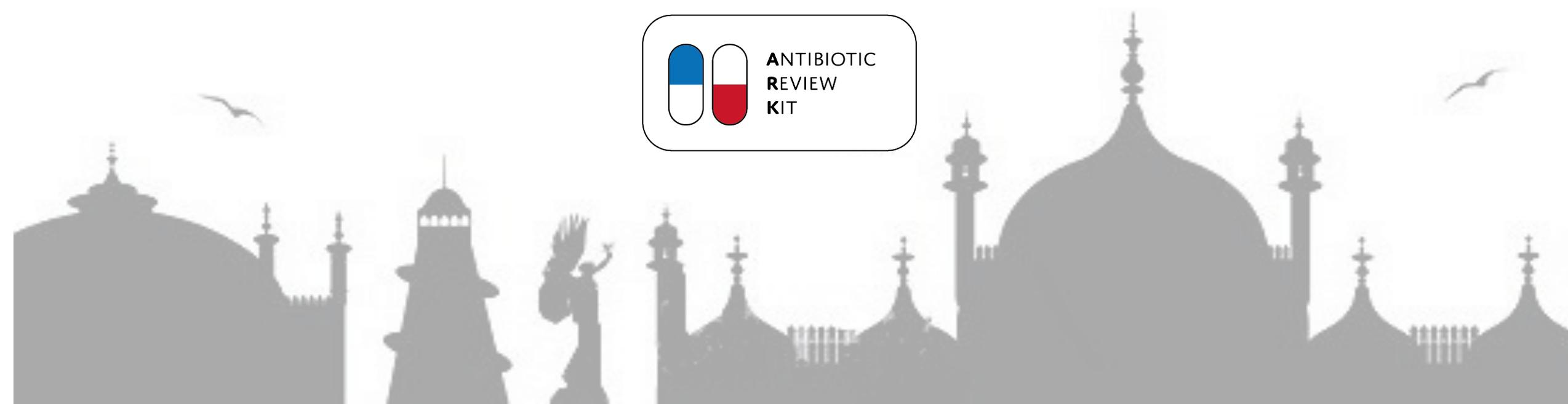
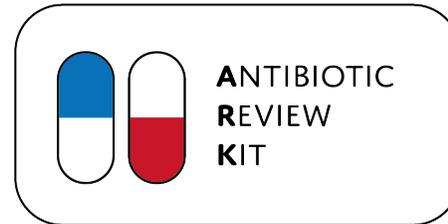




# Antibiotic Review Kit - Hospital (ARK-hospital)

**Martin Llewelyn**

Brighton and Sussex Medical School



# The challenge of antibiotic resistant GNRs in the UK

Rates of resistance to key agents...

