

Antibiotic review kit for hospitals (ARK-Hospital): a stepped-wedge cluster-randomised controlled trial



Martin J Llewelyn*, Eric P Budgell*, Magda Laskawiec-Szkonter, Elizabeth L A Cross, Rebecca Alexander, Stuart Bond, Phil Coles, Geraldine Conlon-Bingham, Samantha Dymond, Morgan Evans, Rosemary Fok, Kevin J Frost, Veronica Garcia-Arias, Stephen Glass, Cairine Gormley, Katherine Gray, Clare Hamson, David Harvey, Tim Hills, Shabnam Iyer, Alison Johnson, Nicola Jones, Parmjit Kang, Gloria Kiapi, Damien Mack, Charlotte Makanga, Damian Mawer, Bernie McCullagh, Mariyam Mirfenderesky, Ruth McEwen, Sath Nag, Aaron Nagar, John Northfield, Jean O'Driscoll, Amanda Pegden, Robert Porter, Neil Powell, David Price, Elizabeth Sheridan, Mandy Slatter, Bruce Stewart, Cassandra Watson, Immo Weichert, Katy Sivyer, Sarah Wordsworth, Jack Quaddy, Marta Santillo, Adele Krusche, Laurence S J Roope, Fiona Mowbray, Kieran S Hand, Melissa Dobson, Derrick W Crook, Louella Vaughan, Susan Hopkins, Lucy Yardley†, Timothy E A Peto†, Ann Sarah Walker†

Summary

Background Strategies to reduce antibiotic overuse in hospitals depend on prescribers taking decisions to stop unnecessary antibiotic use. There is scarce evidence for how to support these decisions. We evaluated a multifaceted behaviour change intervention (ie, the antibiotic review kit) designed to reduce antibiotic use among adult acute general medical inpatients by increasing appropriate decisions to stop antibiotics at clinical review.

Methods We performed a stepped-wedge, cluster (hospital)-randomised controlled trial using computer-generated sequence randomisation of eligible hospitals in seven calendar-time blocks in the UK. Hospitals were eligible for inclusion if they admitted adult non-elective general or medical inpatients, had a local representative to champion the intervention, and could provide the required study data. Hospital clusters were randomised to an implementation date occurring at 1–2 week intervals, and the date was concealed until 12 weeks before implementation, when local preparations were designed to start. The intervention effect was assessed using data from pseudonymised routine electronic health records, ward-level antibiotic dispensing, *Clostridioides difficile* tests, prescription audits, and an implementation process evaluation. Co-primary outcomes were monthly antibiotic defined daily doses per adult acute general medical admission (hospital-level, superiority) and all-cause mortality within 30 days of admission (patient level, non-inferiority margin of 5%). Outcomes were assessed in the modified intention-to-treat population (ie, excluding sites that withdrew before implementation). Intervention effects were assessed by use of interrupted time series analyses within each site, estimating overall effects through random-effects meta-analysis, with heterogeneity across prespecified potential modifiers assessed by use of meta-regression. This trial is completed and is registered with ISRCTN, ISRCTN12674243.

Findings 58 hospital organisations expressed an interest in participating. Three pilot sites implemented the intervention between Sept 25 and Nov 20, 2017. 43 further sites were randomised to implement the intervention between Feb 12, 2018, and July 1, 2019, and seven sites withdrew before implementation. 39 sites were followed up for at least 14 months. Adjusted estimates showed reductions in total antibiotic defined daily doses per acute general medical admission (–4.8% per year, 95% CI –9.1 to –0.2) following the intervention. Among 7160421 acute general medical admissions, the ARK intervention was associated with an immediate change of –2.7% (95% CI –5.7 to 0.3) and sustained change of 3.0% (–0.1 to 6.2) in adjusted 30-day mortality.

Interpretation The antibiotic review kit intervention resulted in sustained reductions in antibiotic use among adult acute general medical inpatients. The weak, inconsistent intervention effects on mortality are probably explained by the onset of the COVID-19 pandemic. Hospitals should use the antibiotic review kit to reduce antibiotic overuse.

Funding UK National Institute for Health and Care Research.

Copyright © 2022 The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY 4.0 license.

Introduction

The effect of antimicrobial resistance on global public health is similar to the effects of malaria and HIV, causing an estimated 4.95 million deaths in 2019.¹ Antimicrobial resistance places increased demands on health-care systems, with substantial economic consequences.² Human antibiotic consumption is a major driver of antimicrobial resistance,³ with increased use driving resistance at both

a population level and an individual-patient level.⁴ Although antibiotic use varies widely between and within health-care systems, no evidence exists that clinical outcomes are influenced by this wide variation (eg, between acute hospitals in England).⁵

Antimicrobial stewardship aims to minimise resistance selection by ensuring that antibiotics are prescribed only when clinically indicated and that narrow-spectrum agents

Lancet Infect Dis 2022

Published Online
October 4, 2022
[https://doi.org/10.1016/S1473-3099\(22\)00508-4](https://doi.org/10.1016/S1473-3099(22)00508-4)

This online publication has been corrected. The corrected version first appeared at thelancet.com/infection on November 10, 2022

See Online/Comment
[https://doi.org/10.1016/S1473-3099\(22\)00546-1](https://doi.org/10.1016/S1473-3099(22)00546-1)

*Joint first authors

†Joint last authors

Department of Global Health and Infection, Brighton and Sussex Medical School, University of Sussex, Falmer, UK (Prof M J Llewelyn PhD, E L A Cross BM BS); Nuffield Department of Medicine (E P Budgell MSc, M Laskawiec-Szkonter MA, J Quaddy MSc, Prof T E A Peto DPhil, Prof A S Walker PhD, M Dobson BSc, Prof D W Crook FRCPath), Oxford Respiratory Trials Unit (Magda Laskawiec-Szkonter, Melissa Dobson), and Health Economics Research Centre, Nuffield Department of Population Health (Prof S Wordsworth PhD, L S J Roope PhD), University of Oxford, Oxford, UK; University Hospital of North Tees, Stockton-on-Tees, UK (R Alexander MPharm); Mid Yorkshire Hospitals NHS Trust, Wakefield, UK (S Bond PhD); Morriston Hospital, Swansea, UK (P Coles MSc); Craigavon Area Hospital, Portadown, UK (G Conlon-Bingham MPharm); Northern Devon Healthcare NHS Trust, Barnstaple, UK (S Dymond MPharm); Western General Hospital, Edinburgh, UK (M Evans BMBS); University Hospitals Plymouth NHS Trust,

Plymouth, UK (R Fok MBBS); Airedale NHS Foundation Trust, Keighley, UK (K J Frost MSc); Hampshire Hospitals NHS Foundation Trust, Basingstoke, UK (V Garcia-Arias MSc); William Harvey Hospital, East Kent Hospitals University NHS Foundation Trust, Ashford, UK (S Glass MBChC); Pharmacy Department, Altnagelvin Area Hospital, Western Health and Social Care Trust, Londonderry, UK (C Gormley MSc); Whiston Hospital, St Helens and Knowsley Teaching Hospitals NHS Trust, Prescot, UK (K Gray MBChB); Cumberland Infirmary Carlisle, North Cumbria Integrated Care NHS Foundation Trust, Carlisle, UK (C Hamson MBChB); Wirral University Teaching Hospital NHS Foundation Trust, Upton, UK (D Harvey MBChB); Nottingham University Hospitals NHS Trust, Nottingham, UK (T Hills BPharm); Royal Berkshire NHS Foundation Trust, Reading, UK (S Iyer FRCPath); County Hospital, Wye Valley NHS Trust, Hereford, UK (A Johnson FRCPath); John Radcliffe Hospital, Oxford University Hospitals NHS Trust, Oxford, UK (Prof T E A Peto, N Jones PhD, Prof D W Crook); The Royal Wolverhampton NHS Trust, Wolverhampton, UK (P Kang MPharm); Great Western Hospitals NHS Foundation Trust, Swindon, UK (G Kiapi MSc); Royal Free London NHS Foundation Trust, London, UK (D Mack FRCPath, S Hopkins FRCP); Betsi Cadwaladr University Health Board, Ysbyty Gwynedd, Bangor, UK (C Makanga MSc); York and Scarborough Teaching Hospitals NHS Foundation Trust, York, UK (D Mawer MBChB); South Eastern Health and Social Care Trust, Ulster Hospital, Belfast, UK (B McCullagh MSc); North Middlesex University Hospital NHS Trust, London, UK (M Mirfenderesky FRCPath); Countess of Chester Hospital NHS Foundation Trust, Chester, UK (R McEwen MBChB); James Cook University Hospital, South Tees Hospitals NHS Foundation Trust, Middlesbrough, UK (S Nag FRCP); Antrim Area Hospital, Northern Health and Social Care Trust, Antrim, UK

Research in context

Evidence before this study

Patients who are acutely ill often need antibiotics before full diagnostic information is available. Consequently, reducing overuse of antibiotics in hospitals requires prescribers to review and, when appropriate, stop unnecessary antibiotic prescriptions. Evidence-based tools to support prescribers to stop unnecessary antibiotics do not exist.

