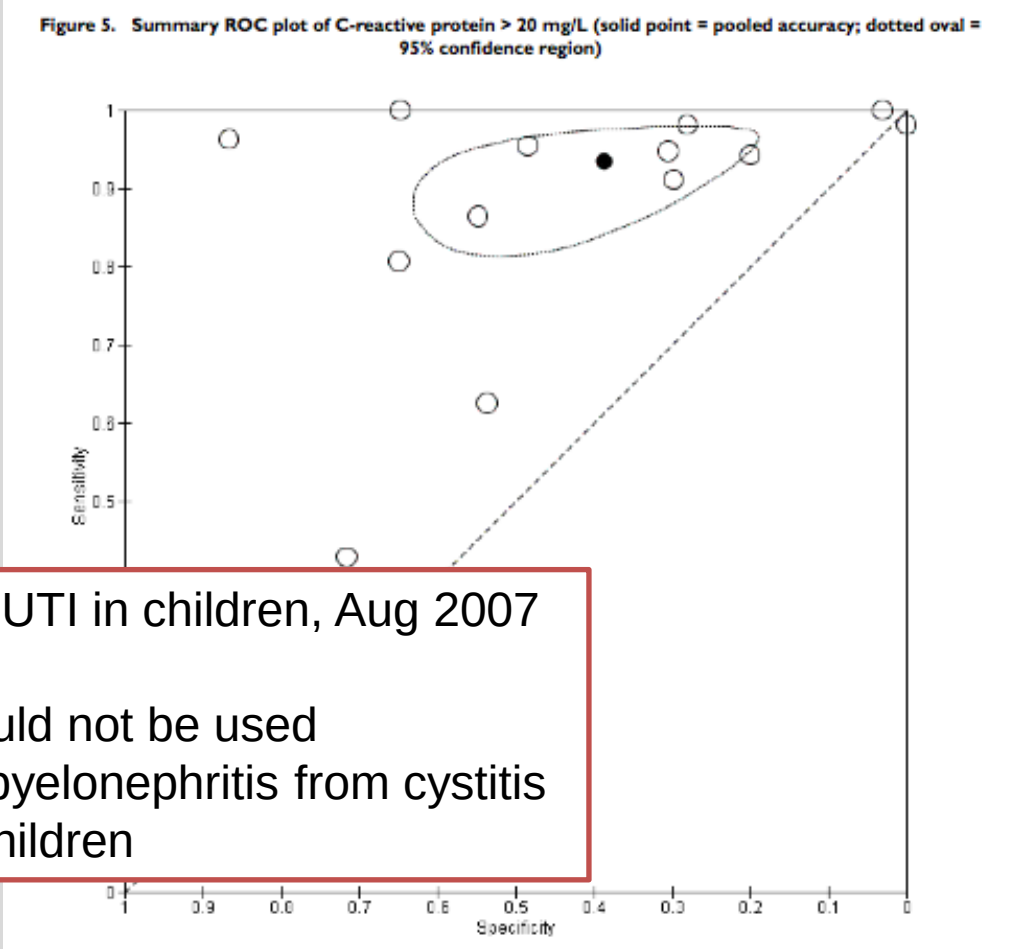
Verbakel 2015, PhD thesis KULeuven

CRP used for the diagnosis of…

- Pyelonephritis in children

- Cochrane review Jan 2015 incl 13 studies
- Differentiate between cystitis and pyelonephritis
- CRP, procalcitonin and erythrocyte sedimentation rate

Pyelonephritis in children



NICE guideline UTI in children, Aug 2007

CRP alone should not be used
to differentiate pyelonephritis from cystitis
in infants and children

CRP used for the diagnosis of

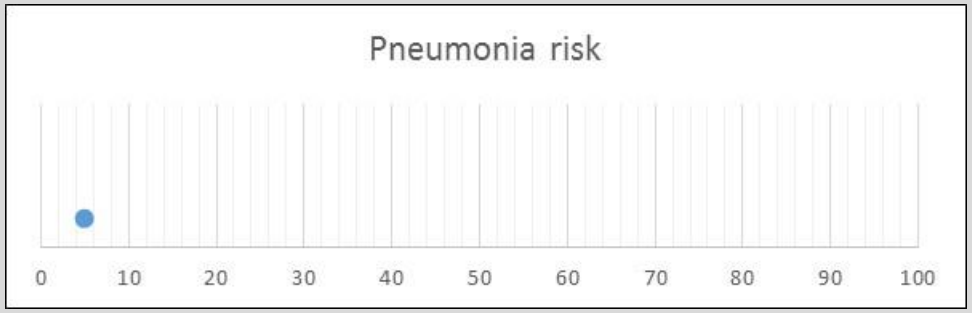
. . . .

- Inflammatory bowel disease (IBD)
  - CRP <5 mg/L excludes IBD

- Appendicitis?
  - Few studies: 3 in children and 2 in adults
  - Results heterogeneous
  - CRP 50 mg/L:
    - Not sensitive enough for ruling out
    - Slightly better for ruling in

CRP used for the diagnosis of

- Community acquired pneumonia
  - CRP 20 mg/L:
    - LR+ 2.1
    - LR- 0.33
- In primary care, signs of lower respiratory tract infection



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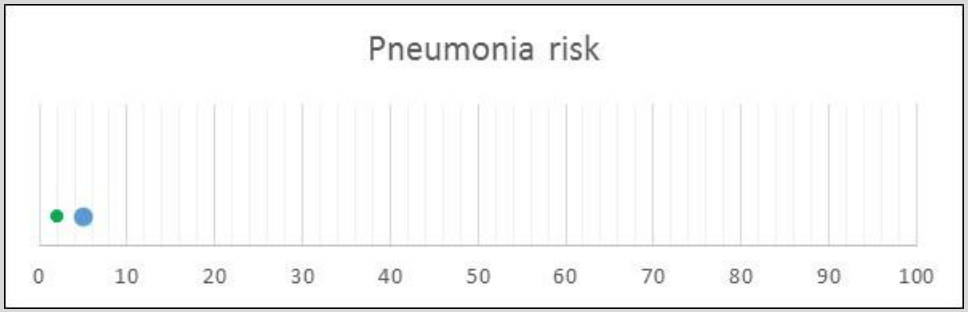

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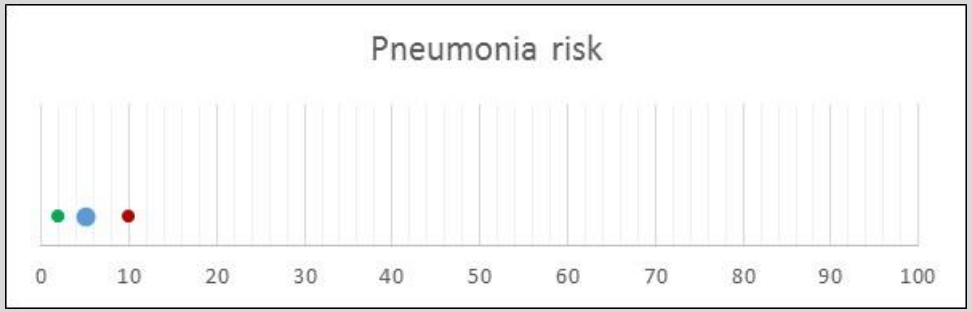


Prediction

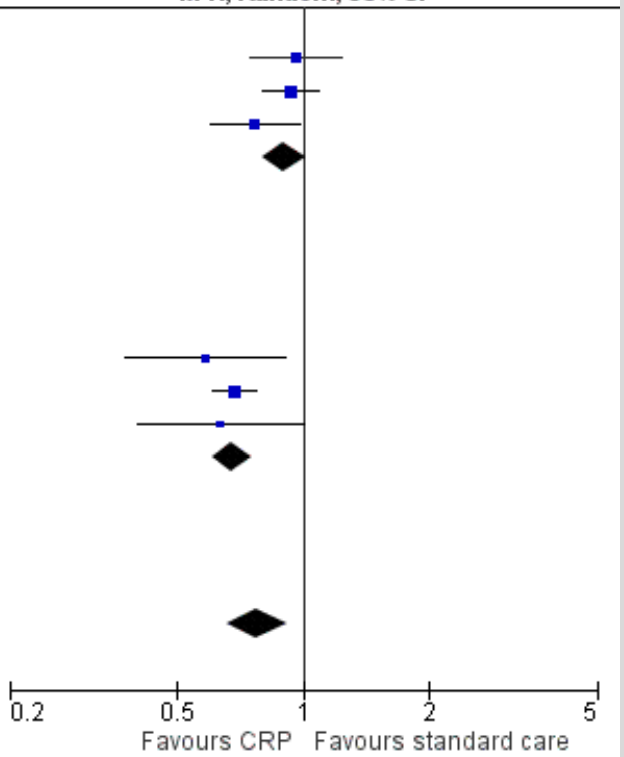
- High-sensitivity CRP
- Unfavourable long-term functional outcome after ischaemic stroke
  - 5 studies found association
  - Correction for confounders??
- Coronary heart disease
  - Yes based on epidemiological data
  - No based on genetic data
  - Clinical relevance? Cost-effectiveness?
- Heart failure
  - 4 studies in general population (>65y)
  - Double risk after 3-6 years if hs-CRP>2.5-7.4 mg/L

Impact on management

- Patients with acute respiratory tract infections

- Cochrane review Dec 2014 incl 6 studies
- Antibiotic prescriptions:
  - Decreased by 22% at index consultation
  - Decreased by 20% within 28 days

