Workpackages 9 and 10

Paul Little
University of Southampton
Chris Butler
Cardiff University
Theo Verheij
University Medical Center Utrecht

Gaps in knowledge on lower respiratory tract infections

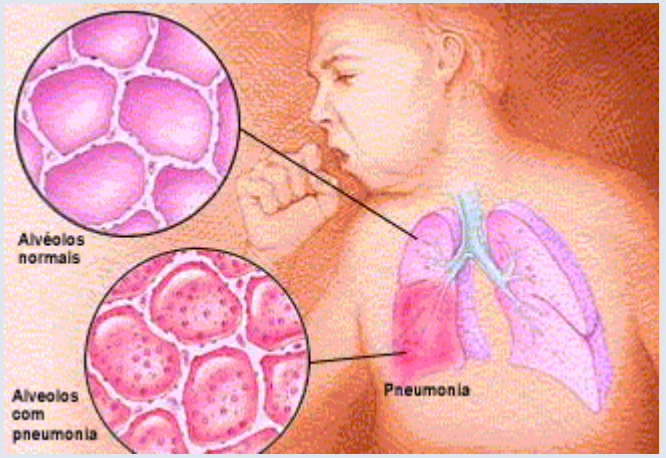
1. Behaviour and expectations of doctors and patients?
2. Aetiology?
3. Diagnostic strategies?
4. Treatment: overall and in subgroups?
5. Prediction of poor outcome?
6. Cost-effectiveness?
7. Potential of genetics to enhance clinical care?

Questions on aetiology

- Are all lower respiratory syndromes infectious?
- Similar in all European regions?
- Carriership?
- How are the bacterial resistance rates in primary care in the different countries?

Questions on diagnosis I

- How to detect pneumonia?
- 10-15% of patients with acute cough have pneumonia



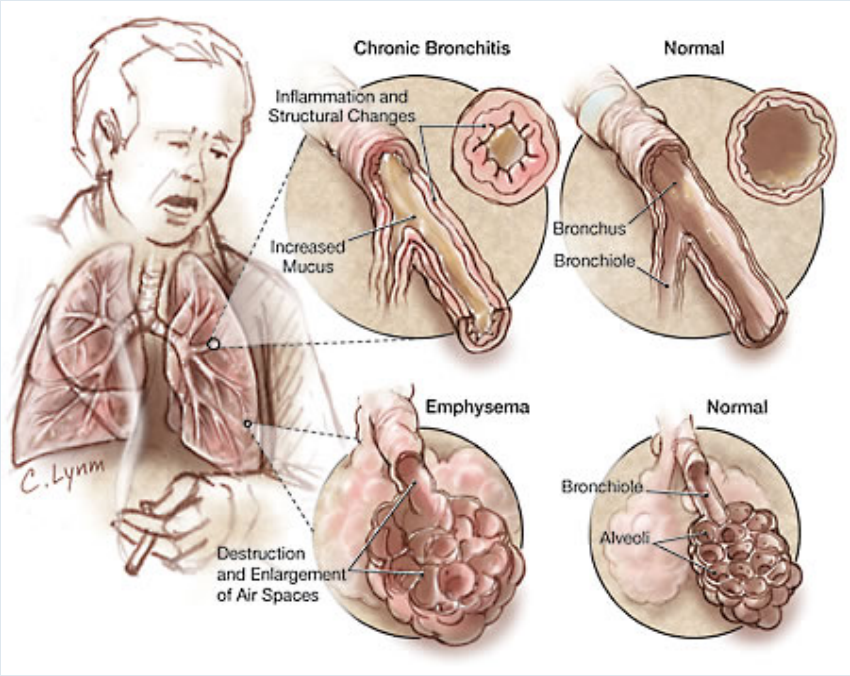
- Diagnostic value of signs and symptoms ???
- Additional value of tests? (C-reactive protein, PCT)

Questions on diagnosis II

- How to detect/rule out bacterial LRTI?
- Two small studies in primary care with conflicting results