Gentamicin

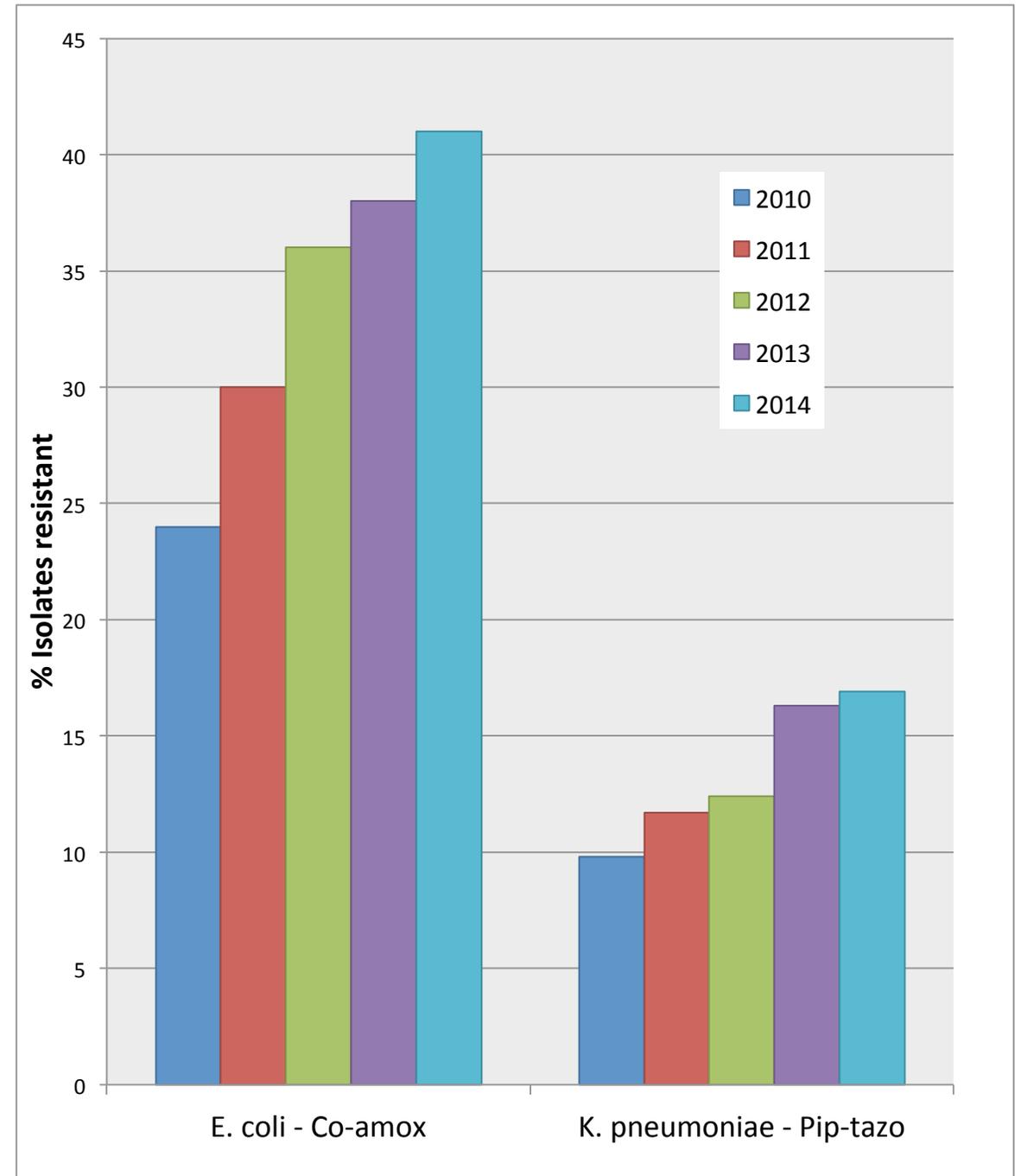
Ciprofloxacin

Co-amoxiclav

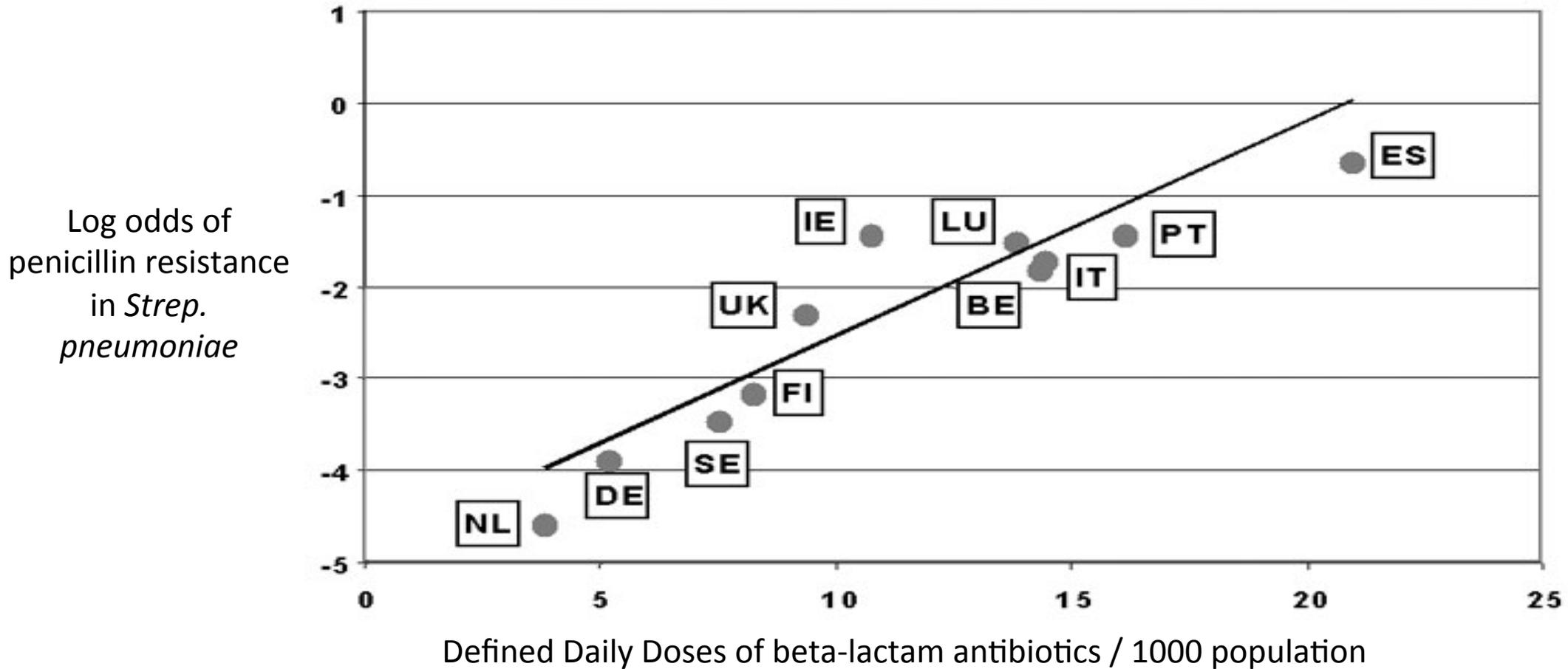
Piperacillin – tazobactam

....now compromise reliability as empiric treatment choices

46% of *E. coli* bacteraemia isolates now reported as co-amoxiclav resistant



# Antibiotic consumption correlates with antibiotic resistance



# Antibiotics also place individual patients at risk of resistant infection

## Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis

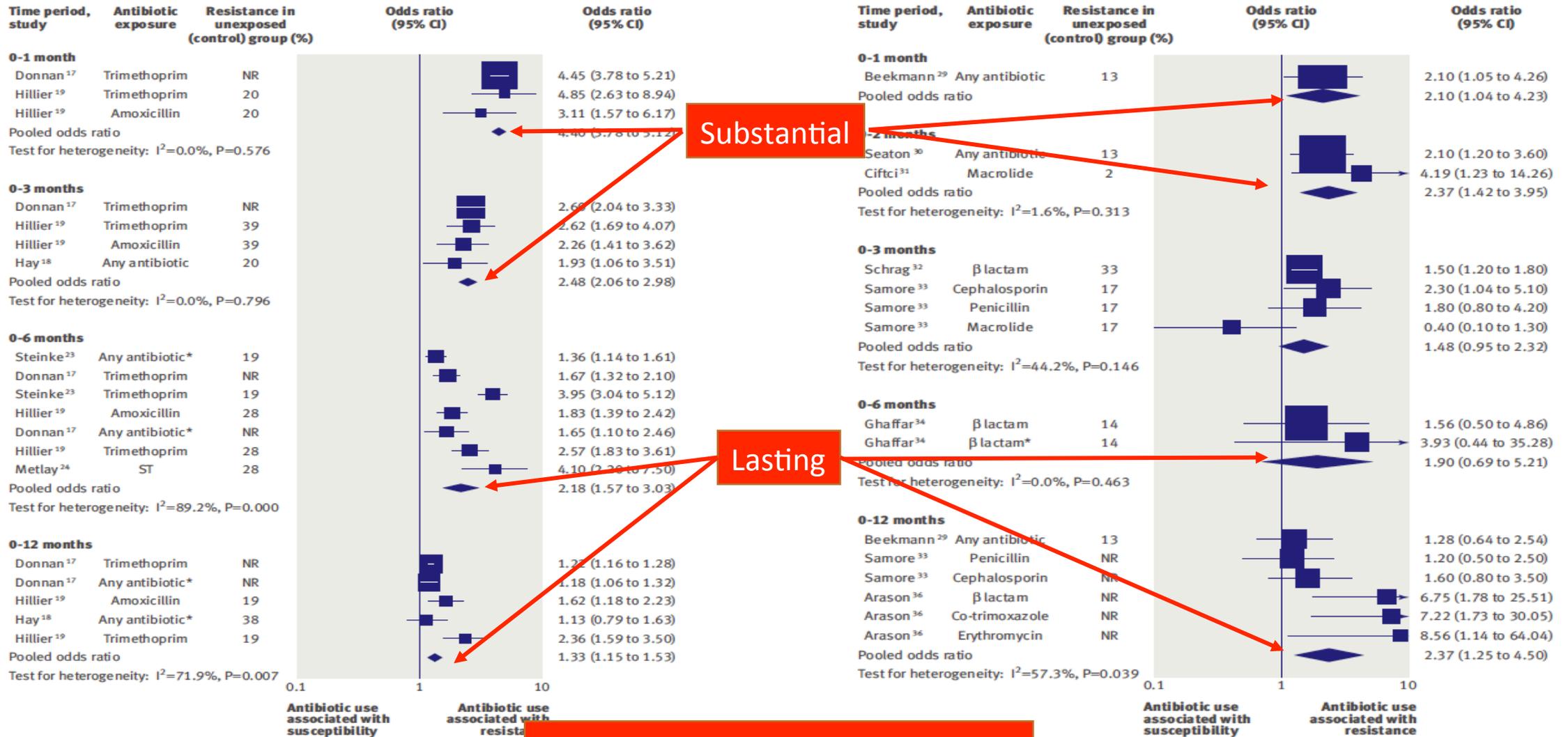
BMJ

Céire Costelloe, research associate,<sup>1</sup> Chris Metcalfe, senior lecturer in medical statistics,<sup>2</sup> Andrew Lovering, consultant clinical scientist,<sup>3</sup> David Mant, professor of general practice,<sup>4</sup> Alastair D Hay, consultant senior lecturer in primary health care<sup>1</sup>

Cite this as: *BMJ* 2010;340:c2096  
doi:10.1136/bmj.c2096

- Explored relationship between prior antibiotic use and antibiotic resistance
- Reviewed 24 studies
  - 19 Observational
  - 5 RCTs
  - >27,000 participants
- Urinary Infections
- Respiratory Tract infections

# Forest plots of included studies



Urinary Infection

Impact on risk of resistant infection

Respiratory Tract Infection

# Giving less antibiotics reduces this risk

## 1. Chastre J et al JAMA 2003

- 401 patients with VAP on 51 French ICUs