Study or Subgroup	CRP Events	CRP Total	Standard care Events	Standard care Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
1.1.1 Individually randomised trials							
Melbye 1995	54	108	68	131	17.1%	0.96 [0.75, 1.24]	1995
Diederichsen 2000	179	414	184	398	22.7%	0.94 [0.80, 1.09]	2000
Cals 2010	56	129	73	129	17.2%	0.77 [0.60, 0.98]	2010
Subtotal (95% CI)		**651**		**658**	**56.9%**	**0.90 [0.80, 1.02]**	
Total events	289		325				
Heterogeneity: Tau² = 0.00; Chi² = 2.11, df = 2 (P = 0.35); I² = 5%							
Test for overall effect: Z = 1.71 (P = 0.09)							
1.1.2 Cluster-randomised trials (modified sample size)							
Cals 2009	20	65	31	59	9.4%	0.59 [0.38, 0.91]	2009
Little 2013a	304	920	407	844	24.8%	0.69 [0.61, 0.77]	2013
Andreeva 2013	18	49	22	38	8.9%	0.63 [0.40, 1.00]	2013
Subtotal (95% CI)		**1034**		**941**	**43.1%**	**0.68 [0.61, 0.75]**	
Total events	342		460				
Heterogeneity: Tau² = 0.00; Chi² = 0.54, df = 2 (P = 0.76); I² = 0%							
Test for overall effect: Z = 7.08 (P < 0.00001)							
Total (95% CI)		**1685**		**1599**	**100.0%**	**0.78 [0.66, 0.92]**	
Total events	631		785				
Heterogeneity: Tau² = 0.02; Chi² = 15.41, df = 5 (P = 0.009); I² = 68%							
Test for overall effect: Z = 3.01 (P = 0.003)							
Test for subgroup differences: Chi² = 12.08, df = 1 (P = 0.0005), I² = 91.7%							



Impact on management

- Patients with acute respiratory tract infections

- Cochrane review Dec 2014 incl 6 studies
- Decreased antibiotic prescriptions:
  - Similar recovery rate at day 7 (3 studies)
  - 1 study found increased hospital admission rates after CRP test

NICE guideline pneumonia

- December 2014
- For people presenting with symptoms of lower respiratory tract infection in primary care
- Consider a point-of-care CRP test if after clinical assessment a diagnosis of pneumonia has not been made and it is not clear whether antibiotics should be prescribed.
  - CRP <20 mg/L: Do not routinely offer antibiotic therapy
  - CRP 20-100 mg/L: Consider a delayed antibiotic prescription
  - CRP >100 mg/L: Offer antibiotic therapy

Point-of-care tests

- At the bedside of the patient
  - In the GP's surgery
  - At the patient's home
- Disruptive
  - Result available faster
  - Changes clinical pathway
  - Spectrum shift – indication creep

Spectrum effects

Test threshold will lower:

- More easily available
  - More people get tested
- Less invasive
  - Different people get tested

Effects:

- Lower prevalence of target condition

➔ More false positives

- Less or differently selected population

➔ Spectrum shift

➔ Different treatment efficacy

In conclusion

- CRP most useful for acute infections
  - Improves the diagnosis of serious infections in children
  - Can reduce antibiotic prescribing in adults with lower respiratory tract infection
- Rigorous studies required to estimate impact on patient outcome and healthcare resources

NUFFIELD DEPARTMENT OF
PRIMARY CARE
HEALTH SCIENCES

UNIVERSITY OF
OXFORD

Uncomplicated urinary tract infection in primary care

Chris Butler, Professor of Primary Care. 18 May 2015


WELCOME | CROESO

Disclosures

- Grants form the EU (R-Gnosis) on UTI management
- Honoraria for talks, attending meetings and supply for equipment for a publically funded research study from Alere

Case

- 38 year old woman
- “I have a UTI doctor: I need a prescription for antibiotics...”

Case continued

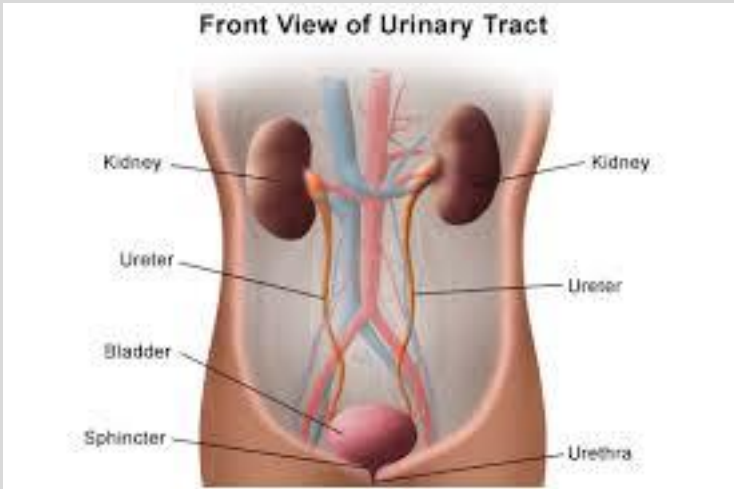
- 38 year old woman
- “I have a UTI doctor: I need a prescription for antibiotics...”
- Dysuria, frequency 3 days
- T36.4C, Pule 80, 130/80
- Abdo: slightly tender suprapubically

Case

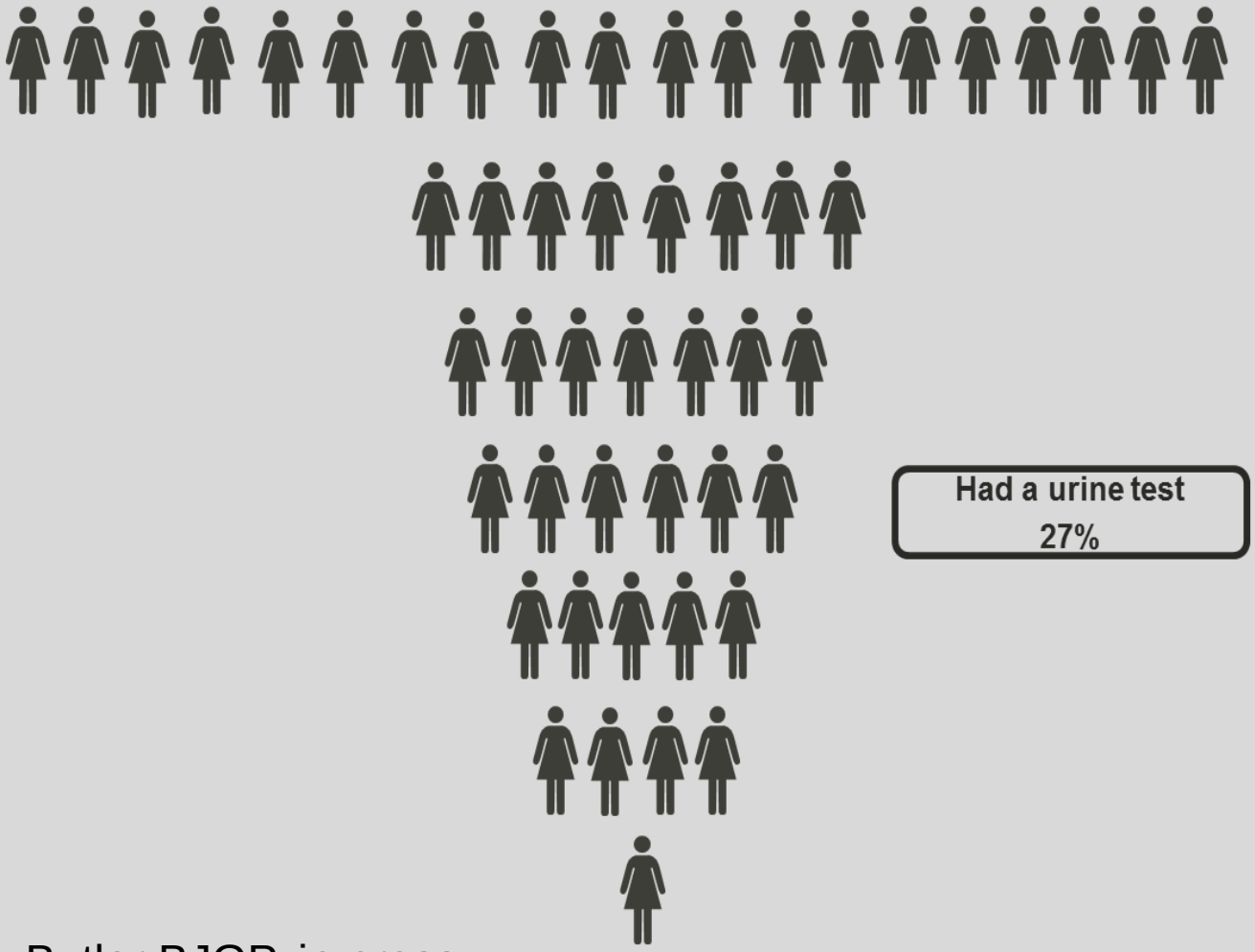
- 38 year old woman
- “I have a UTI doctor: I need a prescription for antibiotics...”
- Dysuria, frequency 3 days
- T36.4C, Pule 80, 130/80
- Abdo: slightly tender suprapubically
- Not pregnant
- Dipstick negative

