UMC Utrecht

How diagnostics reduce antibiotic resistance

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Conflicts of interest

Grants or consulting fees (payments to UMCU)

- Janssen Vaccines
- Pfizer
- Merck
- Astra Zeneca
- Pherecytes
- GSK
- Shionogi

The conventional wisdom

- Antibiotics select for antibiotic resistant bacteria
- Withholding antibiotics does not select for antibiotic resistant bacteria
- Targeted antibiotic therapy – usually - selects less for antibiotic resistant bacteria than untargeted broad-spectrum coverage

RAPID DIAGNOSTICS:
STOPPING UNNECESSARY USE OF ANTIBIOTICS

THE REVIE
ANTIMICR

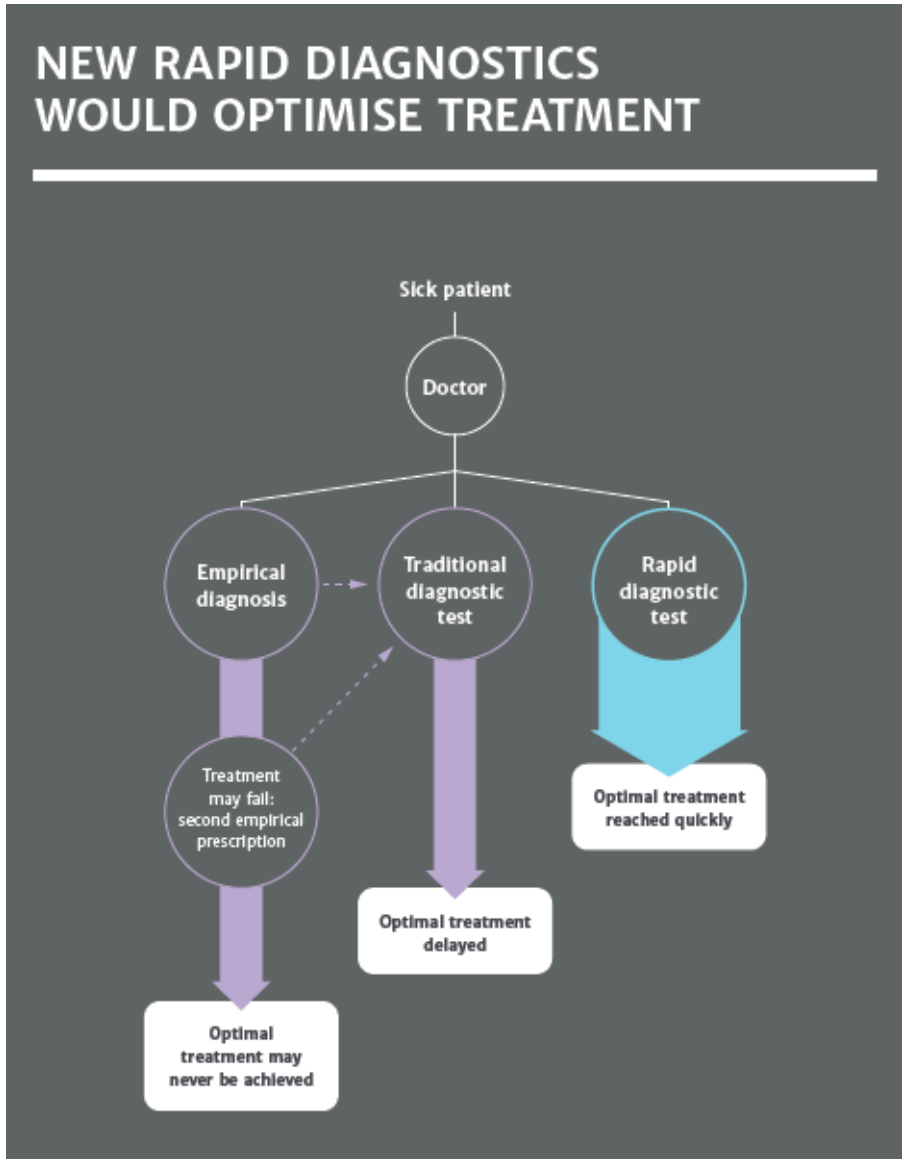
CHAIRED BY JIM O'NEILL

OCTOBER 2015

Rapid point-of-care diagnostic tests are a central part of the solution to this demand problem, which results currently in enormous unnecessary antibiotic use.

For lack of rapid diagnostics, the world vastly overuses antibiotics, in rich and poorer countries alike.