- Randomized to 8 vs 15 days antibiotic treatment
- Short course patients had
  - equivalent outcomes on every safety measure
  - half as much antibiotic exposure
  - Lower risk of resistant re-infection

## 2. Singh N et al Am J Respir Crit Care Med 2000

1. 81 patients treated for suspected VAP randomised to review and revise at 3 days or standard course
2. Lower risk of resistance / super-infection in the review and revise group (15 vs 35% p = 0.017).

# Giving less antibiotic probably improves clinical outcome

## Current evidence on hospital antimicrobial stewardship objectives: a systematic review and meta-analysis

Emelie C Schuts, Marlies E J L Hulscher, Johan W Mouton, Cees M Verduin, James W T Cohen Stuart, Hans W P M Overdiek, Paul D van der Linden, Stephanie Natsch, Cees M P M Hertogh, Tom F W Wolfs, Jeroen A Schouten, Bart Jan Kullberg, Jan M Prins

*Lancet Infect Dis* 2016; 16: 847-56

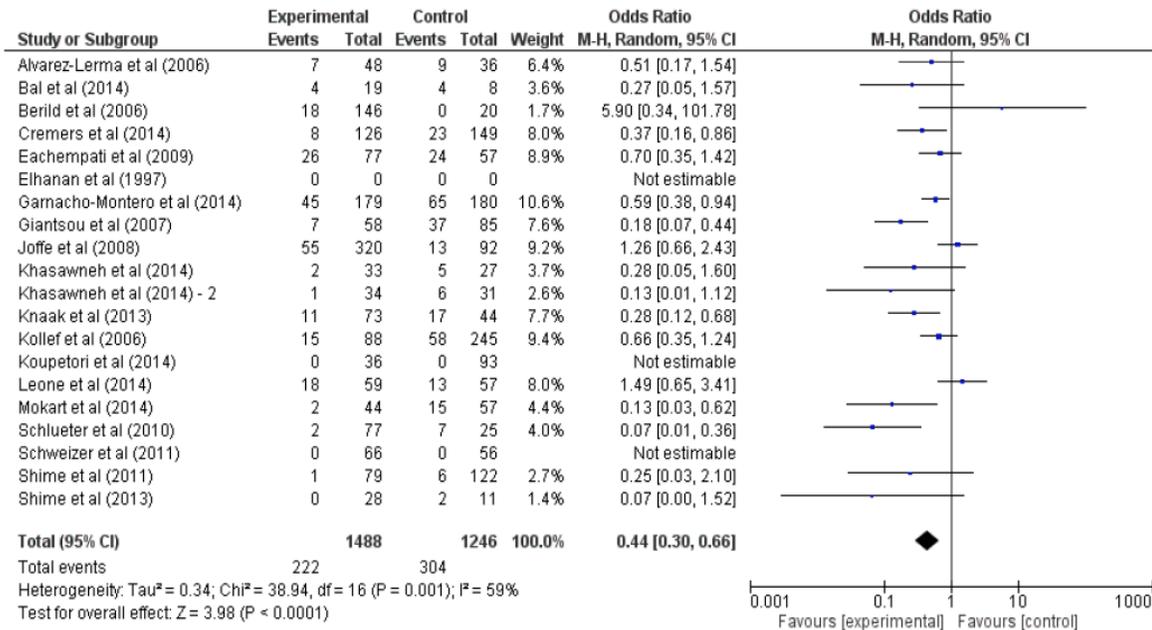
### Interventions to improve antibiotic prescribing practices for hospital inpatients (Review)

Davey P, Marwick CA, Scott CL, Charani E, McNeil K, Brown E, Gould IM, Ramsay CR, Michie S. Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database of Systematic Reviews* 2017, Issue 2. Art. No.: CD003543. DOI: 10.1002/14651858.CD003543.pub4.