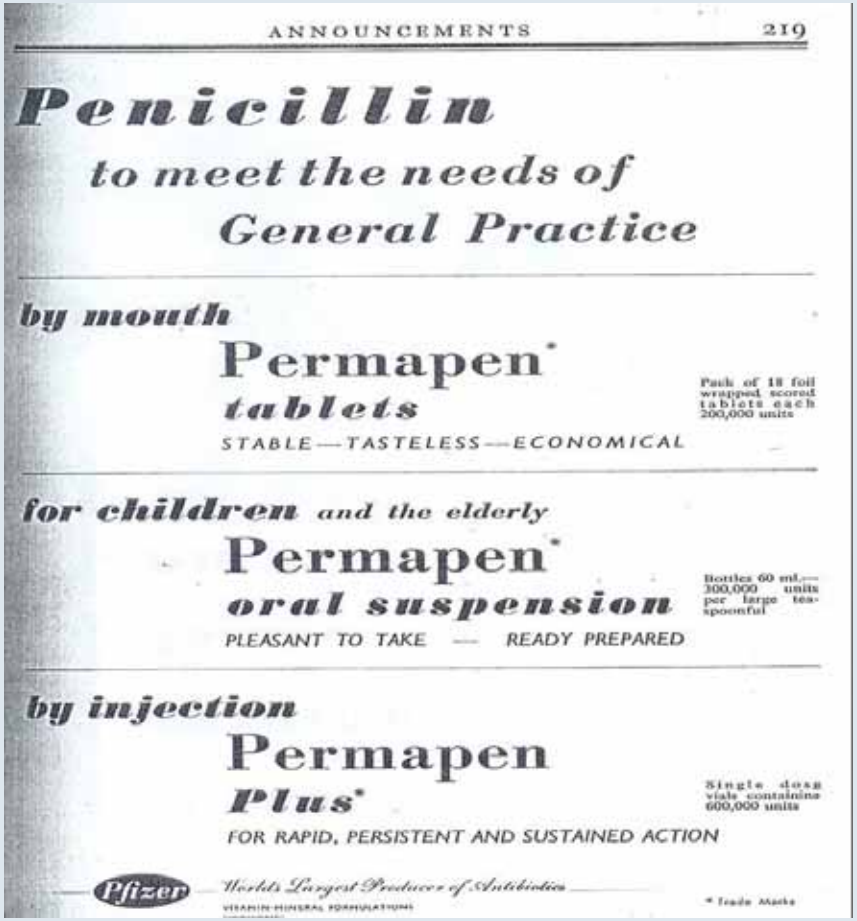
Questions on diagnosis III

- How to detect underlying chronic diseases?
- 45% of patients with cough > 2 weeks have unknown asthma/COPD!



Questions on antimicrobial therapy

- Not effective in healthy adults with acute bronchitis (9 RCTs) but systematic review is very small (<1000)
- One trial showed relevant effect in patients with more severe symptoms and in elderly
- Other subgroups?
  - Microbiology (+/- clinical score?)
  - CRP; procalcitonin?;
  - COPD asthma?;
  - Genetics?



Questions on prognosis

- Most prediction rules developed in hospital
- How to predict poor outcome in primary care?

Methods: Aetiology

Case-control study

3000 adults with LRTI

3000 healthy adults

Cases: samples at presentation and after four weeks (bacteriology, virology, serology, genetics)

Controls: If a case is included, a control (age, gender matched) is included the same week

WP 9 and 10: inclusion criteria

Inclusion criteria:

- Aged 18 years/60 years and over (1500 patients under 60 and 1500 patients of 60 years and older)
- An illness where an acute or worsened cough is the main or dominant symptom, or a clinical presentation suggesting LRTI, ≤ 28 days duration
- Consulting for the first time within this illness episode
- Able to fill out study materials
- Who have provided written, informed consent to participate

WP 9 and 10: inclusion criteria

Further inclusion criteria:

- Not been on antibiotic treatment in the previous month
- Not pregnant
- Immunocompetent
- Not been included earlier in the current GRACE trial, either as a case or control

GP will ask informed consent for trial and/or observational study.