We searched PubMed, with no language or date restrictions, on Jan 31, 2022, for clinical studies that focused on improving antibiotic use for adults who were admitted to hospital using the terms “anti-bacterial agents therapeutic use” and “antibiotic stewardship”. Among the 427 studies found, most were uncontrolled evaluations of different approaches to education, decision support, and feedback. These studies included one before-and-after study, which identified no effect of unsupported clinician-led prescription review on antibiotic use. Three small, hospital-level, cluster-randomised trials were identified. One trial evaluated different approaches to feedback, one compared different hospital specialties, and one reported that intense feedback was effective in reducing antibiotic use. All three trials were small and none considered clinical outcomes or sustainability. Research is needed to deliver effective interventions that are ready for implementation into clinical practice. This weak evidence base explains the differences that exist in national policy recommendations around clinician-led

are used whenever appropriate.⁶ However, translating research on antimicrobial stewardship into practice is hampered by the poor quality of evidence, particularly weaknesses in the intervention design process and the study designs used, which are usually underpowered, not experimental, and do not consider clinical outcomes.^{7,8}

In primary care, restrictive strategies for antimicrobial stewardship, such as avoiding or delaying antibiotics in respiratory tract infection, can be safe and effective.^{9,10} By contrast, hospital antimicrobial stewardship interventions that enable improved prescribing are more acceptable than restrictive strategies and can reduce overuse and length of stay without compromising mortality.¹¹ The need to ensure that patients with serious bacterial infections are treated promptly before a diagnosis is confirmed means that ongoing review and revision of hospital antibiotic prescriptions is required to safely minimise unnecessary use. In England, the Department of Health’s guidance Start Smart—Then Focus requires prescribers to review and revise antibiotic prescriptions every 48–72 h.¹² In the USA, the analogous term antibiotic timeouts is used, but revised Centers for Disease Control and Prevention guidance in 2019 prioritised pharmacist-led audit and feedback to prescribers,¹³ in light of a non-interventional study that reported that prescriber-led reviews did not reduce overall consumption.¹⁴

After introducing Start Smart—Then Focus in 2011, antibiotic consumption in English hospitals continued to

antibiotic prescription review for hospital antibiotic stewardship between, for example, the UK and the USA.

Added value of this study

We evaluated a multifaceted intervention to support clinician-led antibiotic prescription review (ie, the antibiotic review kit [ARK] intervention) and showed that ARK was effective in achieving safe sustained reductions in organisation-level antibiotic use among acute, general medical hospital admissions. Our findings deal with the uncertainty about whether clinician-led prescription review is an effective approach to antibiotic stewardship in hospital practice by being highly pragmatic, evaluating sustainability, and robustly exploring potential patient-level harms of this approach to reducing antibiotic use. Furthermore, the ARK-Hospital Programme delivers resources to support effective clinician-led prescription review ready for adoption into clinical practice.

Implications of all available evidence

The ARK intervention is safe and effective in reducing antibiotic use among adult acute, general medical hospital admissions. The tools used are now freely available for adoption into practice. Available evidence comes from research using paper-based prescribing and future research should establish how antibiotic prescription reviews should be built into electronic prescribing systems.

rise year on year until the COVID-19 pandemic in 2020.¹⁵ This increase was despite financial incentives to reduce hospital prescribing, first through a Commissioning for Quality and Innovation framework in 2016–18 and then its incorporation into the National Health Service (NHS) standard contract for acute hospitals.¹⁶ Although high rates of prescription review were achieved,¹⁷ most review decisions were to adjust rather than stop antibiotics.

The antibiotic review kit (ARK) programme for hospitals aimed to develop and evaluate a multifaceted behaviour change intervention to safely reduce antibiotic use in acute general medical inpatients. The ARK programme created a four-component intervention to help prescribers to take appropriate decisions to stop or continue antibiotics at prescription review, comprising a novel prescribing decision aid, an online training tool supporting use of the decision aid, guidance for implementing audit and feedback, and a patient leaflet.^{18,19} In this study we report the immediate and sustained effect of the ARK intervention on antibiotic consumption at the hospital level and clinical outcomes at the patient level.

Methods

Study design

Following a feasibility evaluation at Brighton and Sussex University Hospitals NHS Trust, an acute hospital,²⁰ the ARK intervention was evaluated at eligible participating hospitals across all UK nations by use of a stepped-wedge

cluster-randomised controlled trial.²¹ A cluster design was essential to avoid contamination from health-care professionals moving between teams within a hospital. A stepped-wedge design was essential given the few UK secondary care organisations that could be randomised (appendix p 46).

Ethical approval was from the South Central Oxford C Research Ethics Committee (17/SC/0034) and the Confidentiality Advisory Group (17/CAG/0015) without individual patient consent because electronic health records were pseudonymised and no personal identifiable data was collected other than date of death.

Clusters and participants

The unit of observation was a hospital organisation offering services for non-elective medical admissions (appendix p 3). Sites were approached through professional networks and the Society for Acute Medicine. Eligible sites needed to admit adult (ie, aged >15 years) general or medical inpatients, have a local representative (known as a champion) who was willing to lead intervention implementation, and be able to provide the required study data. Since the intervention targeted prescribers on acute general medical wards and used electronic health records to ascertain patient-level outcomes, the study population was defined using the consultant specialty codes that were most often used to admit adult general medicine inpatients (appendix p 45).²¹ Sites were asked to exclude patients who opted out of having their health records used for research purposes (appendix pp 3–4). The protocol is included in the appendix (p 156).

Randomisation and masking

Eligible sites were randomised by use of a computer-generated list by the trial statistician (ASW), including the pilot sites (one block of three sites) and main trial sites (six blocks of six sites and one block of seven sites), to an intervention implementation date. Implementation was staggered across sites in 1–2 week intervals, with breaks over the Christmas period and in August given the high rate of staff holidays or when the funder requested a pause on randomisation (appendix p 46). To avoid contamination, complete information about the intervention and allocation sequence was concealed from the site until the point of randomisation, when sites were told that their randomised implementation date was 12 weeks in the future, ensuring that all sites had 12 weeks for implementation preparation.

Procedures

The intervention comprised a decision aid that was intended to be embedded in the hospital prescription process, prompting prescribers to clarify the level of diagnostic uncertainty at antibiotic initiation by classifying infection risk as possible or probable, and then either stopping the prescription if a clear indication for ongoing antibiotic treatment could not be established at 48–72 h

review or finalising the prescription if a clear indication could be established; online training to motivate and support use of the decision aid; implementation guidance, including audit and feedback tools; and a patient leaflet.^{18,19} The ARK tools are freely available through the British Society for Antimicrobial Chemotherapy. By supporting decisions to stop antibiotics at clinical review, the intervention aimed to safely reduce antibiotic use through reducing treatment duration, rather than by targeting the appropriateness of initial prescriptions. Fidelity of intervention implementation was assessed with eight pre-defined criteria by the study team at each individual site up to 16 weeks after implementation (table).

Study data were collected from 24 months before implementation at the first main trial site until at least 14 months following implementation of the final site, to facilitate outcome assessment before and after implementation. Time periods for the co-primary outcomes are shown in the appendix (appendix p 46).