Classification of UTI

- **Acute cystitis**: infection of lower urinary tract (bladder); Can occur in conjunction with **pyelonephritis** (infection of the kidney)
- **Uncomplicated**: healthy non pregnant adult women
- **Complicated**: an underlying condition which increases risk of infection or failing therapy (obstruction, anatomic abnormality, multiply-resistant uropathogen)
- **Recurrent UTI:** ≥2 infections in 6 months or ≥3 infections in a year
- **Men**
- **Children**



Percentage of women reporting a UTI in their lifetime, and information, advice and treatment sought with their most recent UTI (n=2,424)



All women
100%

Had a UTI in lifetime
37%

Contacted a health professional
33%

Had a urine test
27%

Prescribed antibiotics
27%

Given other advice
24%

Took the antibiotics prescribed
17%

Went to Out of Hours service
5%

Butler BJGP, in press

Pathogenesis

- Colonisation of vaginal intoitus by faecal flora
- Ascends via urethra to balder
- Pyelonephritis: ascends from bladder to kidneys via ureters or seeds from blood in septicaemia
- Risk factors:
  - Spermicides
  - Wiping front to back

Microbiology

- *Escherichia coli* 75-95%

Also

- *Proteus mirabilis*
- *Klebsiella pneumoniae*
- *Staphylococcus saprohpyticus*
- **Common contaminants:**
  - Group B *Streptococci*
  - *Lactobacilli*
  - *Enterococci*
  - Coagulase-negative *Staphylococci* (other than *S saprohpyticus*)

Diagnosis: symptoms

- Dysuria
- Frequency
- Urgency
- Suprapubically pain
- Hematuria

- Any one symptom: probability >50%
- Dysuria, frequency, no PV discharge or irritation: probability >90%

- Pyelonephritis:
  - Fever, chills, loin pain, Costovertebral angle tenderness, nausea, shock, sepsis

Diagnosis: physical examination

- Fever
- Pulse, BP
- Abdominal examination
- Costovertebral angle tenderness
- ?Pelvic exam
- ?pregnancy test

Differential diagnosis

- **Vaginitis**: discharge, odor, dyspareunia, pruritus, absence of urgency/frequency: yeast, trichomonas, bacterial vaginosis
- **Urethritis**: dysuria but no bacteria in sexually active women: chlamydia, gonorrhea, trichmonas, candida, herpes simplex virus, contraceptive gel
- **Structural urethral abnormalities**: urethral diverticula
- **Painful bladder syndrome**: diagnosis of exclusion: symptoms but no evidence of infection
- **PID**: lower abdominal pain and fever, even dysuria: mucopurulent endocervical discharge
- **Kidney stones**: flank pain, colic, macroscopic hematuria, with fever unusual

Diagnosis: point of care test: Microscopy dipsticks

- Absence of pyuria suggests an alternative diagnosis
- Microscopy of un-spun urine is most accurate POCT: ≥10 leucocytes per micorL. Casts= upper UTI

- **Dipstick** detects:
  - leucocyte esterase:
  - Nitrite
- Sensitivity75%, specificity 82% for either
- When history is suggestive, a negative test does not reliably rule out UTI

- **Dipslide**: quantification, not sensitivity

- Frequency, nocturia and cloudy urine =PPV of 82%
- Dipstick testing was found to only modestly increase the PPV and did not improve NPV

SEVENTH FRAMEWORK PROGRAMME

R-GNOSIS

Resistance in Gram-Negative Organisms: Studying Intervention Strategies

R-GNOSIS WP2

POETIC

point of care testing for urinary tract infection in primary care

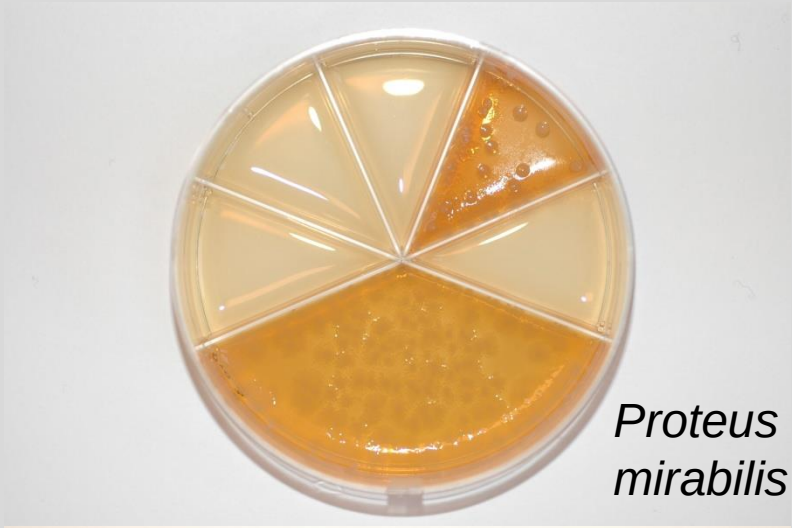
Observational study and RCT of clinical and cost effectiveness

Professor Chris Butler and team
Professor of Primary Care Medicine
Director of Institute of Primary Care and Public Health
Cardiff University

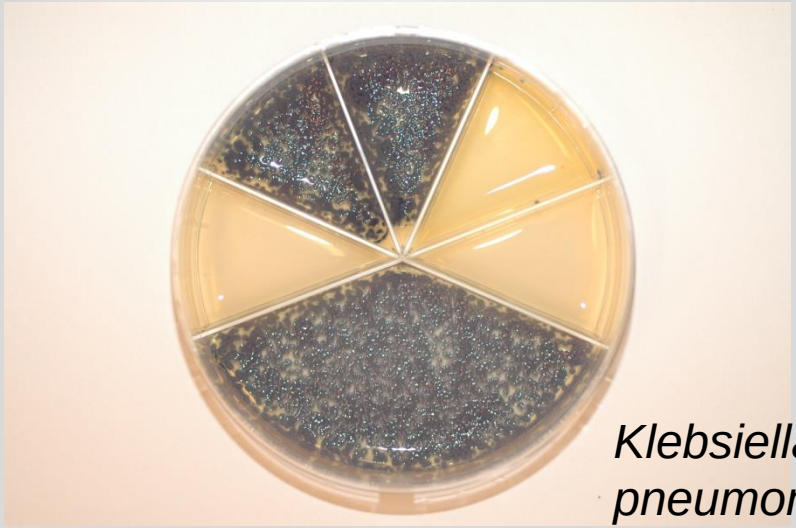
CARDIFF UNIVERSITY
PRIFYSGOL CAERDYDD

The POCT: FLEXICULT™ SSI-Urinary Kit

Statens Serum Institut



Proteus mirabilis



Klebsiella pneumoniae

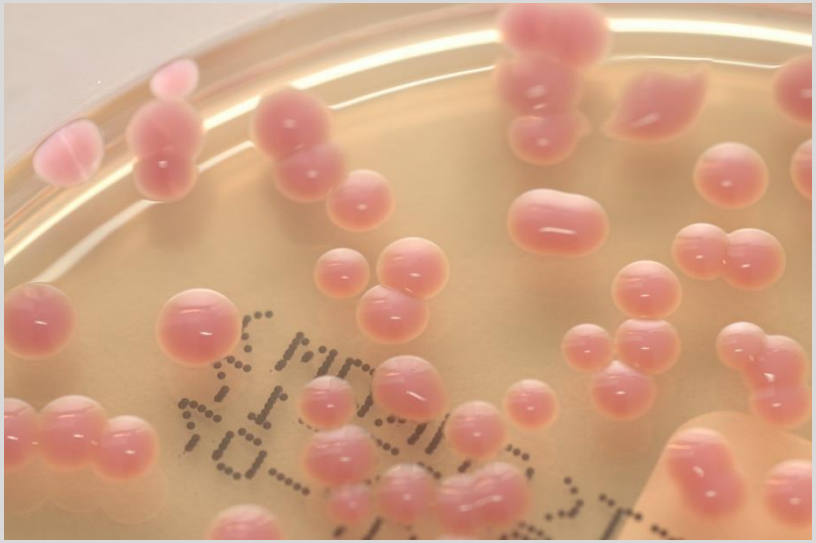
- Agar plate – 6 high-sided compartments
- Chromogenic agar: for bacterial identification
- Control compartment: for quantitation of bacteria
- Antibiotic compartments: for susceptibility testing

UK:
- Trimethoprim (3mg/l)
- Nitrofurantoin (64mg/l)
- Amoxicilin/Clavulanate (16/8mg/l)
- Ciprofloxacin (0.75mg/l)
- Cephalothin (Cephalothin)(16mg/l)

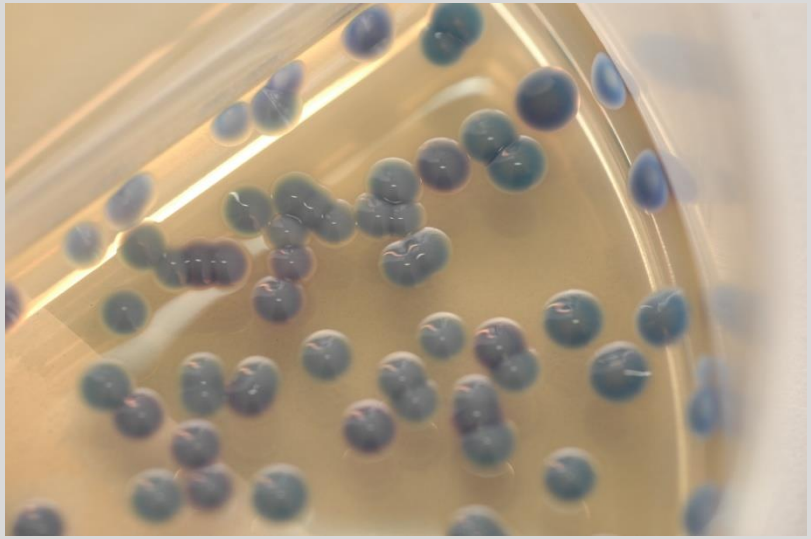
Netherlands:
- Trimethoprim (3mg/l)
- Nitrofurantoin (64mg/l)
- Amoxicilin/Clavulanate (16/8mg/l)
- Ciprofloxacin (0.75mg/l)
- Amoxicillin (Ampicillin) (8mg/l)