- All patients are eligible for observational study
- A few patients must be excluded from trial:
  - Allergic to penicillin, or a contra-indication for amoxicillin because of a major interaction with other medication
  - History/exam. suggestive of community acquired pneumonia (CAP)

Methods: diagnosis

- Observational cross-sectional study

- 3000 adults with LRTI
- Diagnostic variables: signs, symptoms, additional tests (CRP, etc)

Endpoints: bacterial infection (microbiological samples)

pneumonia (chest X-rays)

Methods: prognostic study

- Observational prognostic study
- The same 3000 adults with LRTI
- Measurements: signs, symptoms, samples, chest X-ray
- Endpoints:
  - significant deterioration of illness or death within 28 days (GP registration of notes)
  - symptom severity
  - symptom duration

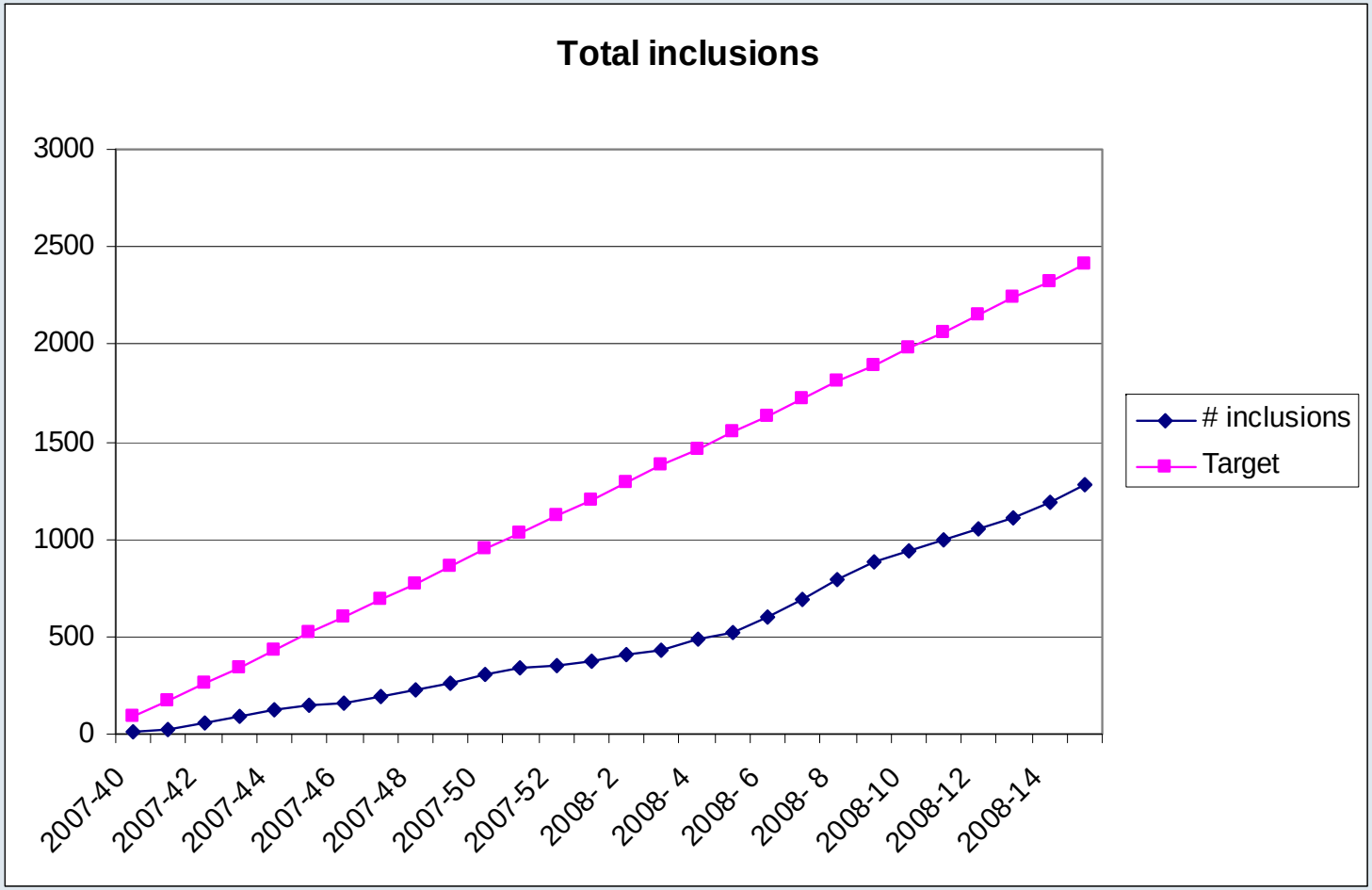
Methods: treatment

- Randomised clinical trial
- 3000 adult patients with LRTI
  - (1500 adults 18-59, 1500 elderly 60 or older)
- Intervention: amoxycillin 1 gr TID or placebo
  - treat 90% of isolates even where higher levels of resistance
  - Balance of acceptability and feasibility (prob. better than QID)
- Endpoints: 1. deterioration of illness
  2. duration and severity of illness

Recruitment & Compliance
(Overview Clinical data)

GRACE WP9-10 Recruitment

Observed vs Target Recruitment Overall

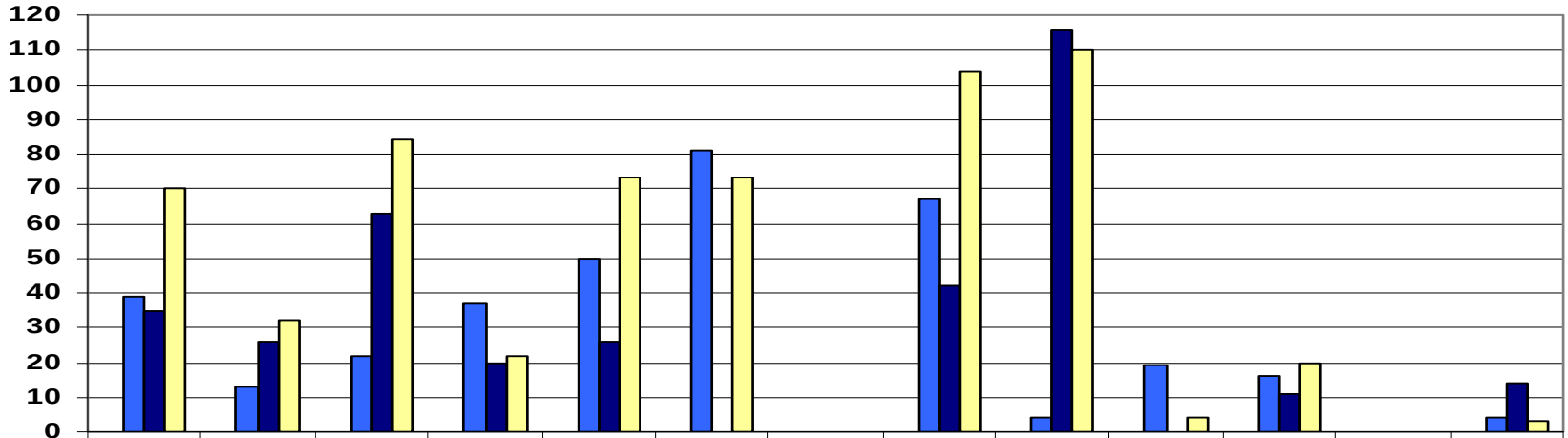


Status 17-04-08:
1300 inclusions

GRACE WP9-10
Inclusion status 17-4-08

Total Inclusions per Network (Controls and Patients)