All outcomes were assessed using pseudonymised electronic health records from adult (age ≥16 years) acute general medical admissions (further details, including data cleaning, are shown in the appendix pp 6–9, 48), bulk antibiotic dispensing on the wards that implemented ARK, and *C difficile* test results. Date of death within 90 days of admission (in or out of hospital) was obtained by sites through linkage with national registries. Patient-level antibiotic data and laboratory results (ie, microbiology, haematology, biochemistry, and imaging tests) were provided by few sites, preventing further analysis of these data (appendix p 5). Uptake of the intervention was assessed through a process evaluation and prescription review audits.

Outcomes

The trial had two co-primary outcomes: antibiotic defined daily doses (DDDs) per adult acute general medical admission (superiority) and all-cause mortality within 30 days of admission (in or out of hospital; non-inferiority, relative margin 5% for an immediate step change associated with implementation, assuming a constant rate before and after implementation). Both outcomes were assessed by estimating the immediate effect and the sustained year-on-year effect.

Secondary antibiotic (superiority) outcomes were total antibiotic DDDs per acute general medical bed-day and DDDs per admission for specific antibiotic groups, including carbapenems, parenteral and oral administration, broad-spectrum and narrow-spectrum antibiotics, and the UK Health Security Agency's interpretations of Access, Watch, and Reserve from WHO's Essential Medicines List (appendix pp 11–12).²² Admissions, rather than bed-days, were used as the denominator in the primary analysis because bed-days can be influenced by non-medical reasons for prolonged hospital stays (eg, awaiting discharge to another place of care). Although

(A Nagar MBBCh); Milton Keynes Hospital NHS Foundation Trust, Milton Keynes, UK (J Northfield DPhil); Buckinghamshire Healthcare NHS Trust, Stoke Mandeville, UK (J O'Driscoll FRCPath); Chesterfield Royal Hospital NHS Foundation Trust, Chesterfield, UK (A Pegden MBBS); Royal Devon and Exeter NHS Foundation Trust, Exeter, UK (R Porter MBBS); Royal Cornwall Hospital NHS Trust, Truro, UK (N Powell MPharm); Freeman Hospital, Newcastle Upon Tyne Hospitals NHS Foundation Trust, Newcastle-upon-Tyne, UK (D Price MD); Poole Hospital NHS Foundation Trust, Poole, UK (E Sheridan FRCPath); Royal United Hospitals Bath NHS Foundation Trust, Bath, UK (M Slatter MSc); East Surrey Hospital, Surrey and Sussex Healthcare NHS Trust, Redhill, UK (B Stewart MBChB); London North West University Healthcare NHS Trust, Harrow, UK (C Watson MPharm); East Suffolk and North Essex NHS Foundation Trust, Ipswich, UK (I Weichert MD); Centre for Clinical and Community Applications of Health Psychology (Prof L Yardley PhD, K Sivyer DPhil, M Santillo PhD, A Krusche DPhil, F Mowbray PhD) and Faculty of Health Sciences (K S Hand FRPharmS), University of Southampton, Southampton, UK; The Nuffield Trust, London, UK (L Vaughan DPhil); UK Health Security Agency, London, UK (S Hopkins); School of Psychological Science, University of Bristol, Bristol, UK (Prof L Yardley)

Correspondence to: Prof Martin J Llewelyn, Department of Global Health and Infection, Brighton and Sussex Medical School, University of Sussex, Falmer, BN1 9PS, UK m.j.llewelyn@bsms.ac.uk

See Online for appendix

For more on the ARK tools see <https://www.antibioticreviewkit.org.uk>

Clusters (n=39)	
Randomisation date	
Median (range)	Aug 6, 2018 (May 25, 2017–April 8, 2019)
Randomised implementation date	
Median (range)	Nov 5, 2018 (Sept 25, 2017–July 1, 2019)
Any implementation delay	
Yes	9 (23%)
Median delay, weeks (IQR; range)	7.4 (6.1–13.0; 5.3–25.0)
Region	
South of England	13 (33%)
North of England	10 (26%)
Midlands and east of England	6 (15%)
Northern Ireland	4 (10%)
London	3 (8%)
Wales	2 (5%)
Scotland	1 (3%)
Size (ie, acute beds available)	
Median (IQR; range)	690 (540–939; 268–1484)
Large (>850 beds)	13 (33%)
Medium (551–850 beds)	14 (36%)
Small (≤550 beds)	12 (31%)
Specialty of the principal investigator	
Microbiologist	19 (49%)
Pharmacist	10 (26%)
Acute medicine	7 (18%)
Microbiology and infectious diseases	2 (5%)
Microbiology and acute medicine	1 (3%)
Prescribing system at implementation	
Paper	25 (64%)
E-prescribing (Cerner)	6 (15%)
E-prescribing (JAC)	3 (8%)
E-prescribing (other)	5 (13%)
How the decision aid was implemented	
Hard stop	21 (54%)
Soft stop	9 (23%)
Neither	9 (23%)
Baseline acute or general medicine admissions	
Median (IQR; range)	38 045 (26 008–56 294; 11 416–77 946)
Baseline DDDs per admission in the 12 months before implementation*†	
Total	3.05 (2.19–5.35; 0.43–16.16)
Parenteral administration	0.91 (0.65–1.43; 0.15–5.00)
Oral administration	2.16 (1.56–3.85; 0.26–13.02)
Broad-spectrum	1.02 (0.72–1.53; 0.03–4.39)
Narrow spectrum	2.23 (1.40–3.44; 0.40–12.61)
Access	1.52 (0.83–2.39; 0.29–9.68)
Access or watch‡	0.77 (0.51–1.21; 0.02–3.97)
Watch	0.88 (0.43–1.19; 0.02–3.96)
Reserve	0.09 (0.05–0.19; <0.01–0.55)
Carbapenems	0.06 (0.03–0.08; 0.00–0.31)
Piperacillin-tazobactam	0.12 (0.05–0.22; <0.01–0.80)
Quinolones	0.26 (0.11–0.42; <0.01–1.43)

(Table continues on next page)

the protocol specified patient-level antibiotic outcomes (ie, days on antibiotics, antibiotic-days per admission or bed-day, and antibiotic restart after discontinuation for >48 h),²¹ only four sites had both the electronic prescribing systems and information technology resources required to provide these data, so these outcomes could not be analysed (figure 1). Secondary non-inferiority outcomes were 90-day mortality, admission to an intensive care unit, length of stay, emergency hospital readmission (to any specialty) within 30 days of discharge, and *Clostridioides difficile* infection or colonisation within 90 days of admission.

DDDs per admission for piperacillin–tazobactam and quinolones and length of stay of 48 h or more were considered in exploratory analyses.

Statistical analysis

An interrupted time series analysis estimated the immediate effect of the intervention (ie, step change) and sustained effect on year-on-year trends after implementation versus before implementation within each site for the co-primary outcomes of antibiotic DDDs per adult acute general medical admission and all-cause mortality within 30 days of admission, by use of the randomised implementation date. All analyses used an intention-to-treat approach that was modified to exclude seven sites that withdrew after randomisation but before implementation, from which no data were collected. Overall intervention effects were then estimated by use of random effects meta-analysis, using meta-regression to assess heterogeneity in effects across prespecified potential effect modifiers. As the intervention did not change after the pilot, following the approved protocol, the primary analysis included pilot and main trial sites to maximise power. With a minimum of 36 sites, the stepped-wedge cluster-randomised design had more than 85% power to exclude an immediate 5% relative increase in 30-day mortality and to detect a 15% relative reduction in antibiotic use associated with intervention implementation.²¹ The 5% relative non-inferiority margin for the 30-day mortality outcome means that to declare non-inferiority, the upper bound of 95% CI for the relative change in mortality had to not exceed a 5% increase. Further details are given in the appendix (appendix pp 9–10).

Monthly antibiotic DDDs per admission were modelled by use of negative binomial regression, and binary outcomes per admission were modelled by use of logistic regression. Length of stay (days) was modelled by use of subhazard regression, treating inpatient deaths as a competing risk and censoring at 90 days, using 0.1 days for those admitted and discharged on the same day, as was emergency 30-day readmission in a sensitivity analysis, with out-of-hospital deaths as the competing event. Due to low event rates (<4% in all sites), sensitivity analyses did not model ICU admission and *C difficile* infection or colonisation by use of subhazard regression. Length of stay of 48 h or longer was considered in an

exploratory analysis by use of logit models and exploratory analyses for DDDs per admission for piperacillin–tazobactam and quinolones were modelled by use of negative binomial regression. All clinical outcomes were modelled by use of a robust variance adjustment by patient.