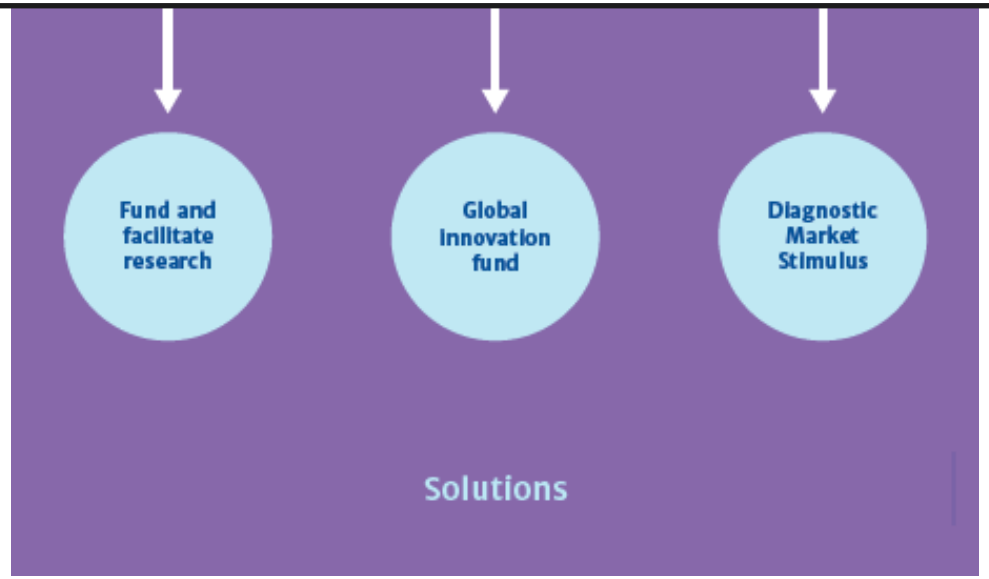
> *"This suggests it is possible that 27 million courses of antibiotics were wasted on patients who didn't need them in one year in the United States alone, for respiratory symptoms only."*



A PLAN TO OVERHAUL DIAGNOSTIC DEVELOPMENT

5.