Cochrane Database of Systematic Reviews

### Effect on mortality of antibiotic de-escalation



Concluded:

Lower use of antibiotics probably does not increase mortality and likely reduces length of stay.

Interventions were successful in safely reducing unnecessary antibiotic use in hospitals, despite the fact that the majority did not use the most effective behaviour change techniques.

Overall 56% (95% CI 34-70%) REDUCED risk of mortality with Antibiotic de-escalation strategies

# For common indications minimum durations of treatment have not been established

## The New Antibiotic Mantra—“Shorter Is Better”

Brad Spellberg, MD

JAMA Internal Medicine Published online July 25, 2016

There is a lack of evidence that recommended durations are **superior** to antibiotic-sparing approaches\*

\*w/exception of otitis media,  
Hoberman A et al New Eng J Med. 2016;375:2446-2456

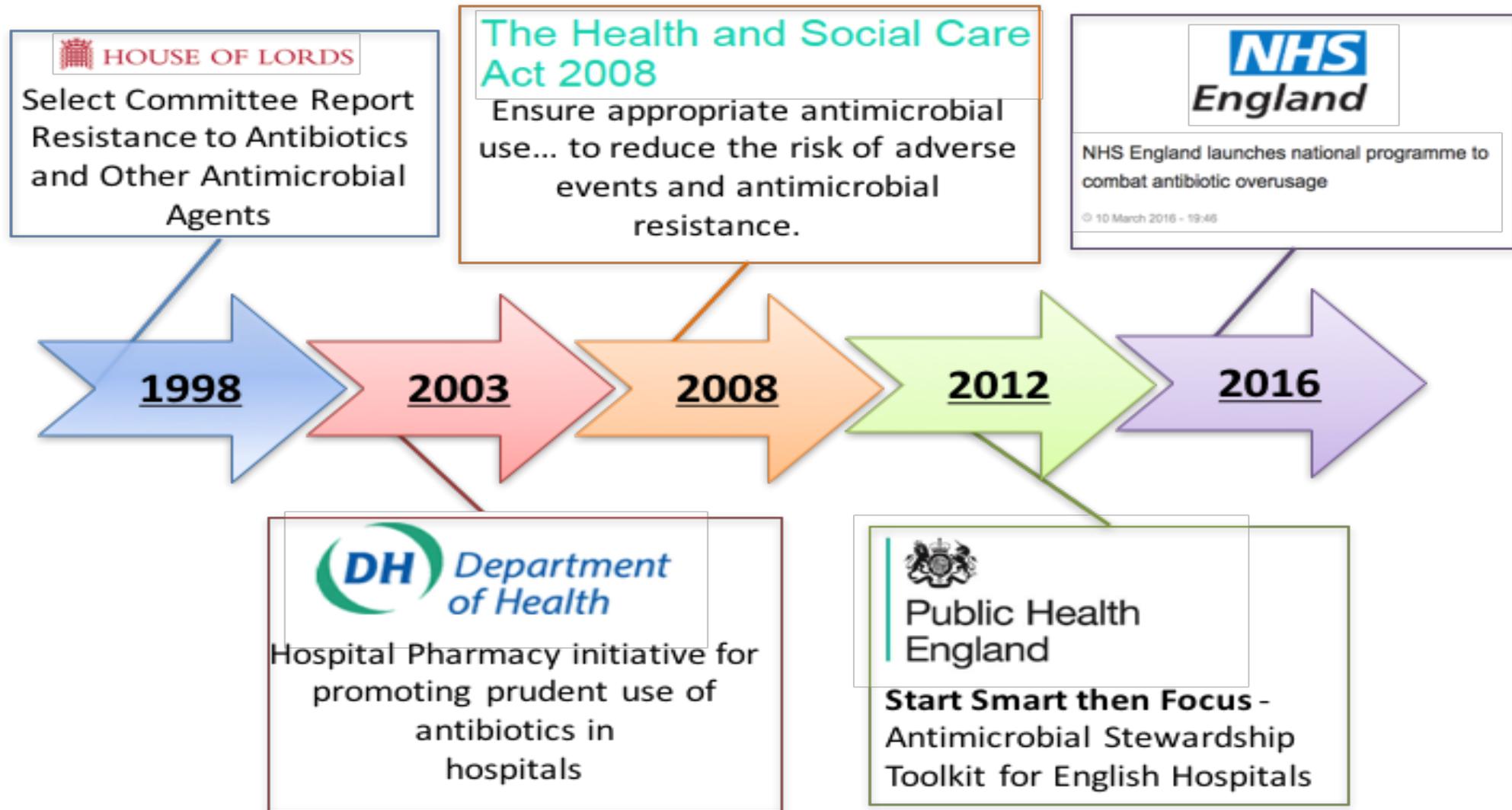
## Recommended course durations have fallen

Table. Infections for Which Short-Course Therapy Has Been Shown to Be Equivalent in Efficacy to Longer Therapy

| Disease   | Treatment, Days |       |
|---|-----------------|-------|
|   | Short           | Long  |
| Community-acquired pneumonia <sup>1-3</sup>                     | 3-5             | 7-10  |
| Nosocomial pneumonia <sup>6,7</sup>                             | ≤8              | 10-15 |
| Pyelonephritis <sup>10</sup>                                    | 5-7             | 10-14 |
| Intraabdominal infection <sup>11</sup>                          | 4               | 10    |
| Acute exacerbation of chronic bronchitis and COPD <sup>12</sup> | ≤5              | ≥7    |
| Acute bacterial sinusitis <sup>13</sup>                         | 5               | 10    |
| Cellulitis <sup>14</sup>  | 5-6             | 10    |
| Chronic osteomyelitis <sup>15</sup>                             | 42              | 84    |

Abbreviation: COPD, chronic obstructive pulmonary disease.