Since the COVID-19 pandemic profoundly affected both primary and secondary outcomes, models included a binary indicator for March–June, 2020, for antibiotic outcomes (measured monthly) and March 1–June 30, 2020, for patient-level clinical outcomes, unless otherwise noted. Sensitivity analyses excluded admissions after March 1, 2020, including 12 sites with less than 12 months of data after implementation as a result. Antibiotic models additionally adjusted for seasonal effects by including month of year as a $\sin() + \cos()$ function to ensure smooth risk changes year to year. Non-antibiotic models also adjusted for individual admission-level covariates, regardless of statistical significance (based on the findings of Walker and colleagues²³): sex, age, immunosuppression, deprivation percentile, Charlson comorbidity index and its interaction with age, admission method, admission source, admission specialty, patient classification, admission day of the week (ie, weekend vs weekday), admission day of year and time of day (both modelled as a $\sin() + \cos()$ function, with an interaction between time of day and day of week), and number of overnight admissions and any previous overnight complex (ie, >1 consultant episode, excluding episodes in the emergency department and rehabilitation) admission in the past year. Ethnicity was missing for a median of 8.8% admissions (IQR 4.5–18.4) per site so was not adjusted for. Further details are shown in the appendix (pp 4–5, 21–28).

All analyses used Stata/MP version 17.0. The data monitoring committee reviewed outcome data three times during the trial, using a Haybittle-Peto statistical rule for early stopping. This trial is registered with ISRCTN, number ISRCTN12674243.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

58 UK acute hospital organisations expressed an interest in participating, of which 46 sites agreed to join the pilot or main trial. Three pilot sites implemented the intervention between Sept 25–Nov 20, 2017; 43 further sites were randomised to implement between Feb 12, 2018, and July 1, 2019, of which seven withdrew before implementation and were excluded from analyses as no data were collected (figure 1). 39 sites were included in the analysis of 30-day mortality and 38 sites were included in the analysis of total antibiotic DDDs per adult acute general medical admission because antibiotic

Clusters (n=39)	
(Continued from previous page)	
Achieved prespecified implementation fidelity criteria	
C1: provision of a list of essential people by implementation date	31 (79%)
C2: achieving at least 20 people per 100 acute beds having done the online learning by the end of the implementation phase (ie, 12 weeks)	25 (64%)
C3: introduction of the ARK categories into the prescribing process by the implementation date	31 (79%)
C4: process in place for making patient leaflets available to acute medical patients by the implementation date	25 (64%)
C5: submission of baseline audit data by the implementation date	19 (49%)
C6: process in place for ongoing audit and feedback by the implementation date	37 (95%)
C7: submission of postimplementation audit data by week 4	30 (77%)
C8: submission of electronic patient research data by week 16 following implementation [§]	21/36 (58%)
Total criteria achieved	6 (5–7; 2–8)
Co-primary outcome: 30-day mortality	
Preimplementation follow-up, months	33 (27–39; 20–41)
Postimplementation follow-up, months	22 (19–30; 16–38)
Co-primary outcome: total DDDs per general medical admission*	
Pre-implementation follow-up, months	33 (27–37; 20–41)
Post-implementation follow-up, months	23 (18–28; 14–37)
Data are median (IQR; range) or n (%), unless otherwise specified. DDD=defined daily dose. *Site 3 was not included in analyses of antibiotic use (appendix p 29). †Includes two sites that shared hospital-level DDDs due to limitations posed by local pharmacy information systems (sites 22 and 30). Further details are given in the appendix (p 50). ‡Antibiotics in this category can be considered either access or watch depending on indication. Since indication was unknown, they were analysed separately. §These data were not required for pilot sites, so this criterion was treated as achieved in the analysis for those sites.	
Table: Site characteristics	

data were not available from one site (figure 1, appendix p 29).

13 sites were classed as large (ie, >850 beds available, median 991), 14 medium (ie, 551–850 beds, median 670), and 12 small (ie, ≤550 beds, median 487; table). Sites were distributed across the UK, with the largest number in the south of England. Most champions were microbiologists. At implementation, prescribing was paper based at most sites. 21 (54%) of 39 sites implemented the decision aid with a hard stop to the initial prescription unless revised by 72 h, nine sites (23%) implemented as a soft stop, emphasising the need to stop or finalise within 72 h, and nine (23%) sites did neither.

Antibiotic use in the 12 months before randomised implementation varied widely, both in total DDDs per admission and specific agents, classes, and Access, Watch, and Reserve categories (table; appendix p 48). Access antibiotics accounted for 30.7–85.2% of total DDDs, Watch for 4.8–44.1%, and Reserve for 0.3–5.7%.

Site champions named a median of 19 (IQR 14–34, range 5–72) people as essential for doing the online training; a median of 78% (63–90) completed the training by 12 weeks, with 16 (41%) of 39 sites below the target of 70% or higher (figure 2A). The total number of staff completing training also varied substantially, with a median of 24 (IQR 15–41) staff trained per 100 acute

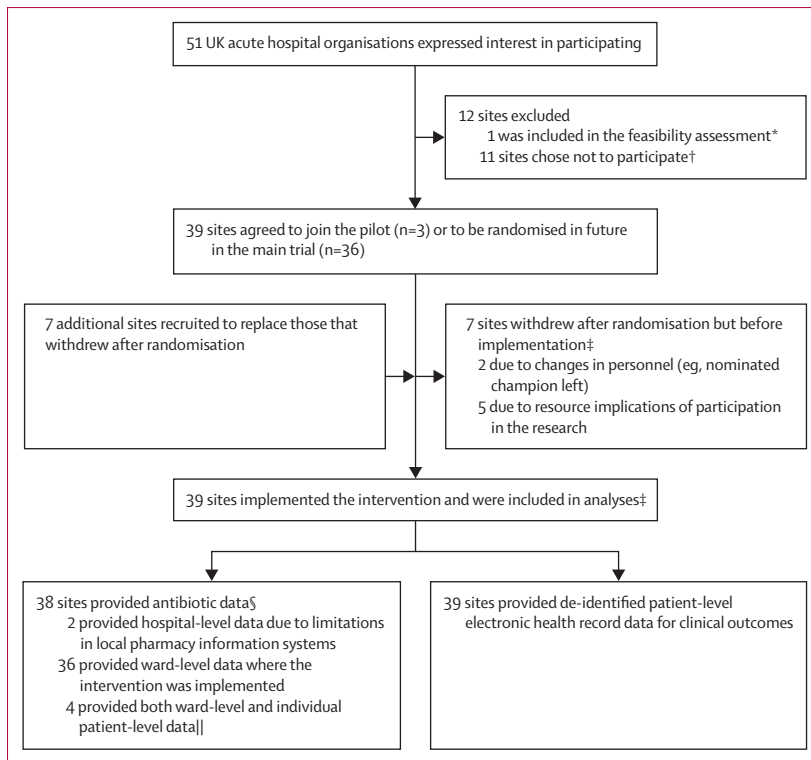


Figure 1: Flow diagram of participating hospital organisations

*One site implemented the intervention in the feasibility phase of the research. These data were published previously and were not included in the main analysis.²⁰ †These sites declined to participate after full review of study materials typically due to the resource implications of participation in the research, conflicts with local antimicrobial stewardship initiatives, or being unable to provide mandatory electronic health record data. ‡The decision not to fund data collection in sites withdrawing before implementation was made because, as mortality was a non-inferiority comparison, it was more important to replace these sites than use resources collecting data from sites that never implemented the intervention and hence would show no intervention effect on mortality. §One pilot site introduced an electronic prescribing system 6 months after implementation leading to an immediate decline (>90%) in reported antibiotic defined daily doses, which prevented valid assessment of trends in antibiotic use after implementation. ||Individual-level data were not analysed due to scarcity.

beds and 12 (31%) of 39 sites training less than 20 staff (figure 2B–C) by 12 weeks, although this number fell to nine (23%) sites overall. Actual implementation was delayed at nine sites, by a median of 7.4 weeks (IQR 6.1–13.0, range 5.3–25.0) after the randomisation date, typically because of delays with implementing the decision aid into prescribing processes. Nine (23%) sites achieved four or fewer of the eight implementation criteria.