WE CAN IMPROVE OUR USE OF ANTIBIOTICS TODAY BASED ON EXISTING DIAGNOSTICS, COUPLED WITH PUBLIC EDUCATION

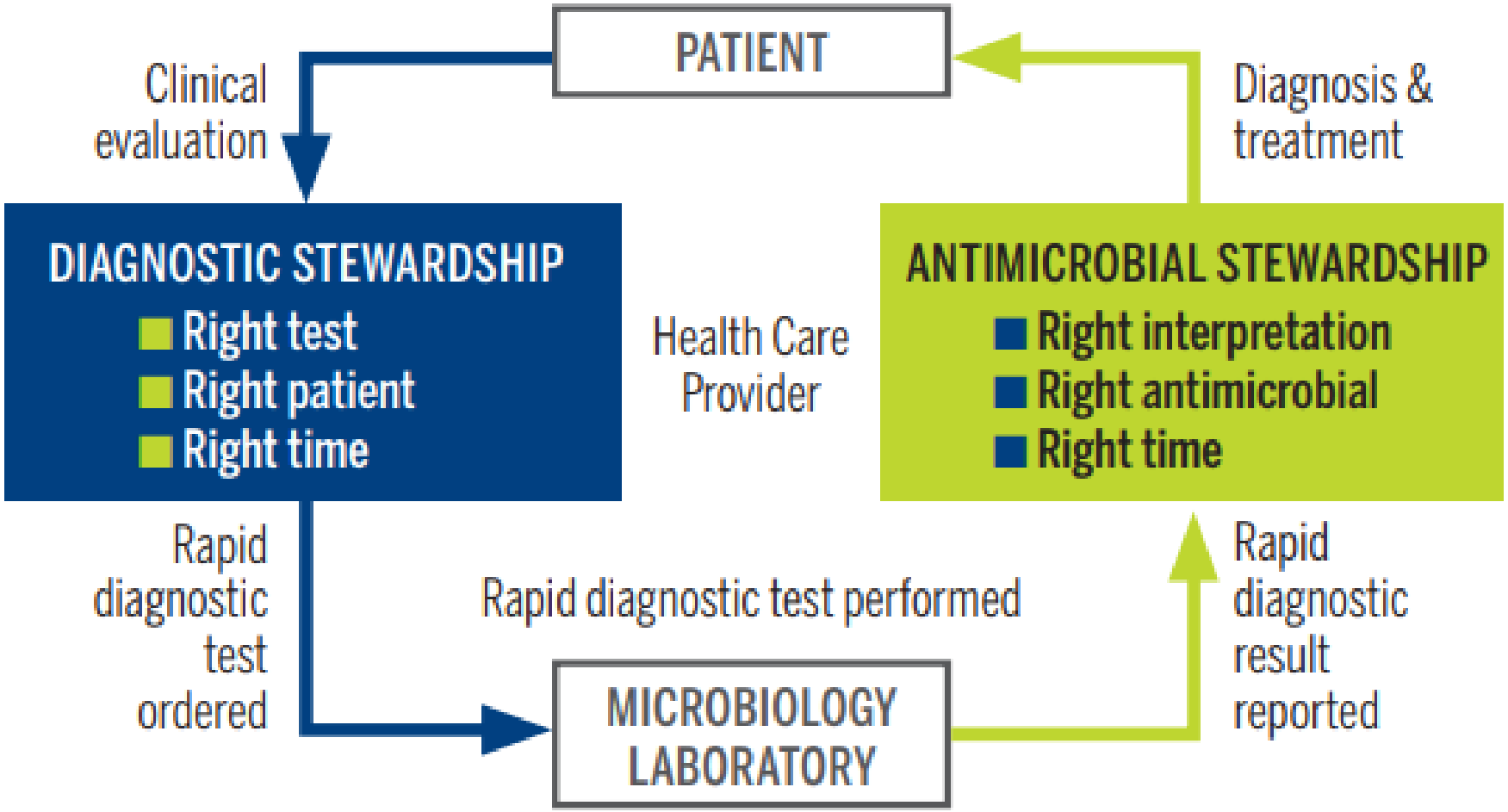


Community acquired acute respiratory tract infection (CA-ARTI)

- leading cause of morbidity and mortality
- common reason for consulting Emergency Department
- microbiological cause of infection mostly unknown at time of disease onset
- frequent cause of inadequate antibiotic prescription

Highly sensitive molecular assays increase detection of respiratory pathogens, but the **impact in clinical decision making** has not been properly evaluated.

Adapted from Messacar et al. *J. Clin. Microbiol.* 2017;55:715-723



Objective of antimicrobial/diagnostic stewardship

Can we safely reduce hospital admissions and/or antibiotic use with rapid diagnostic testing?

The impact of rapid diagnostic testing of patients with CA-ARTI on:

- (1) hospital admission rates
- (2) antimicrobial prescriptions

} *Superiority endpoints*

- (3) clinical outcome

→ *Non-inferiority endpoint*

Clinical Microbiology and Infection 25 (2019) 555–561

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

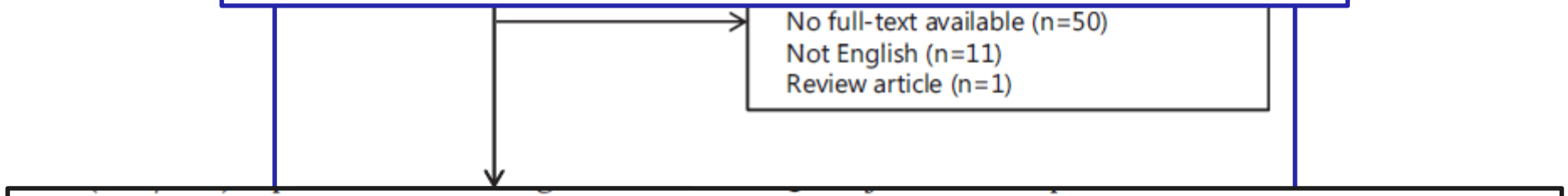
Systematic review

The quality of studies evaluating antimicrobial stewardship interventions: a systematic review

V.A. Schweitzer [1,*], I. van Heijl [2], C.H. van Werkhoven [1], J. Islam [3], K.D. Hendriks-Spoor [2], J. Bielicki [4], M.J.M. Bonten [5], A.S. Walker [6], M.J. Llewelyn [3]on behalf of the Consensus on Antimicrobial Stewardship Evaluations (CASE) study group[†]

Table 3
Design quality features of the included studies stratified by studies performed in the community and the hospital setting