Spain:
- Fosfomycin (32mg/l)
- Nitrofurantoin (64mg/l)
- Amoxicillin/Clavulanate (16/8mg/l)
- Ciprofloxacin (0.75mg/l)
- Cefuroxime (8mg/l)

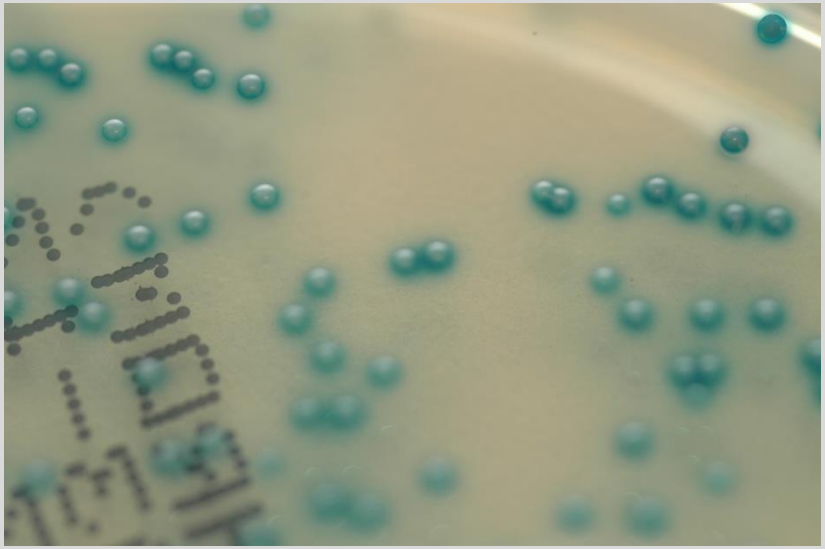
Flexicult™ - Identification of Bacteria:



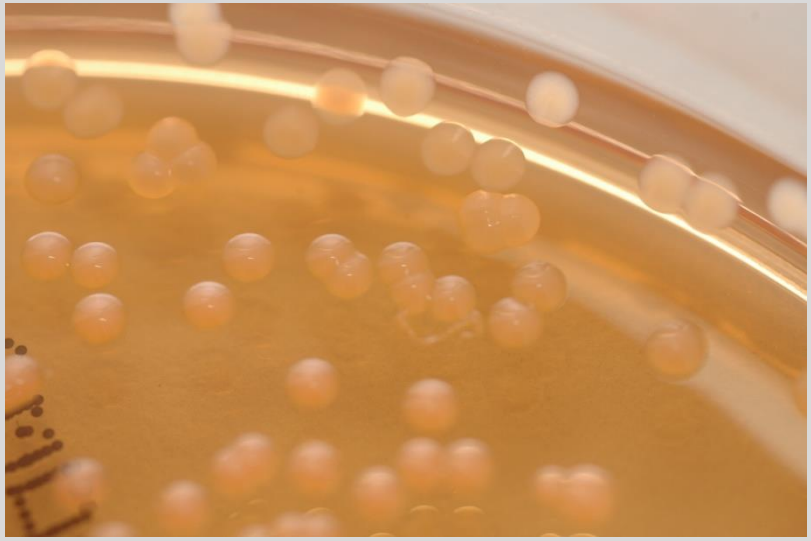
E.coli



Klebsiella sp



E. faecalis



Proteus spp

Laboratory culture

- ≥10^5 Colony Forming Units per ml usual
- Cells sometimes taken into account
- E. coli can be pathogen or contaminant

- **HPA**
- Single organism ≥10^4 CFU/ml
- ≥10^5 CFU/ml mixed growth with one predominant organism
- ≥10^3 CFU/ml of E. coli of Staphylococcus saprohpyticus
- ≥10^5 CFU/ml white cells= inflammation: if absent, true UTI less likely

Cite this article as: BMJ, doi:10.1136/bmj.38496.452581.8F (published 22 June 2005)

Primary care

Response to antibiotics of women with symptoms of urinary tract infection but negative dipstick urine test results: double blind randomised controlled trial

Dee Richards, Les Toop, Stephen Chambers, Lynn Fletcher

- Double blind placebo controlled RCT of trimethoprim 300mg daily for 3 days
- General practice
- 59 women with dysuria and frequency and dipstick of MSU neg. for leucocytes and nitrites
- Day 3: 5 (tri) vs 20 (placebo) had ongoing symptoms
- Day 7: 2 (tri) vs 7(placebos) had ongoing symptoms
- NNT 4
- Dipsticks accurately predicted negative urine culture but response to antibiotic treatment

Management: HPA guideline

- If **severe,** or ≥ 3 of:
  - dysuria
  - frequency
  - suprapubic tenderness
  - urgency
  - hematuria

And

- No vaginal irritation or discharge:
- Then **treat empirically** (90% will be culture positive)

Management: mild or ≤ 2 symptoms

- Urine ***not cloudy***, NPV 97% so consider another diagnosis
- If ***cloudy***, dipstick:
- Nitrite and leucocyte and blood, or nitrite alone, treat with first line agent
- Nitrite negative, leucocyte positive: treat if severe, consider delayed prescription, culture
- Negative nitrite leucocyte and blood, 76% NPV
- Negative nitrite and leucocyte but positive blood or protein: consider other diagnosis, symptomatic treatment, safety net

Older people

- Do not send culture in asymptomatic elderly with positive dipsticks
- Only send for culture if ≥ 2 signs of infection especially dysuria, fever >38C, new incontinence
- Do not treat asymptomatic bacteriuria as it does not reduce mortality or prevent symptomatic episodes, but increases side effects and resistance

Asymptomatic bactiuria in pregnancy

- Do not treat (SIGN)

Antibiotic treatment HPA

- **First line**:
- Trimethoprim 200mg or nitrofurantoin 100mg m/r BD for 3 days (do not use nitrofurantoin if e-GFR ≤60

- **Second line**: perform culture in all treatment failures:
- Nitrofurantoin: minimal resistance; >90% sensitive, little change since 1950's: active against ESBLs; can be used in pregancey; few side effects from short courses
- Fosfomycin: 3g single dose minimal resistance: active against ESBLs but does not treat pyelonephritis
  - Fluoroquinolones: reserve for other infections: rapidly increasing resistance
  - Cephpodoxime is less effective than ciprofloxacin
  - Ampicillin and amoxicillin: >50% resistance

Antimicrobial agents for treating uncomplicated urinary tract infection in women (Review)

Zalmanovici Trestioreanu A, Green H, Paul M, Yaphe J, Leibovici L

THE COCHRANE COLLABORATION®

Cochrane Review: search 2010

- 21 studies (6016 participants)
- Trimethoprim-sulfamethoxazole as effective as fluoroquinolones short term and long term symptomatic cure
- Beta-lactams as effective as TMP-SMX short and long term
- Nitrofurantoin similar to TMP-SMX short term and longer term
- Fluoroquinolones more effective in achieving microbiological short term bacteriological cure but of uncertain clinical significance
- Minimal data on the emergence of resistance after treatment

KEEP CALM AND CHECK THE BNF

BNF recommendations

- *Uncomplicated lower urinary-tract infections* often respond to **trimethoprim, nitrofurantoin, or amoxicillin** given for 7 days (3 days may be adequate for infections in women; see also Table 1, section 5.1); those caused by fully sensitive bacteria respond to two 3-g doses of amoxicillin (section 5.1.1.3). Widespread bacterial resistance to ampicillin, amoxicillin, and trimethoprim has been reported. Alternatives for resistant organisms include co-amoxiclav (amoxicillin with clavulanic acid), an oral cephalosporin, nitrofurantoin, pivmecillinam, or a quinolone.
- Fosfomycin [unlicensed] can be used, on the advice of a microbiologist, for the treatment of uncomplicated lower urinary-tract infections caused by multiple-antibacterial resistant organisms when other antibacterials cannot be used; in adults, it is given as a single oral dose of 3 g.

Duration of antibacterial treatment for uncomplicated urinary tract infection in women (Review)

Milo G, Katchman E, Paul M, Christiaens T, Baerheim A, Leibovici L

THE COCHRANE COLLABORATION®

Duration of antibiotics

- Meta analysis of 32 trials showed that a 3 day course of antimicrobials was equivalent to a 5 to 10 day course in achieving symptomatic cure.
- Shorter courses were associated with fewer adverse effects.

Actual practice: the POETIC Study

(in progress, unpublished, not peer reviewed!)