Postimplementation audit data were available for 37 sites, of which 31 sites provided baseline audit data. During the 12 weeks following randomised implementation, a median of 51.6% (IQR 31.4–75.9) of audited antibiotic prescriptions were categorised by use of the decision aid at the initial prescription (figure 2D). At 12 weeks, a median of 89.9% (IQR 80.8–96.5) of audited prescriptions were reviewed versus 91.0% (78.6–95.8) at baseline (Wilcoxon matched-pairs $p=0.21$), with greater increases in sites with lower baseline rates (figure 2E). A median of 16.2% (IQR 12.8–23.3) were stopped at review and revise versus 12.7% (15.4–21.4) at

baseline ($p=0.0060$), again with greater increases in sites with lower baseline rates (figure 2F).

Sites contributed a median 23 months (range 14–37) of antibiotic data after implementation (appendix p 46). Adjusting for the effects of COVID-19 and interrupted time series trends (shown by site in appendix pp 51–127), the intervention was associated with a -1.0% (95% CI -4.0 to 2.1) immediate change in total antibiotic DDDs per admission and a sustained -4.8% (-9.1 to -0.2) change per year subsequently (figure 3, 4), with little association between the immediate and longer-term intervention effects across sites ($r=-0.088$, $p=0.60$; appendix p 128). There was substantial heterogeneity in trajectories of DDDs per admission before intervention and after intervention (appendix p 129). Intervention effects were similar unadjusted (figure 3) and excluding all follow-up from March, 2020 (appendix pp 13–15).

There was no evidence that immediate effects on total DDDs per admission at implementation (-0.5% , 95% CI -2.7 to 1.7 , per additional fidelity criteria achieved) and on year-on-year trends after versus before intervention (-1.4% , -4.9 to 2.3 , per additional fidelity criteria achieved) were associated with overall implementation fidelity (figure 4). Immediate reductions in total DDDs per admission were greater among sites with processes for ongoing audit and feedback in place by implementation (by -16.6% , 95% CI -28.5 to -2.8 , relative to sites that did not have processes in place by implementation) and greater among sites that submitted postimplementation audit data within 4 weeks following implementation (by -8.3% , -15.1 to -1.0 , relative to sites that did not submit audit data within 4 weeks). However, the relative reduction in immediate implementation effect among sites that submitted postimplementation audit data within 4 weeks was not observed after we adjusted for whether the site had a process in place for ongoing audit and feedback by the implementation date in a multivariate model (appendix pp 16–20). We found non-significantly greater sustained reductions in total DDDs per admission among sites that introduced ARK categories into the prescribing process by implementation than among sites that had not introduced ARK categories by implementation (by -11.5% , 95% CI -22.9 to 1.7 , relative to the reference group; appendix p 16) and among sites with higher uptake of the online learning by implementation (ie, with ≥ 20 people per 100 acute beds completing the training) than among sites with lower uptake (by -9.9% , 95% CI -19.7 to 1.1 , versus sited training <20 people per 100 acute beds). Medium-sized sites also had non-significantly greater reductions in DDDs at implementation (by -7.4% , 95% CI -14.6 to 0.5 , relative to small sites), with evidence for sustained year-on-year increases (by 14.6% , 0.1 to 31.3 , relative to small sites; appendix pp 16–20).

Sites contributed a median 24 months (IQR 19–30, range 16–38) of data for all-cause 30-day mortality (in or out of hospital) after implementation (appendix p 46).

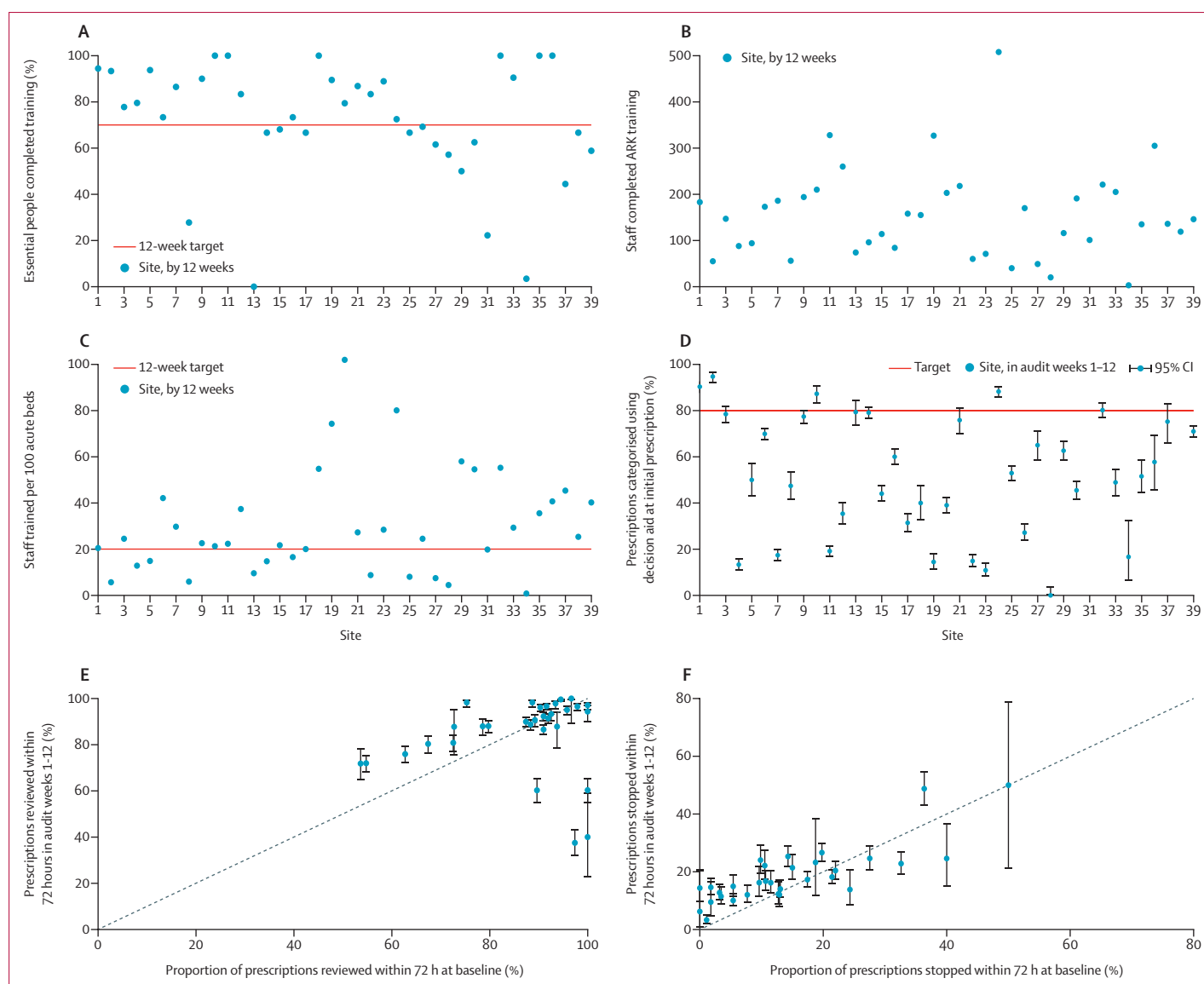


Figure 2: Intervention adherence during the first 12 weeks of implementation

Panels show the proportion of essential people who completed ARK training (A), staff who completed ARK training (B), staff who completed training per 100 acute beds (C), proportion of antibiotic prescriptions categorised using the decision aid at the initial prescription (D), proportion of antibiotic prescriptions reviewed versus baseline (E), and proportion of antibiotic prescriptions stopped at review and revise versus baseline (F). Sites are identified numerically by the order in which they were randomised to implement. The targets for 70% of essential people and more than 20 staff per 100 acute beds to complete ARK training are arbitrary but were prespecified for the funder as part of trial agreements and as part of prespecified fidelity criteria. Audit data were unavailable at two of 39 hospitals (ie, sites 31 and 38) and these sites are excluded from panels D–F. Six hospitals (sites 13, 18, 21, 27, 28, and 30) were missing baseline audit data and are therefore excluded from panels E–F.