Quality feature	Community ($n = 205$), n (%)	Hospital ($n = 620$), n (%)
Randomized research design	95 (46)	55 (9)
External control group	129 (63)	99 (16)
Multicentre	148 (72)	101 (16)
Sample size calculation reported	77 (38)	96 (15)
Prospective data collection	144 (70)	288 (46)
Correction for confounding factors	113 (55)	157 (25)
Primary outcome defined	116 (57)	272 (44)
Clinical outcome reported	61 (30)	337 (54)
Microbiological outcome reported	17 (8)	173 (28)
Sustainability assessed (≥12 months)	115 (56)	347 (56)



Implications: Overall quality of antimicrobial stewardship studies is low and has not improved over time. Most studies do not report clinical and microbiological outcome data. Studies conducted in the community setting were associated with better quality. These limitations should inform the design of future stewardship evaluations so that a robust evidence base can be built to guide clinical practice.
V.A. Schweitzer, Clin Microbiol Infect 2019;25:555

Routine molecular point-of-care testing for respiratory viruses in adults presenting to hospital with acute respiratory illness (ResPOC): a pragmatic, open-label, randomised controlled trial

Nathan J Brendish, Ahalya K Malachira, Lawrence Armstrong, Rebecca Houghton, Sandra Aitken, Esther Nyimbili, Sean Ewings, Patrick J Lillie, Tristan W Clark

Lancet Respir Med 2017; 5: 401–11

Pragmatic, parallel-group, open-label, randomised controlled trial;

Adults (aged ≥18 years) within 24 h of presenting to the emergency department or acute medical unit of a large UK hospital with acute respiratory illness or fever (≤7 days duration), or both, over two winter seasons.

Patients were randomly assigned (1:1) to have a molecular POC test for respiratory viruses or routine clinical care.

The primary outcome was the proportion of patients who received antibiotics while hospitalised (up to 30 days).

	POCT (n=360)	Control (n=354)	Difference (95% CI)	Odds ratio (95% CI)	Number needed to test (95% CI)	p value
Patients tested for viruses	360 (100%)	158 (45%)	55·4% (50·1 to 60·0)	..	..	<0·0001
Patients with any virus detected	161 (45%)	52 (15%)	30·0% (23·3 to 36·8)	4·70 (3·28 to 6·74)	4 (2·8 to 4·2)	<0·0001
Influenza A or B	61 (17%)	37 (10%)	6·5% (1·5 to 11·5)	1·75 (1·13 to 2·71)	16 (9 to 68)	0·0124
Rhinovirus or enterovirus (unspecified)*	55 (15%)	..	..	..	..	..
Coronavirus*	18 (5%)	..	..	..	..	..
Human metapneumovirus	14 (4%)	5 (1%)	2·5% (0·1 to 4·8)	..	..	0·060
Parainfluenza	11 (3%)	2 (<1%)	2·5% (0·6 to 4·4)	..	..	0·0214
RSV	9 (3%)	6 (2%)	0·8% (−1·3 to 2·9)	..	..	0·60
Adenovirus	1 (<1%)	2 (<1%)	−0·3% (−1·2 to 0·7)	..	..	0·62
Viral co-detection	8 (2%)	0	2·2% (0·7 to 3·7)	..	..	0·0075
Turnaround time (h)	2·3 (1·4)†	37·1 (21·5)	−34·7 (−38·1 to −31·4)			<0·0001

Data are n (%) or mean (SD). Medians are presented in the appendix for completeness. POCT=point-of-care testing. RSV=respiratory syncytial virus. *Not tested for by laboratory PCR. †Assessed in 356 patients.

***Table 2*: Patients tested for viruses, rate of detection, and turnaround time**

	POCT (n=360)	Control (n=354)	Risk difference (95% CI)	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)	Number needed to test (95% CI)	p value
All antibiotics							
Antibiotics given	301 (84%)	294 (83%)	0·6% (−4·9 to 6·0)	1·04 (0·70 to 1·54)	0·99 (0·57 to 1·70)	..	0·96*
Single dose only	31/301 (10%)	10/294 (3%)	6·9% (2·9 to 11·0)	3·26 (1·59 to 6·68)	..	15 (9 to 35)†	0·0010
Given for <48 h	50/301 (17%)	26/294 (9%)	7·8% (2·5 to 13·1)	2·05 (1·40 to 3·39)	..	13 (8 to 41)‡	0·0047
Duration (days)	7·2 (5·1)	7·7 (4·9)	−0·4 (−1·2 to 0·4)§	0·95 (0·85 to 1·05)¶	0·91 (0·80 to 1·04)‖	..	0·17*
Intravenous antibiotics							
Intravenous antibiotics given	196 (54%)	183 (52%)	2·7% (−4·6 to 10·0)	1·15 (0·83 to 1·50)	..	..	0·46
Single dose only	50/196 (26%)	37/183 (20%)	5·3% (−3·1 to 14·0)	1·35 (0·84 to 2·19)	..	..	0·22
Given for <48 h	106/196 (54%)	100/183 (55%)	−0·5% (−11·0 to 9·5)	0·98 (0·65 to 1·46)	..	..	0·91
Duration (days)	3·1 (4·6)	2·9 (3·7)	0·3 (−0·6 to 1·1)§	1·09 (0·86 to 1·40)¶	..	..	0·48