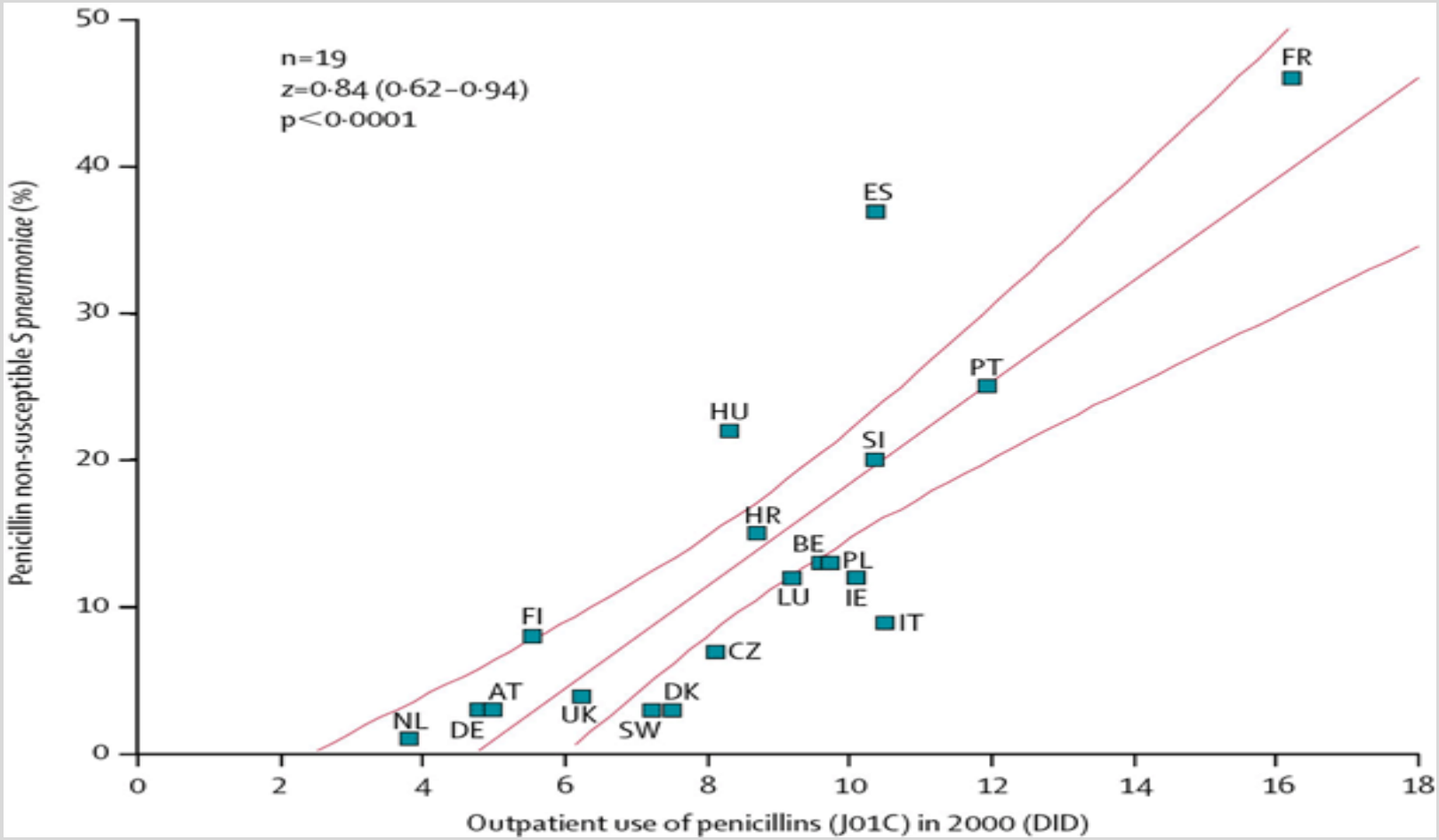
- Explore the resistance profiles of isolated pathogens
- Symptomatic recovery
- UTI related use of health service resources

Antibiotic Prescription

	Wales		England		Spain		The Netherlands		Total	
	n	%	n	%	n	%	n	%	n	%
Any antibiotic prescribed?	196	92.9	232	95.1	195	95.1	79	59.4	702	88.5
Trimethoprim	150	76.5	107	46.1	0	0.0	9	11.4	266	37.9
Nitrofurantoin	34	17.3	112	48.3	6	3.1	63	79.7	215	30.6
Fosfomycin	0	0.0	0	0.0	148	75.9	5	6.3	153	21.8
Co-amoxiclav	1	0.5	1	0.4	21	10.8	0	0.0	23	3.3
Ciprofloxacin	2	1.0	0	0.0	17	8.7	1	1.3	20	2.8
Amoxicillin	4	2.0	6	2.6	0	0.0	0	0.0	10	1.4
Cefalexin	3	1.5	5	2.2	0	0.0	0	0.0	8	1.1
Cefuroxime	0	0.0	0	0.0	2	1.0	0	0.0	2	0.3

Why is better targeted treatment important?

Antibiotic use and resistance



Correlation between penicillin use and prevalence of penicillin non-susceptible S pneumoniae
Gossens H, Lancet2005:365:579-587

Journal of Antimicrobial Chemotherapy (2007) **60**, 92–99
doi:10.1093/jac/dkm141
Advance Access publication 30 May 2007

JAC

Prior antibiotics and risk of antibiotic-resistant community-acquired urinary tract infection: a case–control study

Sharon Hillier[1], Zoe Roberts[1], Frank Dunstan[1], Chris Butler[2], Anthony Howard[3] and Stephen Palmer[1]*

[1]*Department of Epidemiology, Statistics and Public Health, Centre for Health Sciences Research, Cardiff University, Neuadd Meirionydd, Heath Park, Cardiff CF14 4YS, UK;* [2]*Department of General Practice, Centre for Health Sciences Research, Cardiff University, Neuadd Meirionydd, Heath Park, Cardiff CF14 4YS, UK;* [3]*National Public Health Service for Wales, Temple of Peace and Health, Cathays Park, Cardiff CF10 3NW, UK*

Received 2 January 2007; returned 5 February 2007; revised 4 April 2007; accepted 10 April 2007

Background: To assess the effect of previous antibiotic use on the risk of a resistant *Escherichia coli* urinary tract infection (UTI), we undertook a case–control study with prospective measurement of outcomes in 10 general practices in the UK.

Methods: Urinary samples from all patients with symptoms suggestive of UTIs were sought, and those with a laboratory-proven *E. coli* infection were interviewed and their medical records examined. Case patients were those with ampicillin- or trimethoprim-resistant infections and control patients had infections that were susceptible to antibiotics, including ampicillin and trimethoprim.

Results: Risk of ampicillin-resistant *E. coli* infection in 903 patients was associated with amoxicillin prescriptions of ≥7 days duration in the previous 1 month [odds ratio (OR) = 3.91, 95% CI 1.64–9.34] and previous 2–3 months (2.29, 1.12–4.70) before illness onset. For prescriptions <7 days duration, there was no statistically significant association. Higher doses of amoxicillin were associated with lower risk of ampicillin resistance. For trimethoprim-resistant *E. coli* infections, the OR was 8.44 (3.12–22.86) for prescriptions of trimethoprim of ≥7 days in the previous month and 13.91 (3.32–58.31) for the previous 2–3 months. For trimethoprim prescriptions of <7 days, the OR was 4.03 (1.69–9.59) for the previous month but prescribing in earlier periods was not significantly associated with resistance.

Conclusions: Within the community setting, exposure to antibiotics is a strong risk factor for a resistant *E. coli* UTI. High-dose, shorter-duration antibiotic regimens may reduce the pressure on the emergence of antibiotic resistance.

- Risk of ampicillin resistant E coli in 903 women associated with amoxicillin prescription ≥ 7 days in the previous month (OR 3.9; 1.65-9.34)
- And in 2-3 months (OR 2.29; 1.12-4.70)
- Higher doses, shorter duration associated with lower risk
- Trimethoprim resistant E. coli infections: Tri ≥ 7 days in previous month (OR 8.44; 3.12-22.86)
- And 2-3 months (OR 13.91; 3.31-58.3)

Antibiotic-resistant infections in primary care are symptomatic for longer and increase workload:

outcomes for patients with *E.coli* UTIs

Christopher C Butler, Sharon Hillier, Zoë Roberts, Frank Dunstan, Anthony Howard and Stephen Palmer

ABSTRACT

Background

Antimicrobial resistance is considered to be one of the major threats to public health. However, the practical implications for patients and workload in primary care are largely unknown.

Aim

To determine outcomes for patients managed in primary care with an antibiotic resistant compared to an antibiotic sensitive *Escherichia coli* (*E. coli*) urinary tract infection (UTI).

Design

Nested case control study with prospective measurement of outcomes.

Setting

Ten general practices in South Wales.

Method

Patients consulting with symptoms suggestive of UTI identified through systematic sampling, and with a laboratory proven *E. coli* infection, were followed up by interview 1 month after their consultations and by searching of their medical records.

Results

Nine hundred and thirty-two patients were interviewed and had their medical records reviewed. The risk of patients reporting 'feeling poorly', 'frequency or pain on urinating' and being 'out of action' for more than 5 days after consulting was significantly increased for patients with resistant compared to sensitive infections. After adjusting for risk factors, there was an increased risk of 'frequency or pain on urinating' and 'being out of action' for those infected with a resistant *E. coli*. The median number of maximum reported days with at least one symptom was 12 days for patients with *E. coli* infections resistant to trimethoprim, 7 days for infections resistant to ampicillin, 7 days for infections resistant to any antibiotic, and 5 days for infections sensitive to all tested antibiotics. Even if treated with an appropriate antibiotic, infections caused by a resistant strain were symptomatic for longer. For those infected with an organism resistant to at least one antibiotic, the odds ratio (OR) for re-visiting their GP within the next 30 days for the UTI was 1.47 (95% confidence interval [CI] = 1.10 to 1.95). The OR was 1.49 (95% CI = 1.11 to 2.00) for ampicillin resistance and 2.48 (95% CI = 1.70 to 3.59) for trimethoprim resistance.