# And yet it appears to be very hard to reduce antibiotic use in hospitals

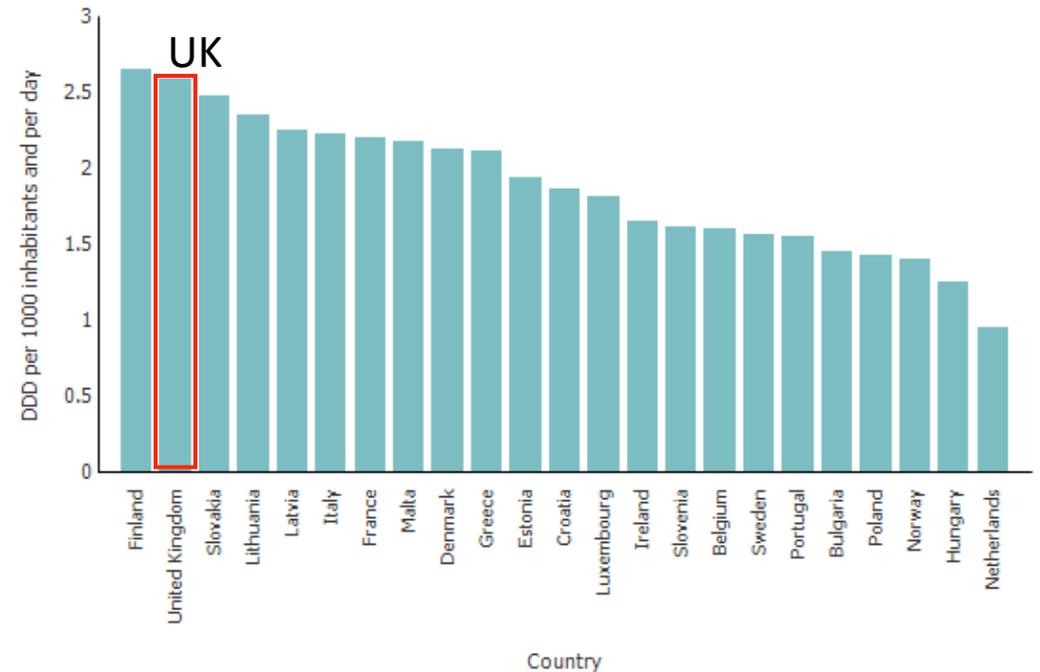


# Hospital antibiotic use in England

Total and broad-spectrum antibiotic prescribing NHS England 2010 - 2014



Consumption of systemic antibacterials in the hospital sector in Europe 2014



[https://www.gov.uk/government/uploads/system/uploads/attachment\\_data/file/477962/ESPAUR\\_Report\\_2015.pdf](https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/477962/ESPAUR_Report_2015.pdf) (accessed August 2016)

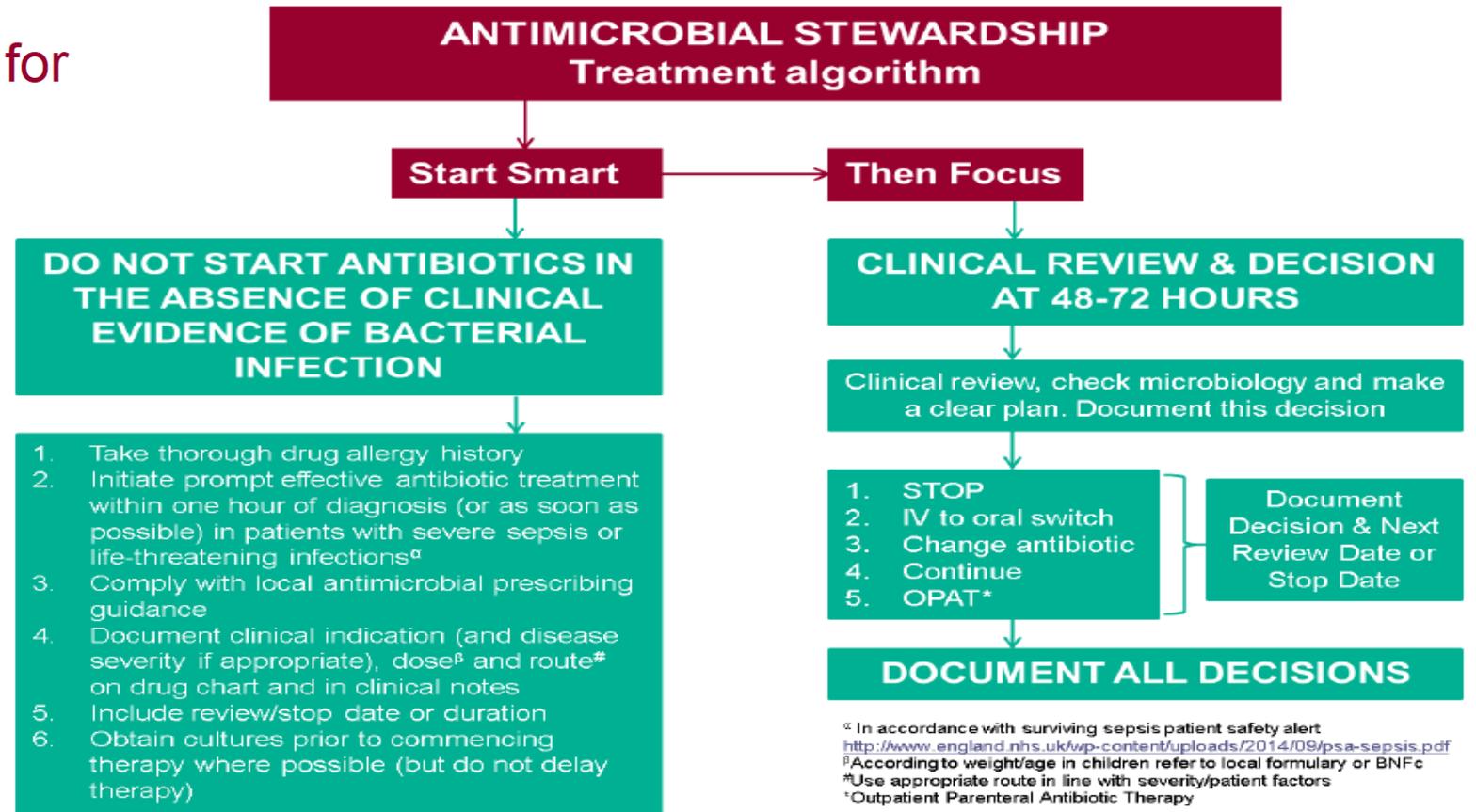
[http://ecdc.europa.eu/en/healthtopics/antimicrobial\\_resistance/esac-net-database/Pages/Antimicrobial-consumption-rates-by-country.aspx](http://ecdc.europa.eu/en/healthtopics/antimicrobial_resistance/esac-net-database/Pages/Antimicrobial-consumption-rates-by-country.aspx) (accessed August 2016)