Data are n (%) or mean (SD). POCT=point-of-care testing. *Applies to adjusted effect sizes. †Number needed to test to change a standard course to a single dose. ‡Number needed to test to change a standard course to a brief course. §Mean difference. ¶Unadjusted rate ratio. ‖Adjusted rate ratio.

***Table 3*: Comparison of antibiotic use**

Narrow-spectrum antibiotics for community-acquired pneumonia in Dutch adults (CAP-PACT): a cross-sectional, stepped-wedge, cluster-randomised, non-inferiority, antimicrobial stewardship intervention trial

Valentijn A Schweitzer, Inger van Heijl*, Wim G Boersma, Wouter Rozemeijer, Kees Verduin, Marco J Grootenboers, Sanjay U C Sankatsing, Akke K van der Bij, Winnie de Bruijn, Heidi S M Ammerlaan, Ilse Overdevest, J M Milena Roorda-van der Vegt, Elske M Engel-Dettmers, Florence E Ayuketah-Ekokobe, Michiel B Haeseker, J Wendelien Dorigo-Zetsma, Paul D van der Linden, C H Edwin Boel, Jan J Oosterheert, Cornelis H van Werkhoven, Marc J M Bonten, on behalf of the CAP-PACT Study Group*

Lancet Infect Dis 2021

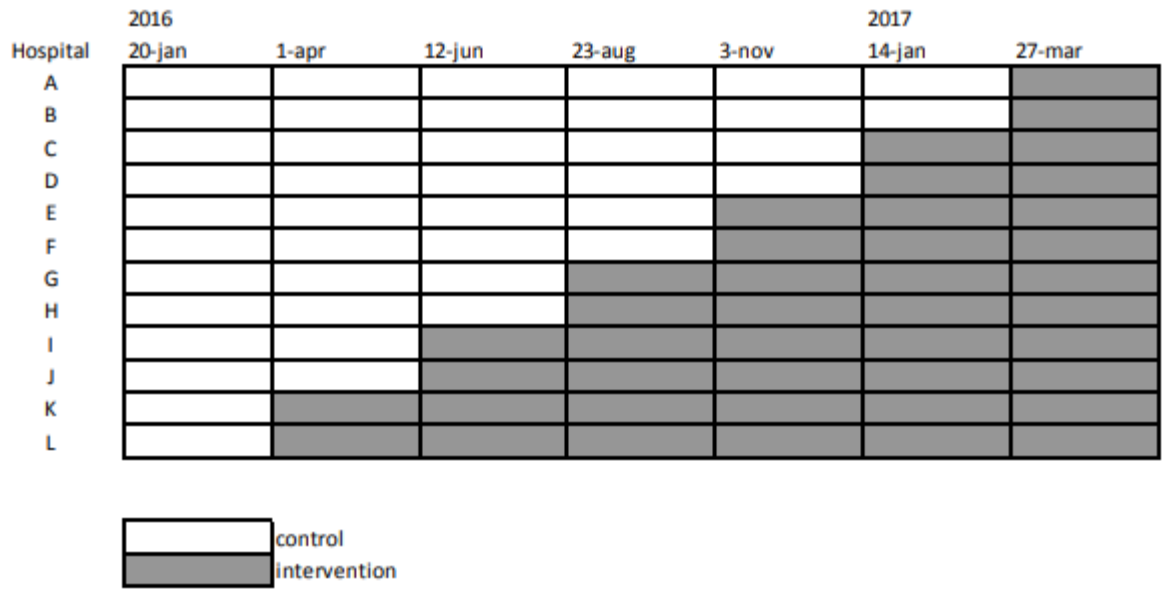
Published Online
October 7, 2021
https://doi.org/10.1016/
S1473-3099(21)00255-3

… we investigated whether an antibiotic stewardship intervention would reduce the use of broad-spectrum antibiotics in patients with moderately severe community-acquired pneumonia without compromising their safety.