Analysis included 7160421 admissions (appendix p 47); 314313 (4.4%) people died within 30 days (2.6–7.2% across sites, median 4.6%, IQR 4.0–5.0). Overall, the ARK intervention was associated with a -2.7% (95% CI -5.7 to 0.3) immediate change in 30-day mortality odds (consistent with non-inferiority) and a 3.0% (-0.1 to 6.2) sustained change after versus before implementation (figure 3, 5). Sites with larger immediate mortality reductions tended to have larger sustained increases in mortality after versus before implementation ($r=-0.28$, $p=0.082$; appendix p 145). This inverse association

suggests that the weak overall effects could be an artefact from the individual interrupted time series (appendix pp 51–127), given the substantial heterogeneity in trajectories of 30-day mortality before and after intervention (appendix p 146), potentially related to the varying capture of electronic health record data at sites over time (appendix pp 29–34). There was no evidence that effects on 30-day mortality were associated with implementation fidelity (immediate effect was 1.3% per additional fidelity criteria achieved, 95% CI -6.8 to 3.3 ; change in year-on-year trend after vs before implementation was -0.1% ,

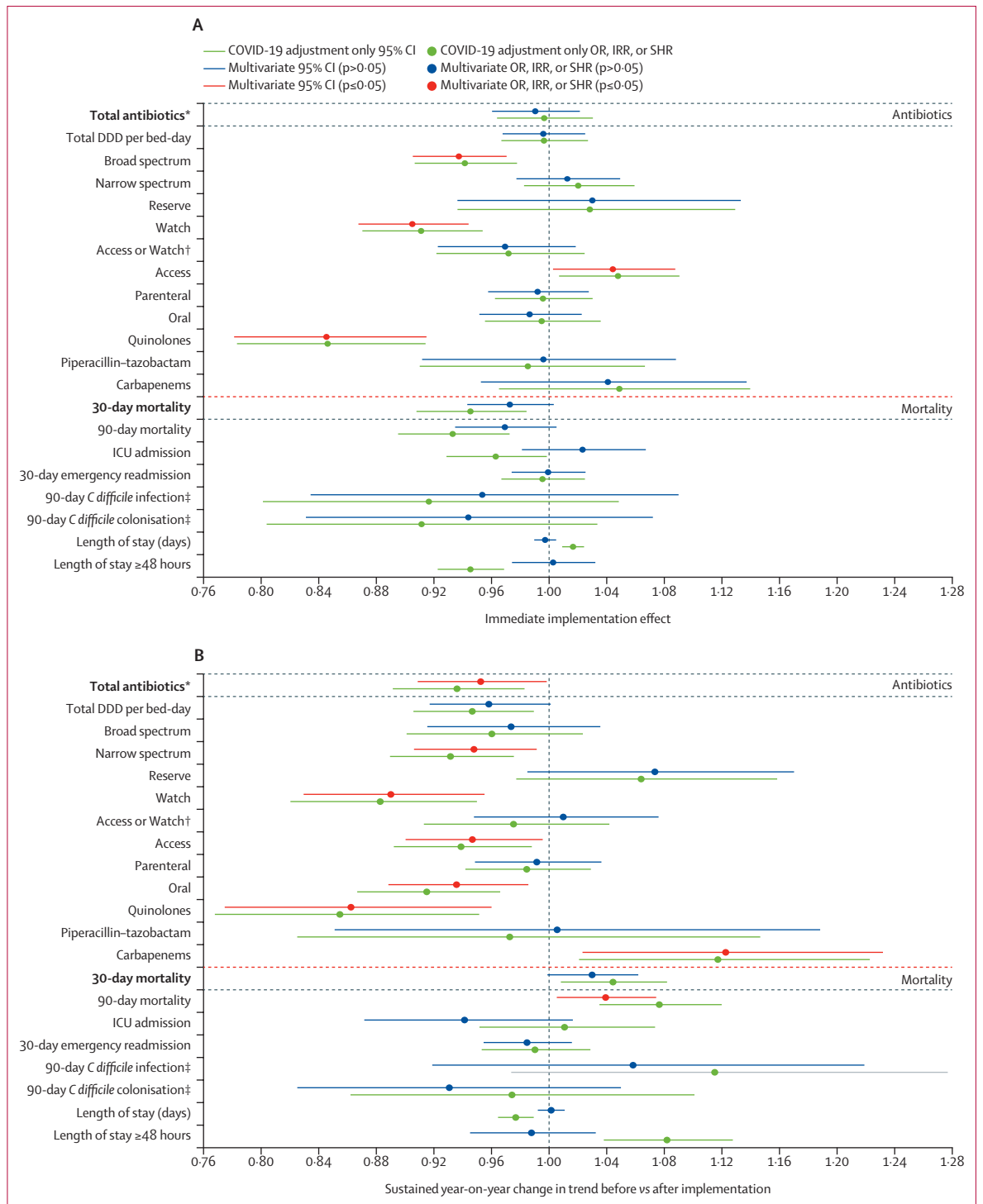


Figure 3: Effects of the ARK intervention

Immediate effect at implementation (A) and effect on sustained year-on-year trend after versus before implementation (B). The top part of each panel shows the antibiotic primary (bold) and secondary outcomes, and the bottom part shows the clinical primary (bold) and secondary outcomes. Effects that were adjusted only for the effects of COVID-19 are shown in green, and fully adjusted effects are shown in red when there was evidence of an association or otherwise in blue. ARK=antibiotic review kit. *C difficile*=*Clostridioides difficile*. DDD=defined daily dose. ICU=intensive care unit. IRR=incidence rate ratio (negative binomial regression). OR=odds ratio (logistic regression). SHR=subhazard ratio (competing risks regression). *Antibiotics are measured as DDDs per admission unless indicated otherwise. †Access or Watch depending on indication (analysed as a mutually exclusive category, since indication was unknown). ‡Modelled without a COVID-19 adjustment (effects plotted in green are therefore unadjusted).