# Start Smart - Then Focus

## Antimicrobial Stewardship Toolkit for English Hospitals



Public Health  
England



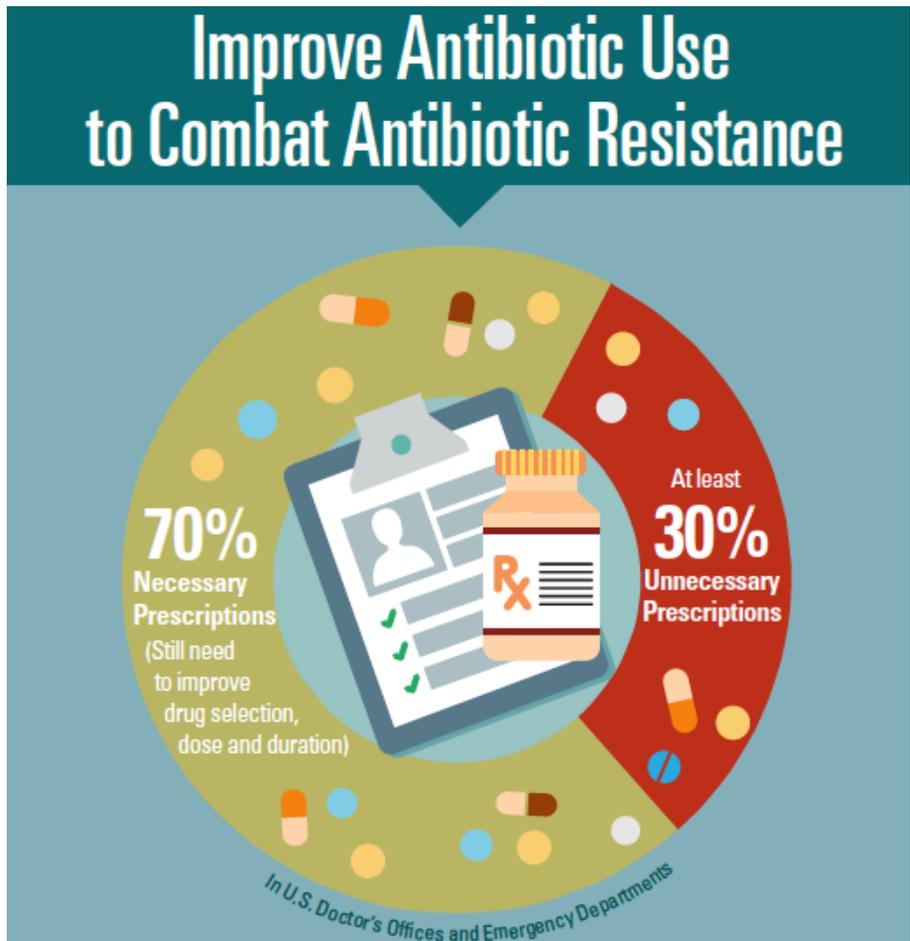
## Antibiotic policies in acute English NHS trusts: implementation of 'Start Smart—Then Focus' and relationship with *Clostridium difficile* infection rates

Martin J. Llewelyn<sup>1\*</sup>, Kieran Hand<sup>2</sup>, Susan Hopkins<sup>3</sup> and A. Sarah Walker<sup>4</sup>

*J Antimicrob Chemother* 2015; **70**: 1230–1235

Start 'smart' without 'focus' may actually *increase* antibiotic overuse

# How much could antibiotic use be cut?



<https://www.cdc.gov/features/antibioticuse/>

**NATIONAL ACTION PLAN FOR COMBATING ANTIBIOTIC-RESISTANT BACTERIA**

MARCH 2015

THE WHITE HOUSE  
WASHINGTON

The cover of the report features a gold eagle emblem at the top center and the White House logo at the bottom center. The title is in a blue serif font.

“By 2020, significant outcomes will include:  
Reduction of *inappropriate* antibiotic use  
By **50%** in outpatient settings  
By **20%** in inpatient settings”

“we will cut inappropriate prescribing in the UK by half by 2020...”



G7 2016 in Japan: PM press statement

**BMJ Open Antibiotic use and clinical outcomes in the acute setting under management by an infectious diseases acute physician versus other clinical teams: a cohort study**

Nicola JK Fawcett,<sup>1</sup> Nicola Jones,<sup>2</sup> T Phuong Quan,<sup>3</sup> Vikash Mistry,<sup>2</sup> Derrick Crook,<sup>3</sup> Tim Peto,<sup>3</sup> A Sarah Walker<sup>3</sup>

Fawcett NJK, *et al. BMJ Open* 2016;**6**:e010969. doi:10.1136/bmjopen-2015-010969

**Acute medical patients under an infection physician receive less antibiotic treatment  
173 vs 282 DOT/100 admissions**

Allowing for case mix ID managed patients were

- Less likely to receive an antibiotic (OR=0.25 (95% CI 0.07 to 0.84), p=0.03)
- More likely to receive a shorter course (RR=0.71 (95% CI 0.54 to 0.93), p=0.01)

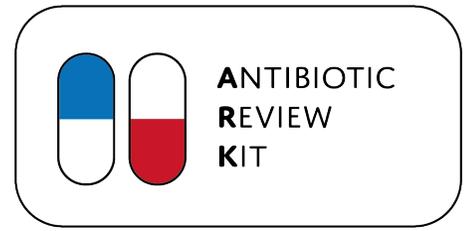
**With no differences in treatment failure or mortality**

But longer hospital stay 2 (2-6) vs 4 (3-6) days

# Anti-Microbial Resistance CQUIN 2016/17

## Part B – Empiric review of antibiotic prescriptions

- **Documented day 3 review**
  - Q1 target 25%: median 81.6%
  - Q2 target 50%: median 88% (38% - 100%). (1 trust <50%; 125 submitted)
  - Q3 target 75%: median 90.0% (50% - 99%). (3 trusts <75%; 125 submitted)
- **Outcomes data of day 3 review (Q1);** 111 trusts entered voluntary data
  - **Stop 10%**
  - Continue 63%
  - IVOS 16%
  - switch AB 12%
  - OPAT 0.5%



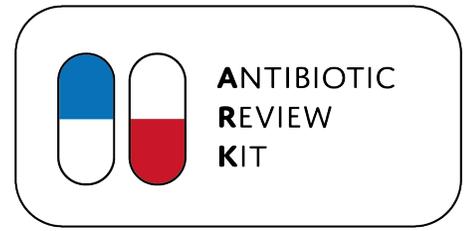
# What is ARK-hospital?