Aiming for benzylpenicillin, amoxicillin or doxycycline instead of amoxicillin-clavulanic acid, cephalosporins, macrolides or fluoroquinolones

A stepped-wedge cluster-randomized design

Figure S1: Stepped-wedge randomisation scheme



Assuming an all-cause 90-day mortality of 10%, a non-inferiority margin of 3%, a one-sided alpha of 0·05, and taking into account the stepped-wedge design, a total of 4464 patients were required for 80% power to detect non-inferiority.

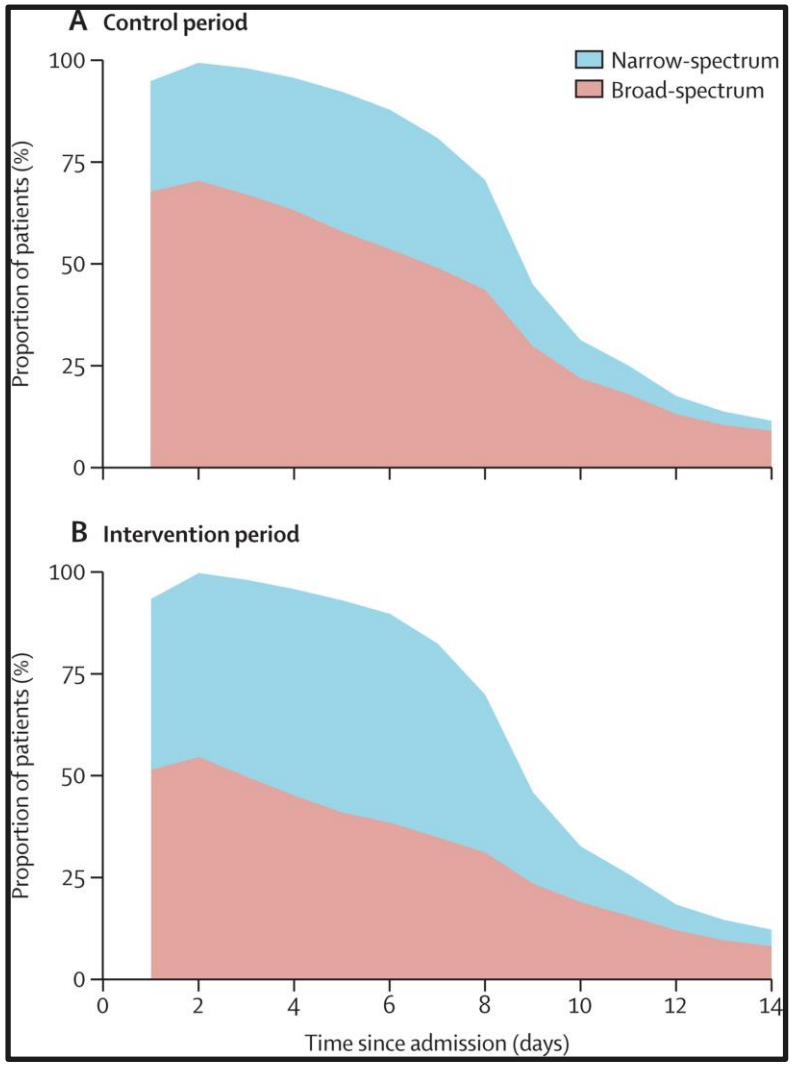
Antbiotic stewardship intervention

Educational activities were targeted at physicians in pulmonary and internal medicine departments and consisted of:

- clinical lessons,
- electronic (e)-learning,
- educational attributes.

Clinical lessons, in which national community-acquired pneumonia guidelines were addressed by use of case-based discussions and feedback, with antibiotic prescribing data of the respective hospitals anonymously benchmarked against other participating hospitals, were given at month 0 of the intervention period and then every 6 months until study completion.

Results: antibiotic use



Narrow-spectrum:

- Benzylpenicillin
- Amoxicllin
- Doxycycline

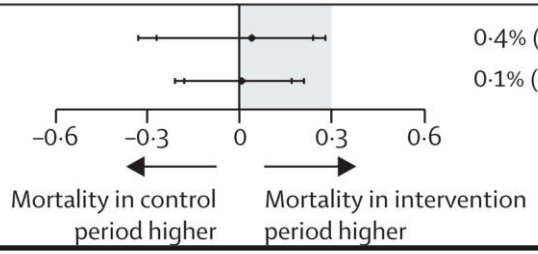
The median total days of therapy per patient were 8 days (IQR 7–10) in the control and 8 days (7–11) in the intervention period.