17-4-2008 7:37 — Total # of inclusions: 1300

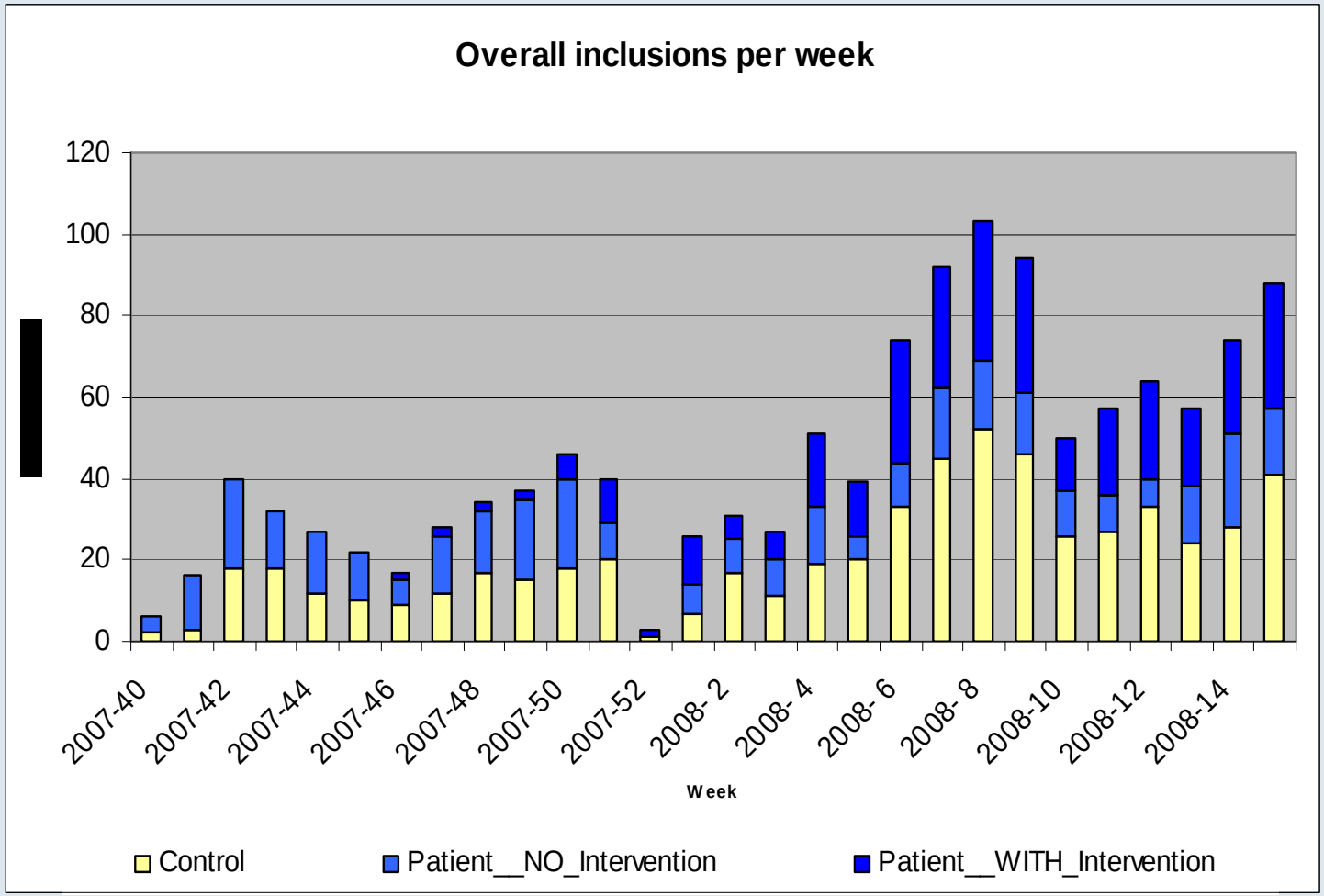


	A Cardiff	B South.	C Utrecht	D Barce.	E- Mataro	F Roten.	G Balato.	H Antw.	I Lodz	J Milano	K Jönk.	N Bratis.	O Ghent
Total	144	71	169	79	149	154	0	213	230	23	47	0	21
WP9	39	13	22	37	50	81	0	67	4	19	16	0	4
WP9/10	35	26	63	20	26	0	0	42	116	0	11	0	14
Control	70	32	84	22	73	73	0	104	110	4	20	0	3

Milan and Rotenburg: ***Approval WP10 missing***
Balatonfured: ***Approvals WP9&10 missing***
Bratislava: ***Delayed contract/money***

GRACE WP9-10 Recruitment

Overall Inclusion Rates per Week



Status 17-04-08:
1300 inclusions

Target per week:
86 inclusions

Best week:
101 inclusions
(target+17%)

GRACE WP9-10

% X-rays for Patients Visit 1 (14-4-08)

Network	Total Number of V1 Patients	% Chest X-ray
A: Cardiff	64	~94%
B: Southampton	26	~80%
C: Utrecht	46	~77%
D: Barcelona	10	~23%*
E: Mataro	60	~98%
F: Rotenburg	68	~77%
G: Balatonfured	0	-
H: Antwerp	90	~98%
I: Lodz	48	~77%
J: Milan	16	0%*
K: Jönköping	17	~87%
N: Bratislava	0	-
O: Ghent	11	~82%
Total	456	

*** No representative values due to data-entry backlog**

GRACE WP9-10

% Diaries/tests for Patients Visit 2 (14-4-08)

Network	Max.Number of V2 on 14-4-08	% Lung Function	% Diary
A: Cardiff	61	84	90
B: Southampton	25	84	88
C: Utrecht	42	76*	64*
D: Barcelona	12	33*	33*
E: Mataro	58	88	98
F: Rotenburg	62	85	87
G: Balatonfured	-	-	-
H: Antwerp	86	88	89
I: Lodz	42	90	43*