A 5-year applied research programme funded by NIHR

The overarching aim of ARK is to reduce the incidence of serious infections caused by antibiotic-resistant bacteria in the future, through substantially and safely reducing antibiotic use in hospitals now

## **Underlying hypotheses:**

- In hospitals, most antibiotics are started appropriately; but there is reluctance to stop them once started
- Short durations of antibiotic treatment are sufficient to treat most genuine bacterial infections in hospitals
- Clinical review will identify those whose condition has not improved who need to continue taking them



# What is ARK-hospital?

A 5-year applied research programme funded by NIHR

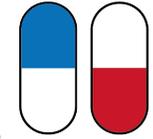
The overarching aim of ARK is to reduce the incidence of serious infections caused by antibiotic-resistant bacteria in the future, through substantially and safely reducing antibiotic use in hospitals now

**The programme applies:**

**Complex behaviour change approaches successful in primary care**

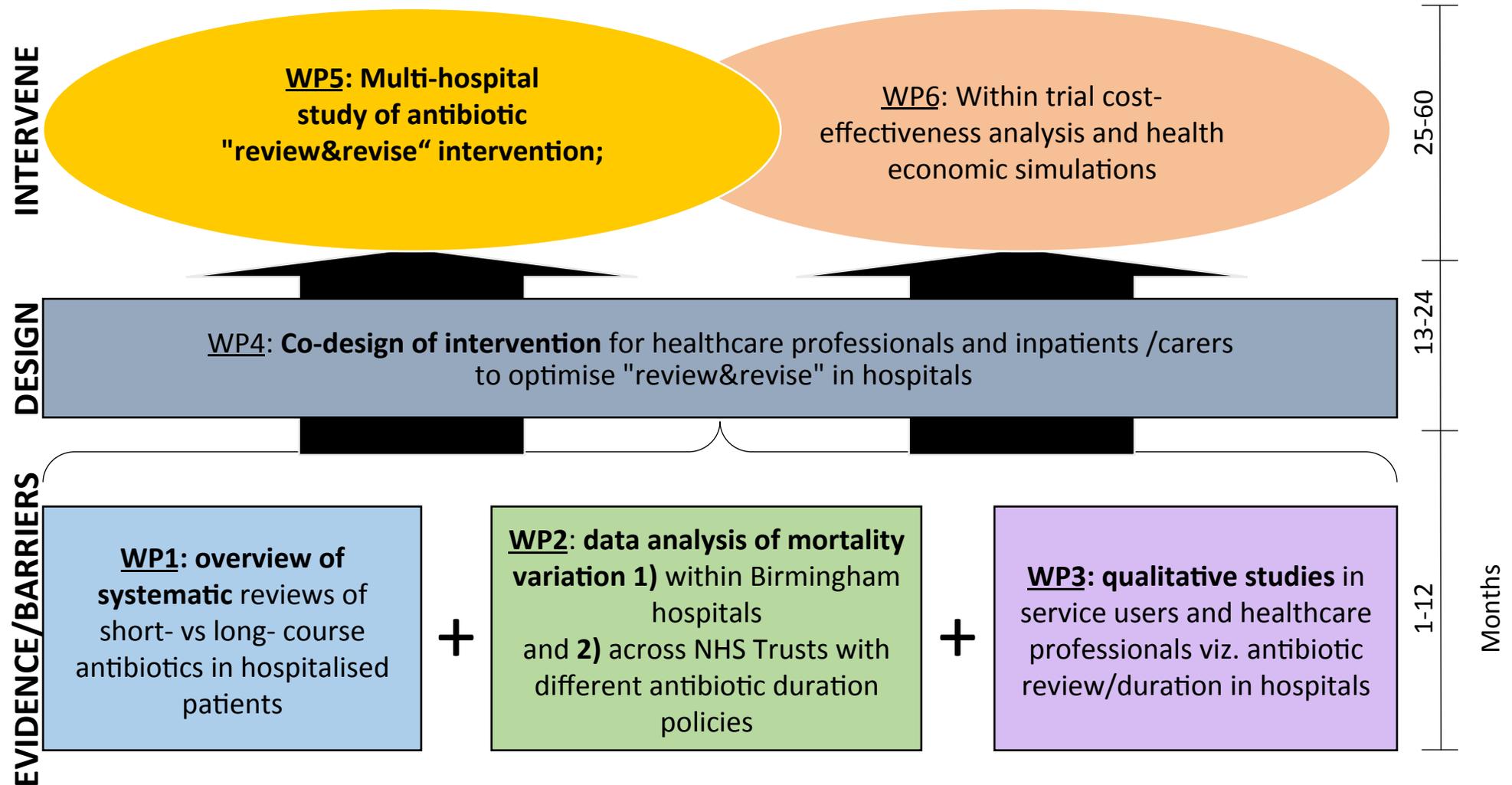
- Grace-INTRO (Internet Training for reducing Antibiotic use)
- STAR (Stemming the tide of antibiotic resistance) Educational programme

**To 'Review and Revise' decisions taken in secondary care: target behaviour being to discontinue antibiotics**



ANTIBIOTIC  
REVIEW  
KIT

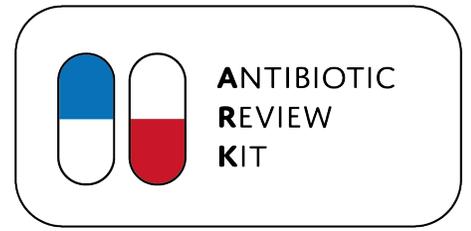
# ARK-hospital has six work packages



# ARK-hospital provides



- **Information for prescribers about Review and Revise decision making**
  - **Why stopping sooner than we do is safe**
  - **Why not stopping sooner can be harmful**