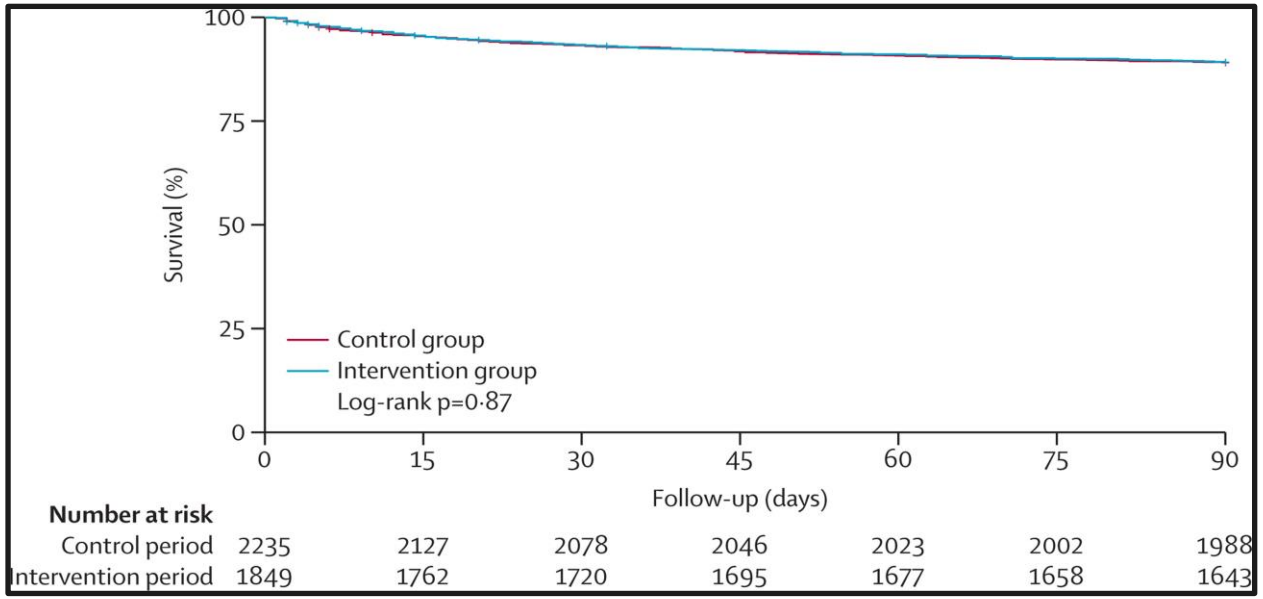
The adjusted mean broad-spectrum days of therapy per patient was reduced from 6·5 days in the control period to 4·8 days in the intervention period, with an adjusted absolute difference of –1·7 days (95% CI –2·4 to –1·1) and an adjusted relative reduction of 26·6% (95% CI 18·0–35·3).