J: Milan	16	0*	0*
K: Jönköping	17	82	82
N: Bratislava	-	-	-
O: Ghent	11	54*	55*
Total	432		

*** No representative values due to data-entry backlog**

N° of Sputa (11-4-08)

Network	N° of sputa (total number of V1 kits)	% sputa
Cardiff	60 (70)	85.7
Southampton	26 (38)	68.4
Utrecht	43 (72)	59.7
Barcelona	4 (8)	50.0
Mataro	60 (76)	78.9
Rotenburg	50 (77)	64.9
Antwerp	68 (106)	64.2
Lodz	96 (102)	94.1
Sweden	18 (23)	78.3
Ghent	9 (17)	52.9
Grand total	**434 (589)**	**73.7**

Sputum Results (1)

- WBC/Epithelial cells
  - total number tested: 360 sputa
  - 49.7% WBC>Epithelial cells
  - 24.2% WBC=Epithelial cells
  - 26.1% WBC<Epithelial cells

Sputum results (2)

- Growth
  - cultures done
    - 17.6% (n=69) *Haemophilus spp.*
    - 5.6% (n=22) *S. pneumoniae*

Isolation from nasopharyngeal swab in Skimmed milk medium

- Only on collection from Antwerp network
- Total tested: 59 samples V1
  - 3.4% (n=2) *Haemophilus spp.*
  - 5.1% (n=3) *S. pneumoniae*
  - 6.8% (n=4) no growth at all

Conclusion

- A novel design nesting observational studies and a large trial which will provide a major contribution to the literature
- Major success in starting recruitment in several Networks across Europe
  - high quality samples and data collection
  - unprecedented data from primary care
  - remarkable achievement already for such a demanding study
- Still major challenges, but with grace, GRACE WP9 and 10 will succeed!