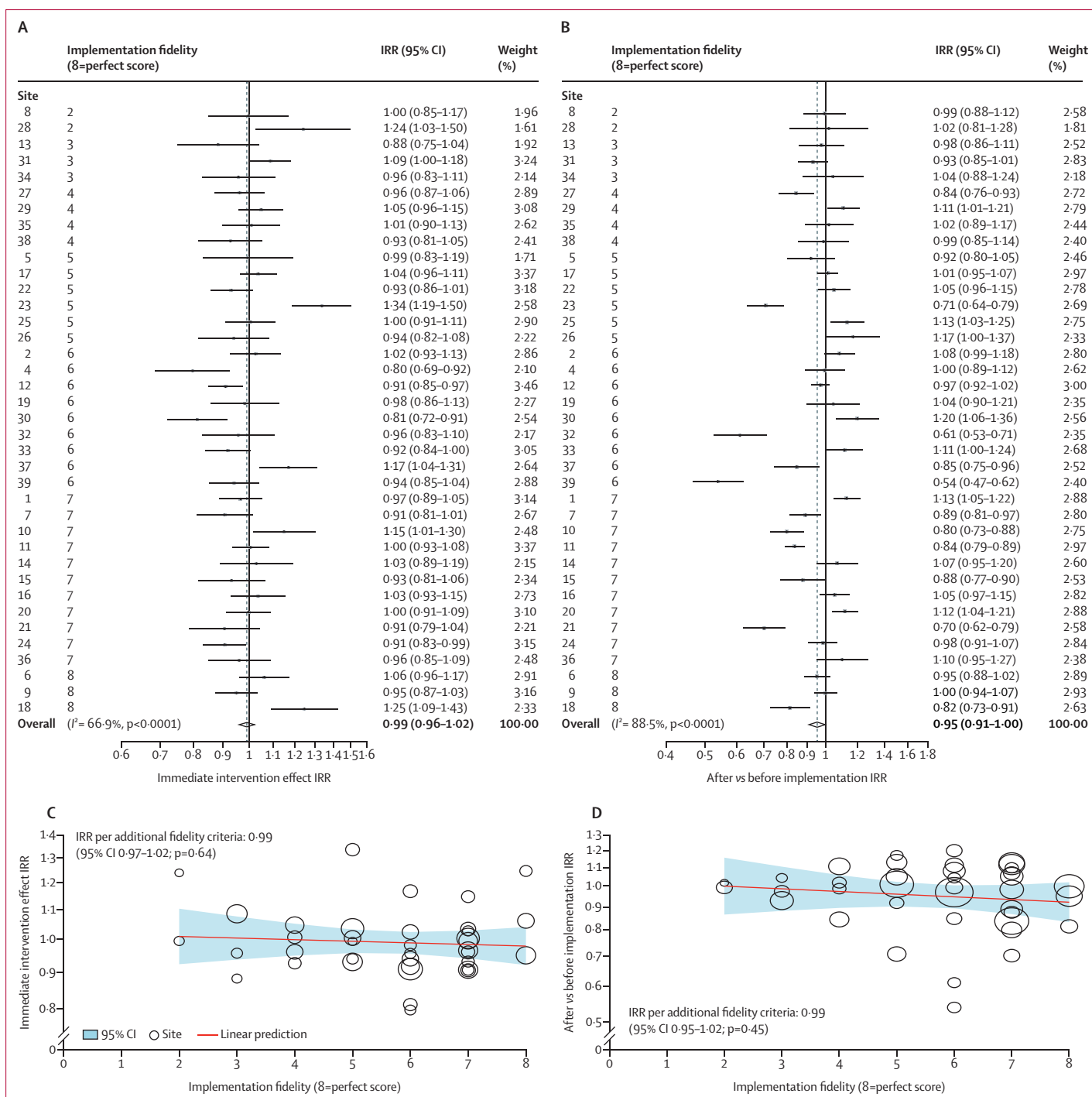


Figure 4: Effect on total antibiotic DDDs per admission
 Overall immediate effect at implementation (A), overall effect on year-on-year trend after versus before implementation (B), immediate effect at implementation by implementation fidelity (C), and effect on year-on-year trend after versus before implementation by implementation fidelity (D). Sites are identified numerically by the order in which they were randomised to implement and are ordered by the number of fidelity criteria achieved (appendix pp 13–15). The size of the symbols in panels C and D reflects the precision of each estimate (inverse of the within-hospital variance). Weights are from random effects analysis. IRR=incidence rate ratio.

–2.1 to 1.9; figure 5). Intervention effects on unadjusted 30-day mortality were similar to those of adjusted 30-day mortality (figure 3). There was weak evidence for a

sustained increase in adjusted 30-day mortality, but this effect was not observed after excluding all follow-up from March 1, 2020 (appendix pp 13–15).

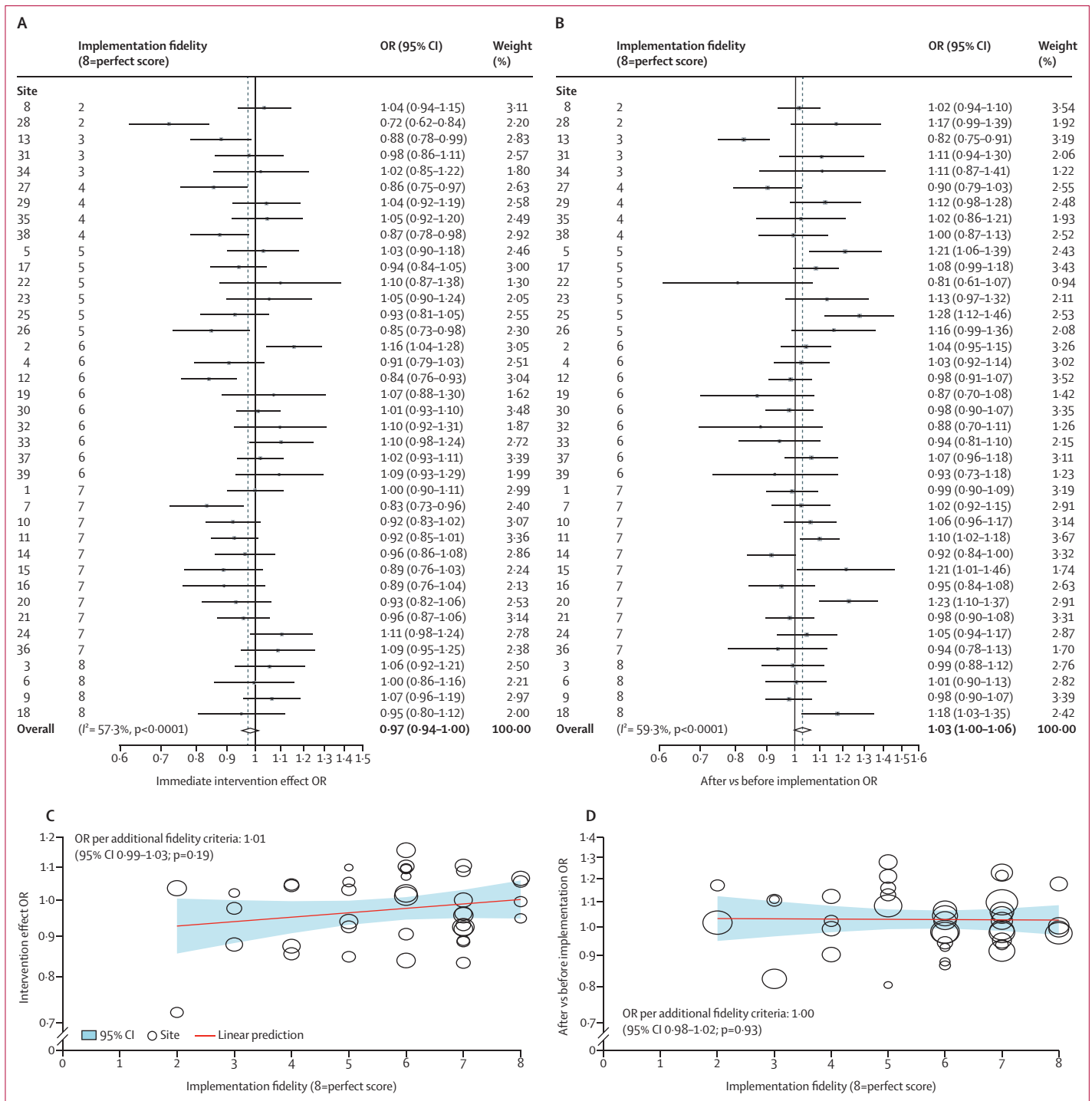


Figure 5: Adjusted 30-day mortality

Overall immediate effect at implementation (A), overall effect on year-on-year trend after versus before implementation (B), immediate effect at implementation by implementation fidelity (C), and effect on year-on-year trend after versus before implementation by implementation fidelity (D). Sites are identified numerically by the order in which they were randomised to implement and are ordered by the number of fidelity criteria achieved (appendix pp 13-15). Weights are from random effects analysis. The size of the symbols in panels C and D reflects the precision of each estimate (inverse of the within-hospital variance). OR=odds ratio.

We identified weak evidence for sustained reductions in 30-day mortality among sites that introduced the ARK categories into the prescribing process by implementation than among sites that did not (−7.2%, 95% CI −14.6 to 0.8), among sites implementing a hard stop than among sites implementing no soft or hard stop (−8.2%, −15.0 to −0.9), and among sites implementing in July–September than among sites implementing in January–March (−10.3%, −19.0 to −0.8; appendix pp 16–20).

We did not identify any evidence that sites with greater reductions in antibiotic DDDs per admission had larger immediate ($r=0.044$, $p=0.79$) or sustained ($r=0.011$, $p=0.95$) increases in 30-day mortality trends than did sites with smaller reductions in antibiotic DDDs per admission (figure 6).

Adjusted models showed no evidence of an immediate effect on total antibiotic DDDs per bed-day (−0.4%, 95% CI −3.2 to 2.5), with weak evidence of subsequent reductions (by −4.2% per year, −8.3 to 0.1; figure 3; appendix pp 13, 130), similar to effects on total DDDs per admission. At implementation, rates of broad-spectrum and Watch DDDs per admission decreased significantly (−6.3%, 95% CI −9.5 to −3.0 for broad-spectrum DDDs and −9.5%, −13.2 to −5.6 for Watch DDDs), as did quinolones (−15.5%, −21.9 to −8.5), whereas Access DDDs per admission increased slightly (4.4%, 0.3–8.8; figure 3; appendix pp 131–137, 140–144). We did not identify evidence of immediate effects on other secondary antibiotic outcomes at implementation, nor on piperacillin–tazobactam DDDs per admission (figure 3).