Conclusions

Resistant *E. coli* UTIs are symptomatic for longer and cause increased work load in general practice.

Keywords

anti-bacterial agents; cohort study; drug resistance, bacterial; primary health care; treatment outcomes; urinary tract infections.

INTRODUCTION

Antibiotic resistance increases the length of hospital stay[1] and mortality[2] in secondary care, but the situation in primary care is far from clear.[3] Primary care clinicians are concerned about the issue, but only infrequently report encountering treatment failure associated with antibiotic resistance and may see it as a 'public health or hospital issue', remote from prescribing decisions for their individual patients.[4]

If it could be shown clearly that resistant infections were associated with poorer outcomes for patients managed in primary care, this may concentrate attention on the impact of antibiotic resistance for primary care and further promote the appropriate use of antibiotics. We therefore set out to compare outcomes for patients infected with resistant and sensitive *Escherichia coli* (*E. coli*) urinary tract infections (UTIs).

We chose to study UTI because UTI is one of the commonest bacterial infections managed in general

C Butler, MD, professor of Primary Care Medicine; S Hillier, PhD, senior research fellow; Z Roberts, PhD, lecturer; F Dunstan, DPhil, professor; S Palmer, FFPHM, professor of Epidemiology and Public Health, Department of Epidemiology, Statistics and Public Health, Centre for Health Sciences Research, Cardiff University, Heath Park, Cardiff. A Howard, FRCPath, director, Infection and Communicable Disease Service, National Public Health Service for Wales, ICDS Corporate Office Temple of Peace & Health, Cathays Park, Cardiff.

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Submitted: 26 January 2006; **Editor's response:** 28 April 2006; **final acceptance:** 8 June 2006

British Journal of General Practice; 2006; 56: 686–692

932 patients with lab proven E. coli UTI

- Median number of maximum reported days with at least one symptom
- 12 days if resistant to tri
- 7 days if resistant to ampicillin
- 7 days if resistant to any antibiotic
- 5 days if sensitive to all
- Even if treatment with appropriate antibiotic, resistant infections were symptomatic for longer
- Resistant to 1 antibiotic, re-consulting in 30 days more common (OR 1.47;1.10-2.00)
- R. to Ampicillin (OR 1.49;1.11-2.00
- R. to Tri (OR 2.48;1.70-3.59)

Costs and costs of resistance

ELSEVIER

International Journal of Antimicrobial Agents

journal homepage: http://www.elsevier.com/locate/ijantimicag

The additional costs of antibiotics and re-consultations for antibiotic-resistant *Escherichia coli* urinary tract infections managed in general practice

M. Fasihul Alam[a,*], David Cohen[a], Christopher Butler[b], Frank Dunstan[b], Zoe Roberts[b], Sharon Hillier[b], Stephen Palmer[b]

[a] *Health Economics and Policy Research Unit, Faculty of Health, Sport and Science, University of Glamorgan, Pontypridd, Glamorgan CF37 1DL, UK*
[b] *Department of Primary Care and Public Health, School of Medicine, Cardiff University, Heath Park, Cardiff CF14 4YS, UK*

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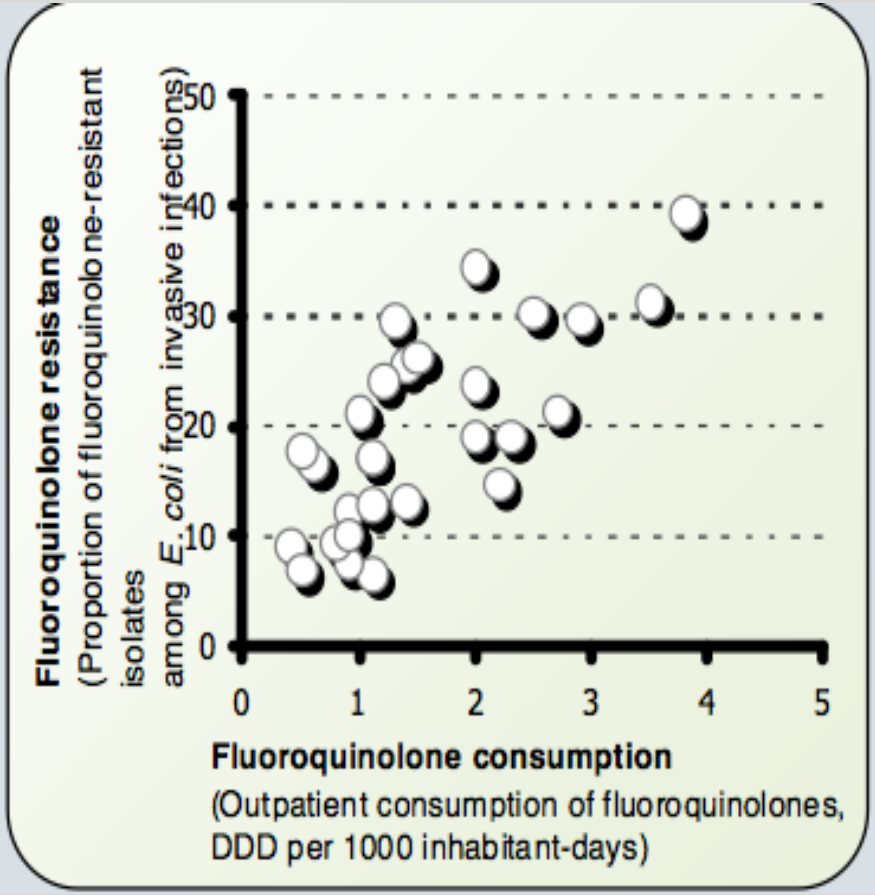
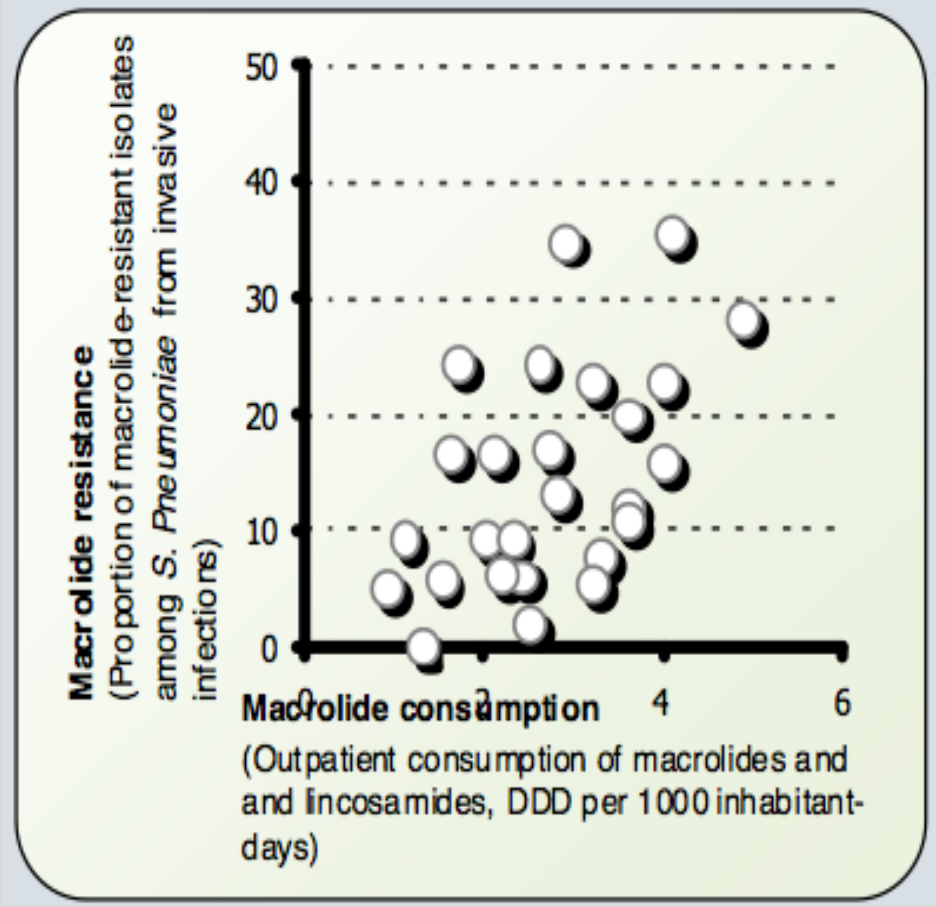
General practice

ABSTRACT

The emergence of antibiotic resistance is a major threat to public health. In the UK, most antibiotics are prescribed in general practice but the extra costs to general practice of resistant infections have not previously been well described. We compared the costs of treating patients presenting with resistant *Escherichia coli* urinary tract infections (UTIs) (resistant to ampicillin, trimethoprim or at least one antibiotic) with the costs of treating patients with UTIs that were sensitive to all six tested antibiotics (ampicillin, trimethoprim, amoxicillin/clavulanic acid, cefalexin, ciprofloxacin and nitrofurantoin) with regard to re-consultations and antibiotics prescribed. There were significantly higher antibiotic costs (mean extra antibiotic cost £1.19/€1.75), re-consultation costs (£2.42/€3.55) and total costs (£3.62/€5.31) for patients whose infections were resistant to at least one antibiotic compared with those with sensitive infections