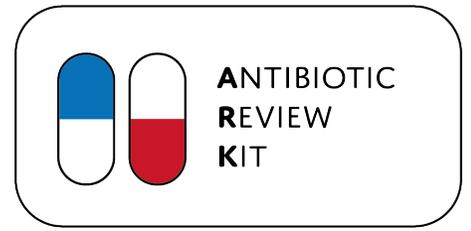
# ARK-hospital provides

- Information for prescribers about Review and Revise decision making

- **A decision aid** which

acknowledges that when antibiotics are started the diagnosis usually isn't certain

Captures the degree of this uncertainty to inform investigation and lower the threshold to stop at Review and Revise



# ARK-hospital provides

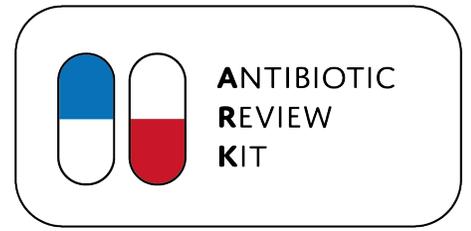
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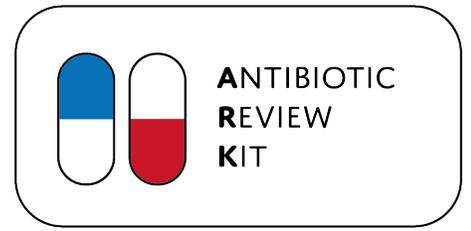
Captures the degree of this uncertainty to inform investigation and lower the threshold to stop at Review and Revise

- **Information for patients**
- Risks and benefits of antibiotics
  - That reviewing occurs



# ARK-hospital provides

- Information for prescribers about Review and Revise decision making
  - A decision aid which acknowledges that when antibiotics are started the diagnosis usually isn't certain  
Captures the degree of this uncertainty to inform investigation and lower the threshold to stop at Review and Revise
  - Information for patients
- **Information for nurses and pharmacists** about ways to support Review and Revise



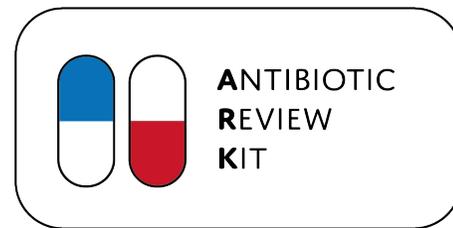
# ARK-hospital provides

- Information for prescribers about Review and Revise decision making
  - A decision aid which acknowledges that when antibiotics are started the diagnosis usually isn't certain  
Captures the degree of this uncertainty to inform investigation and lower the threshold to stop at Review and Revise
  - Information for patients
- Information for nurses and pharmacists about ways to support Review and Revise
  - **Tools and processes for audit and feedback**

# Timelines, feasibility and pilot

- Feasibility trial April-June 2017
- Pilot Sites enroll 1-2 monthly July -Oct 2017
- Main step-wedge trial starts Late 2017 – enrolling some pilot sites to main trial
  
- Primary Outcomes: death 30 days and antibiotic consumption
- Secondary Outcomes: ICU admission, treatment failure, readmission, *C. difficile*, antibiotic consumption, LOS
  
- We need to build network of candidate sites NOW....!

# The ARK-Hospital Team



- **Gavin Barlow** Consultant Infectious Diseases and General Medicine Physician **Hull**
- **Richard Bellamy** Consultant Infectious Diseases Physician **Middlesbrough**
- **Elizabeth Cross** Specialist Registrar in Public Health **HEE South West**
- **Nicola Fawcett** Specialist Registrar in Acute Medicine **HEE Thames Valley**
- **Susan Hopkins** Consultant Infectious Diseases Physician and Medical Microbiologist **London**
- **Kieran Hand** Consultant Antimicrobial Pharmacist **Southampton**
- **Jasmin Islam** Specialist Registrar in Infectious Diseases and Microbiology **HEE Kent, Surrey and Sussex**
- **Nicola Jones** Consultant Acute Medicine, Infectious Diseases Physician, Medical Microbiologist **Oxford**
- **Adele Krusche** Health Psychologist **Southampton**
- **Martin Llewelyn** Consultant Infectious Diseases Physician **Brighton**
- **Tim Peto** Consultant Infectious Diseases, General Medicine Physician, ARK Principal Investigator **Oxford**
- **Chris Roseveare** Consultant Acute Medicine Physician **Southampton**
- **Marta Santillo** Health Psychologist **Southampton**
- **Catherine Sargent** Consultant Acute Medicine and Infectious Diseases Physician **Brighton**
- **Ian Setchfield** Acute Care Nurse Consultant **East Kent**
- **Mike Sharland** Consultant Infectious Diseases Paediatrician **London**
- **Louella Vaughn** Consultant Acute Medicine Physician **London**
- **Sarah Walker** Principal Investigator on ARK study **Oxford**
- **Mark Wilcox** Consultant Medical Microbiologist **Leeds**
- **Martin Wiselska** Consultant Infectious Diseases and General Medicine Physician **Leicester**
- **Juliet Wright** Consultant Elderly Medicine Physician **Brighton**
- **Lucy Yardley** Health Psychologist **Southampton**



*National Institute for  
Health Research*

For more information visit

<http://modmedmicro.nsms.ox.ac.uk/ark/>

Or email

[m.j.llewelyn@bsms.ac.uk](mailto:m.j.llewelyn@bsms.ac.uk)

To sign up as an ARK champion visit

<https://tinyurl.com/jbcfxca>

Diane Ashiru-Oredope – Public Health England  
Kieran Hand – University Hospitals Southampton

# Thank you!

Visit: <http://modmedmicro.nsms.ox.ac.uk/ark/>

Email: [m.j.llewelyn@bsms.ac.uk](mailto:m.j.llewelyn@bsms.ac.uk)

Sign up as an ARK champion: <https://tinyurl.com/jbcfxca>