Results: safety

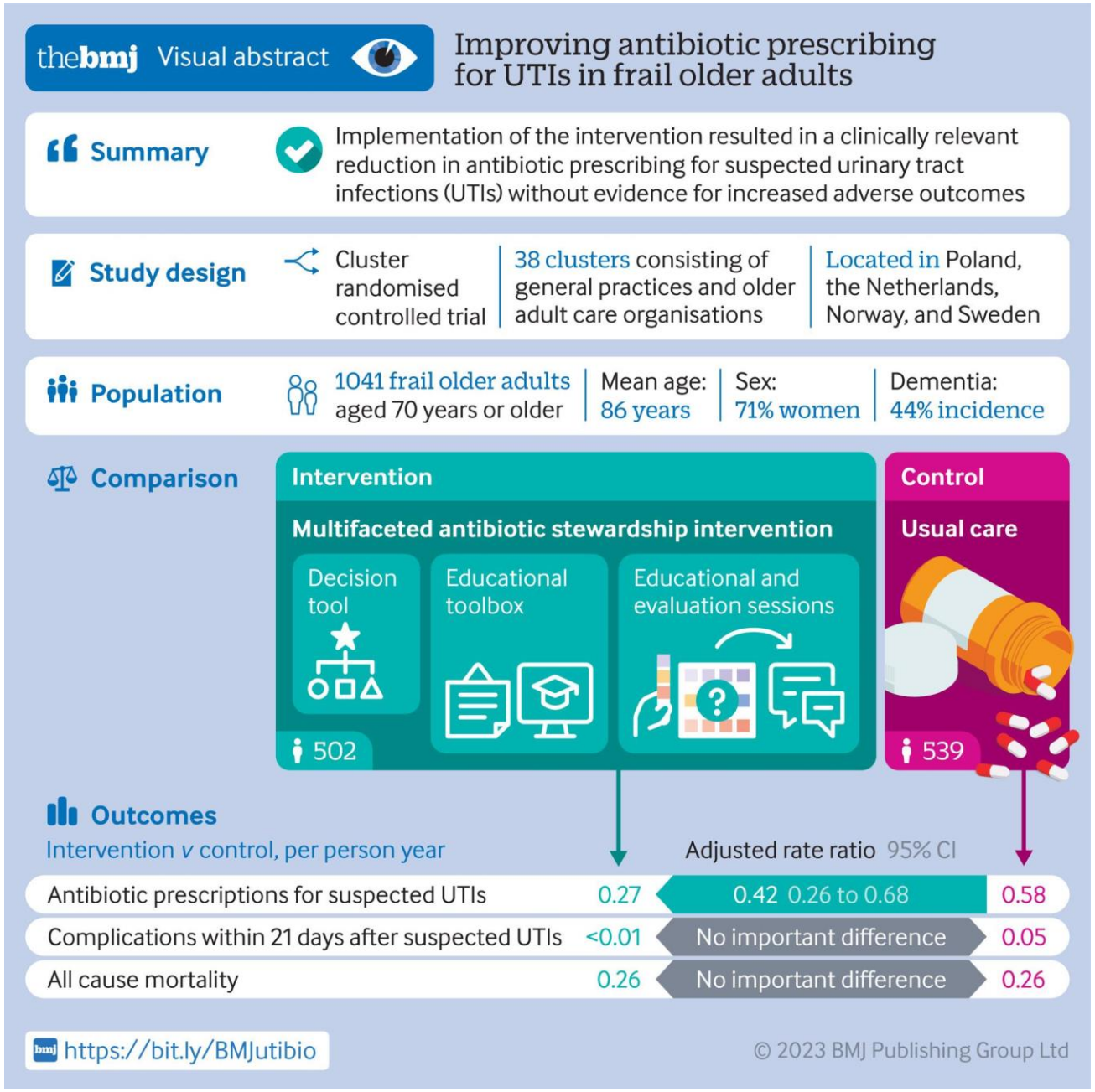
90-day all-cause mortality was 10·9% (242 of 2228 patients died) in the control period and 10·8% (199 of 1841 patients died) in the intervention period

	Control period (n/N)	Intervention period (n/N)	Adjusted risk difference (95% CI)
Intention-to-treat	242/2235	199/1849	0·4% (−3·3 to 2·8)
As-treated	308/2592	132/1491	0·1% (−2·1 to 2·1)





Number at risk							
Control period	2235	2127	2078	2046	2023	2002	1988
Intervention period	1849	1762	1720	1695	1677	1658	1643


thebmj Visual abstract
Improving antibiotic prescribing for UTIs in frail older adults
Summary
Implementation of the intervention resulted in a clinically relevant reduction in antibiotic prescribing for suspected urinary tract infections (UTIs) without evidence for increased adverse outcomes
Study design
Cluster randomised controlled trial
38 clusters consisting of general practices and older adult care organisations
Located in Poland, the Netherlands, Norway, and Sweden
Population
1041 frail older adults aged 70 years or older
Mean age: 86 years
Sex: 71% women
Dementia: 44% incidence
Comparison
Intervention
Multifaceted antibiotic stewardship intervention
Decision tool
Educational toolbox
Educational and evaluation sessions
502
Control
Usual care
539
Outcomes
Intervention v control, per person year
Adjusted rate ratio 95% CI
Antibiotic prescriptions for suspected UTIs
0.27
0.42 0.26 to 0.68
0.58
Complications within 21 days after suspected UTIs
<0.01
No important difference
0.05
All cause mortality
0.26
No important difference
0.26
https://bit.ly/BMJutibio
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Conclusions

- Empiric treatment of infections remains challenging, mostly because a documented causative pathogen hardly ever informs treatment decisions.

- Demonstrating safe reductions of unnecessary antibiotic use requires well-designed pragmatic clinical trials demonstrating the safety/non-inferiority of using less broad-spectrum antibiotics.

- Antimicrobial and diagnostic stewardship are suitable interventions to change practices, but the impact on reducing antibiotic resistance remains to be determined.

- The complexities of integrating diagnostics into the care path should not be underestimated.