Extra costs of trimethoprim resistant infections =£11.21


Fluoroquinolone resistance
(Proportion of fluoroquinolone-resistant isolates among E. coli from invasive infections)
0
10
20
30
40
50
0
1
2
3
4
5
Fluoroquinolone consumption
(Outpatient consumption of fluoroquinolones, DDD per 1000 inhabitant-days)


Macrolide resistance
(Proportion of macrolide-resistant isolates among S. Pneumoniae from invasive infections)
0
10
20
30
40
50
0
2
4
6
Macrolide consumption
(Outpatient consumption of macrolides and and lincosamides, DDD per 1000 inhabitant-days)

Resistant bacteraemias in Wales 2005–2011

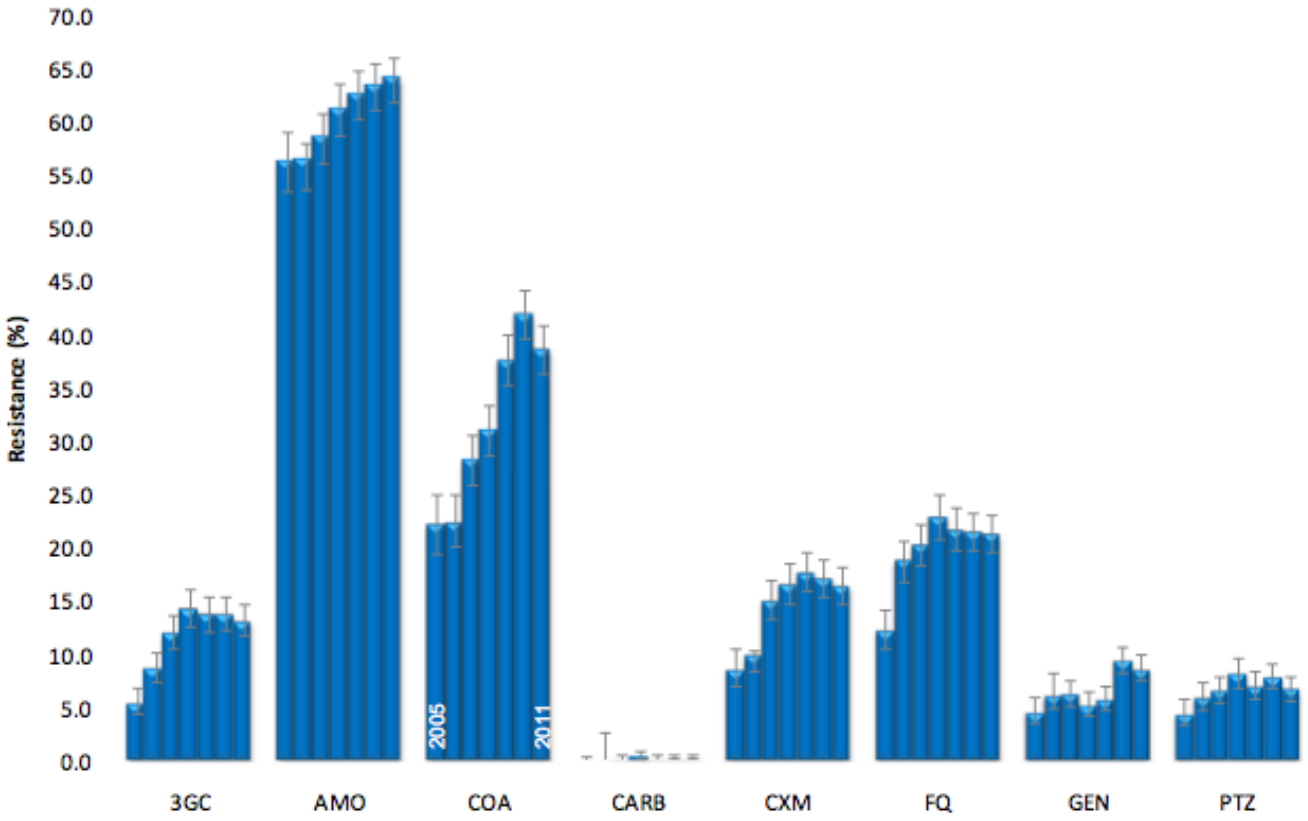
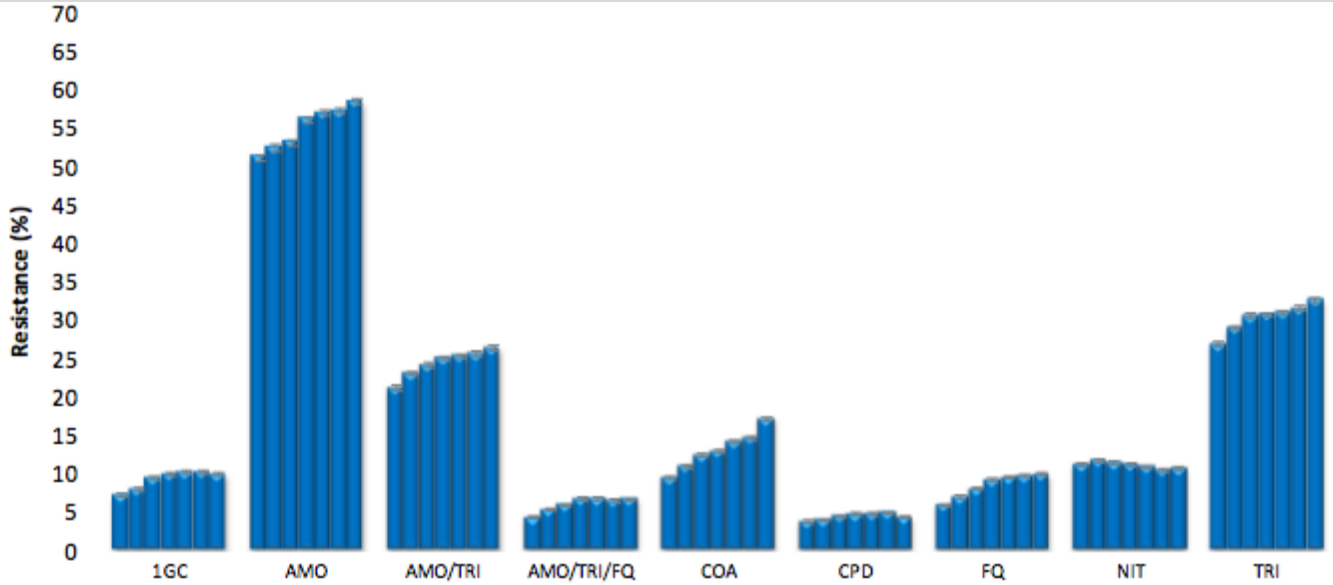


Figure 1: All-Wales resistance rates for *E. coli bacteraemia* (2005 to 2011).

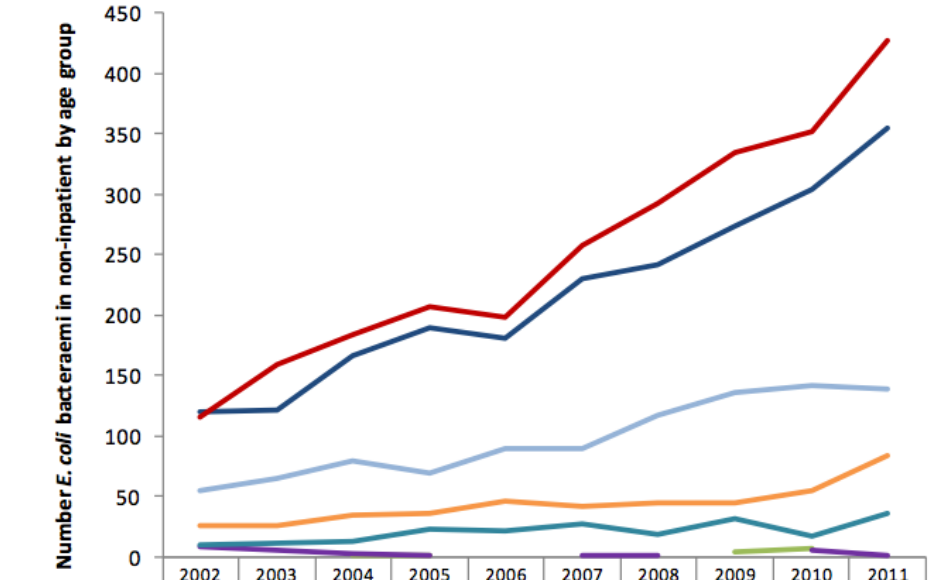
Resistance in coliforms in the community in Wales 2005–2011



	1GC	AMO	AMO/TRI	AMO/TRI/FQ	COA	CPD	FQ	NIT	TRI
2005	7.1	51.2	21.1	4.3	9.4	3.7	5.8	11.2	26.8
2006	7.9	52.5	23.0	5.3	10.8	3.9	7.0	11.6	29.0
2007	9.4	53.1	24.1	5.9	12.3	4.4	8.0	11.3	30.5
2008	9.8	56.0	25.0	6.6	12.9	4.7	9.1	11.1	30.7
2009	10.2	57.0	25.2	6.7	14.0	4.7	9.5	10.8	30.9
2010	10.1	57.3	25.6	6.5	14.6	4.8	9.7	10.3	31.5
2011	9.8	58.4	26.3	6.6	17.2	4.3	9.9	10.7	32.5

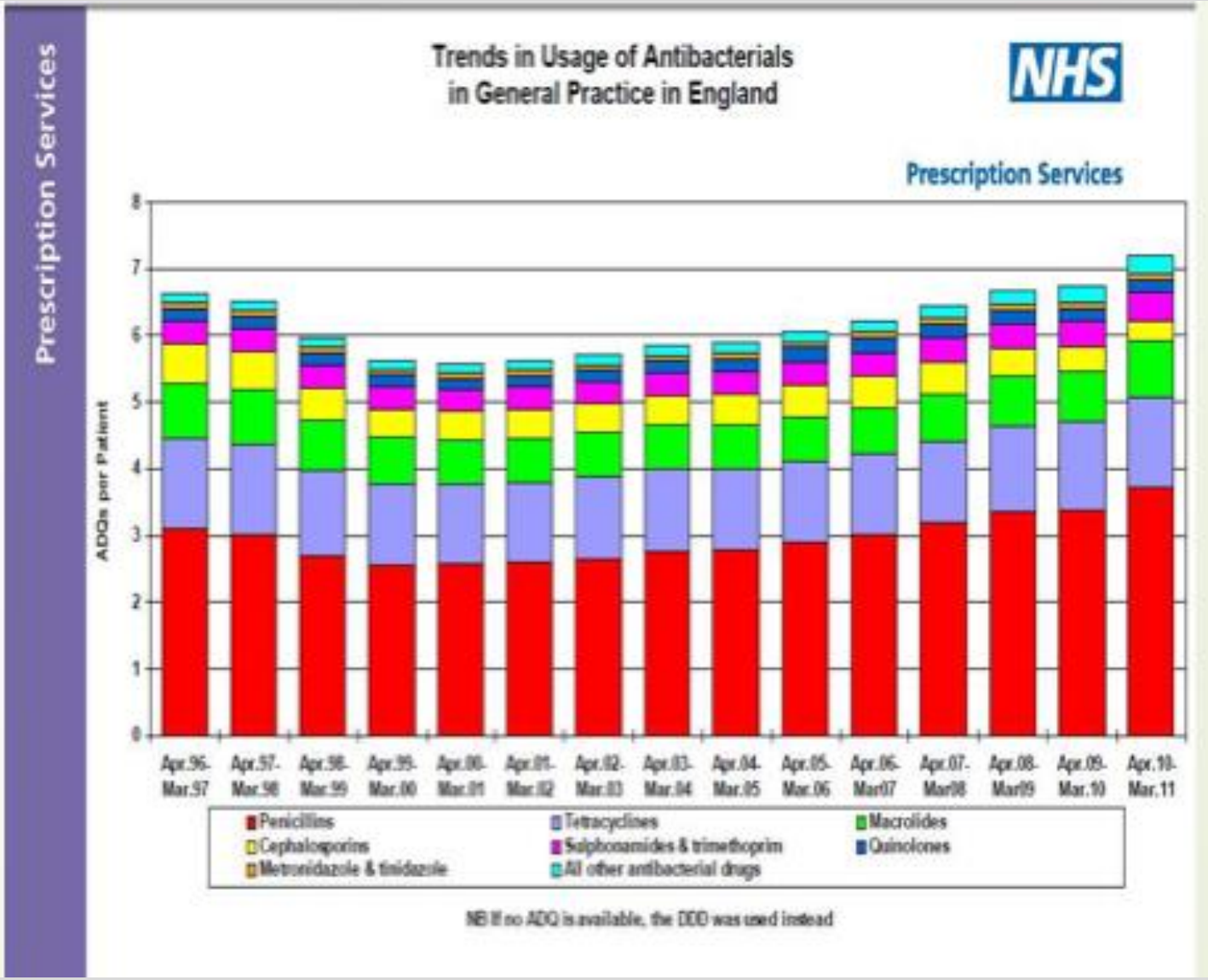
Figure 16: All-Wales antimicrobial resistance rates for coliforms from community urine samples (2005 to 2011)

E. Coli bacteremia by age group 2002-2011



	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
1 and under	2		1	1		2		3	7	
2 to 15	8	5	2	1		1	1		5	1
16 to 29	9	11	13	22	21	27	18	31	17	36
30 to 49	25	26	34	36	46	41	45	44	54	83
50 to 64	55	64	79	69	89	89	117	136	141	139
65 to 79	119	121	166	189	180	230	241	274	304	355
80+	116	159	184	207	198	258	293	334	352	427

Figure 176: *E. coli* bacteraemias by age group for non-inpatients locations


Prescription Services
Trends in Usage of Antibacterials
in General Practice in England
NHS
Prescription Services
ADDs per Patient
0
1
2
3
4
5
6
7
8
Apr.96-Mar.97
Apr.97-Mar.98
Apr.98-Mar.99
Apr.99-Mar.00
Apr.00-Mar.01
Apr.01-Mar.02
Apr.02-Mar.03
Apr.03-Mar.04
Apr.04-Mar.05
Apr.05-Mar.06
Apr.06-Mar07
Apr.07-Mar08
Apr.08-Mar09
Apr.09-Mar.10
Apr.10-Mar.11
Penicillins
Tetracyclines
Macrolides
Cephalosporins
Sulphonamides & trimethoprim
Quinolones
Metronidazole & tinidazole
All other antibacterial drugs
NB If no ADQ is available, the DDD was used instead

Consequences

- 400,000 resistant infections in EU on 2007
- 25,000 excess deaths
- 2.5M extra hospital days
- Costs 1.5BN Euro (excluding preventative measures)
- In US hospitalizations for resistant infections cost extra $6000 to $30000
- Antibiotics of last resort (carbapenems, tigecycline, linezolid, colistin, daptomycin) have high side effect burden and resiatnce has been reported in rapid time; totally resisatn Klebsiella now in Sotuhern Europe

European CDC and European Medicines Agency, 2009

Containing antibiotic resistance:

decreased antibiotic-resistant coliform urinary tract infections with reduction in antibiotic prescribing by general practices

Chris C Butler, Frank Dunstan, Margaret Heginbothom, Brendan Mason, Zoë Roberts, Sharon Hillier, Robin Howe, Stephen Palmer and Anthony Howard

ABSTRACT

Background

GPs are urged to prescribe antibiotics less frequently, despite lack of evidence linking reduced antibiotic prescribing with reductions in resistance at a local level.

Aim

To investigate associations between changes in antibiotic dispensing and changes in antibiotic resistance at general-practice level.

Design of study

Seven-year study of dispensed antibiotics and antibiotic resistance in coliform isolates from urine samples routinely submitted from general practice.

Setting

General practices in Wales.

Method

Multilevel modelling of trends in resistance to ampicillin and trimethoprim, and changes in practice total antibiotic dispensing and amoxicillin and trimethoprim dispensing.

Results

The primary analysis included data on 164 225 coliform isolates from urine samples submitted from 240 general practices over the 7-year study period. These practices served a population of 1.7 million patients. The quartile of practices that had the greatest decrease in total antibiotic dispensing demonstrated a 5.2% reduction in ampicillin resistance over the 7-year period with changes of 0.4%, 2.4%, and -0.3% in the other three quartiles. There was a statistically significant overall decrease in ampicillin resistance of 1.03% (95% confidence interval [CI] = 0.37 to 1.67%) per decrease of 50 amoxicillin items dispensed per 1000 patients per annum. There were also significant reductions in trimethoprim resistance in the two quartiles of practices that reduced total antibiotic dispensing most compared with those that reduced it least, with an overall decrease in trimethoprim resistance of 1.08% (95% CI = 0.005 to 2.10%) per decrease of 20 trimethoprim items dispensed per 1000 patients per annum. Main findings were confirmed by secondary analyses of 256 370 isolates from 527 practices that contributed data at some point during the study period.

Conclusion

Reducing antibiotic dispensing at general-practice level is associated with reduced local antibiotic resistance. These findings should further encourage clinicians and patients to use antibiotics conservatively.

Keywords

antibiotic prescribing; antibiotic resistance; primary care; urinary tract infection.

INTRODUCTION

Antibiotic resistance is a major threat to public health,[1] and has risen among many common community-acquired bacterial pathogens, including urinary tract pathogens.[2,3] Recent antibiotic use is one of the strongest risk factors for infection with antibiotic resistant organisms.[4] Urinary tract infections (UTIs) caused by antibiotic resistant *Escherichia coli* are symptomatic for longer than UTIs caused by sensitive organisms, and increase workload in general practice.[4]

National and international initiatives have encouraged a more conservative approach to antibiotic prescribing. This approach is based on the assumption that if resistant bacteria are 'less fit' than sensitive strains, reduced exposure to antibiotics will reduce selection pressure, limiting the rise in resistance, and potentially resulting in reduced resistance.[5] Many initiatives have been directed at general practices to address this issue,

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- 7 year study
- 164 225 Coliform isolates routinely submitted from 240 general practices serving 1.7 M people
- Quartile that had the greatest reduction in total antibiotic prescribing has a 5.2% reduction in ampicillin resistance
- Changes of0.4%, 2.4%, and -0.3% in other quartiles
- Decrease in trimethoprim resistance in the the two quartiles that reduced prescribing the most

Case revisited

- Urine not cloudy
- Probably don’t send urine for culture
- Explain natural history and triggers to re-consult
- No prescription or delayed prescription of antibiotics

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Infection Q&A