There were sustained reductions in year-on-year trends for most antibiotic outcomes, including narrow-spectrum (−5.2%, 95% CI −9.4 to −0.9; figure 3; appendix pp 131–132), Watch (−11.0%, −17.1 to −4.5), Access (−5.3%, −10.0 to −0.4; appendix pp 133–137), and oral antibiotics (−6.4%, −11.2 to −1.4; appendix pp 138–139). We did not identify evidence of long-term effects on broad-spectrum antibiotics (−2.6%, 95% CI −8.5 to 3.6; appendix p 131), parenteral antibiotics (−0.9%, −5.2 to 3.6; appendix p 138), and antibiotics considered Access or Watch depending on indication (1.0, −5.2 to 7.6; appendix p 133). By contrast, year-on-year trends in DDDs per admissions increased faster after versus before implementation for carbapenems (12.3%, 2.3 to 23.2; appendix pp 140–144) with a similar trend for Reserve antibiotics (7.3%, −1.5 to 17.0; appendix pp 133–137), but from low levels and with wide CIs (table; appendix pp 48–50).

Mortality within 90 days of admission was 8.1% (571173 of 7014694) overall (range 4.6–12.5 by site) and adjusted models showed weak evidence for an immediate decline (−3.1%, 95% CI −6.5 to 0.5) in 90-day mortality odds and evidence of a sustained year-on-year increase of 3.9% (0.5 to 7.4; appendix p 147). However, there was no evidence of a significant association after excluding admissions from the onset of the COVID-19 pandemic in

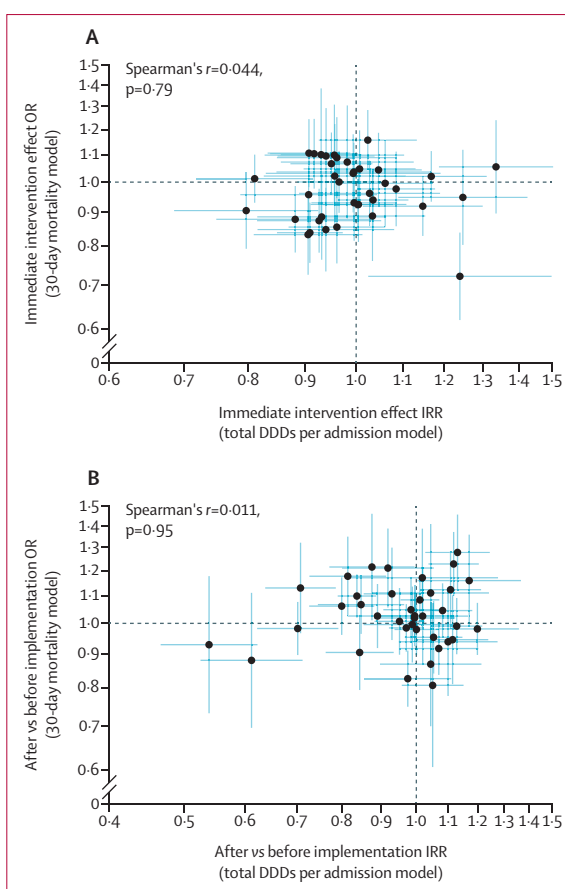


Figure 6: Comparison of intervention effects on 30-day mortality and total antibiotic DDDs per admission

Immediate effect at implementation (A) and effect on year-on-year trend after versus before implementation (B). DDD=defined daily dose. IRR=incidence rate ratio. OR=odds ratio.

March, 2020 (−3.9%, 95% CI −8.3 to 0.7 immediate decline in 90-day mortality odds; 3.2%, −1.5 to 8.2% sustained year-on-year increase; appendix pp 13–15).

Admission to critical care was uncommon (1.5% [97554 of 6499923] overall, range 0.4–4.2), and there was no evidence of an immediate (2.3%, 95% CI −1.9 to 6.7) or sustained implementation effect (−5.9%, −12.8 to 1.6; figure 3; appendix p 148). Similarly, we did not identify any evidence of association between length of stay (median 8.5 h, IQR 3.1–89.2) and the ARK intervention at implementation (−0.3% relative change in subhazard ratio per additional day in hospital, 95% CI −1.0 to 0.5) or year-on-year after versus before implementation (0.1%, −0.8 to 1.1; appendix pp 149–150). Emergency readmission to hospital (to any specialty) was 13.6% (903265 of 6625542; range 8.7–26.4) across sites, with no evidence of an immediate (−0.1%, 95% CI −2.6 to 2.5) or sustained implementation effect (−1.5%, −4.6% to 1.6; appendix p 151). Detection of *C difficile* infection (16475 [0.2%] of 6728437, range 0.1–0.6) and colonisation (27958 [0.5%] of 6092290, range 0.2–1.1)

within 90 days of admission was low. We did not identify any evidence of an intervention effect on *C difficile* infection (−4.6%, 95% CI −16.6 to 9.0) and colonisation (−5.6%, −16.9 to 7.2) within 90 days of admission at implementation, or after versus before implementation (5.8%, −8.1 to 21.9 and −6.9%, −17.5 to 5.0; appendix pp 152–153).

An exploratory analysis of the proportion of admissions with a stay longer than 48 h (2 215 245 [32.6%] of 6 794 684, range 23.1–51.3) also showed no immediate (0.3%, 95% CI −2.6 to 3.2) or sustained (−1.2%, −5.5 to 3.2) implementation effect (appendix pp 13–15, 149–150). There were sustained reductions in year-on-year trends for quinolones (−13.8%, −22.5 to −4.0; appendix pp 140–144). We did not identify evidence of long-term effects on piperacillin–tazobactam (0.6%, −14.9 to 18.8; appendix p 142).

Discussion

Here, we have evaluated the ARK intervention,^{18,20} which aimed to safely reduce antibiotic consumption in adult acute general medical hospital admissions, in a stepped-wedge cluster-randomised trial. In our final model adjusting for COVID-19, the ARK intervention resulted in mean reductions in antibiotic use of 4.8% per year, but no immediate reduction. That the intervention changed prescribing over time rather than suddenly might be expected, given the different components, including training for use of the novel decision aid and audit and feedback to re-enforce learning.²⁴ The change over time could also reflect increasing acceptance that completion of arbitrary antibiotic courses might not reduce risk of resistance.²⁵ Although the trial was powered to detect a 15% immediate reduction associated with the intervention, the effect observed is potentially clinically significant given that the national standard contract for acute trusts in England sought a reduction of only 1% per year. Given the importance of sustainable effects from behaviour change interventions in antibiotic stewardship, it is notable that this reduction was seen over a median of 23 months (range 14–37). Notably, consistent reductions were seen in Access, Watch, narrow-spectrum, and oral antibiotics, but not in broad-spectrum or parenteral antibiotics, antibiotics considered Access or Watch depending on indication, and piperacillin–tazobactam, and there was a significant increase in DDDs for carbapenems and Reserve classes. Since the intervention was targeted at acute general medical admissions, unsurprisingly its effect was seen in narrow-spectrum and Access agents, which are typically used as first-line medication or for de-escalation. The significant increase in carbapenem use after intervention could suggest that decreased use of one set of agents increased use of others. This effect seems unlikely, because the differences measured are relative and the absolute increases are small (appendix pp 49–50). Furthermore, use of carbapenems increased disproportionately across the NHS during the

study period, driven by their inclusion in national treatment guidelines for hospital-acquired pneumonia, shortages of piperacillin–tazobactam, and increasing resistance to other agents.¹⁵ Broad-spectrum agents, such as carbapenems, are typically prescribed when other agents have already been tried for the patient or when microbiology has identified a specific pathogen, and we might simply have observed an increase that the intervention would not be expected to affect.

We found no overall relationship between fidelity of implementation and the effect of the intervention. An absence of relationship might be because complex interactions between intervention elements and the implementation setting are difficult to measure quantitatively in a large-scale trial, or because we took an average of how many fidelity criteria were met, but some of the criteria were likely to have had more of an effect on fidelity than others. The ARK audit tools were designed to support frequent, light-touch feedback to prescribers, sometimes called handshake stewardship,²⁶ which relies on interpersonal factors that we could not analyse but will be considered in forthcoming mixed-methods process analyses. Prescription audits began 12 weeks before intervention to generate baseline data for the intervention's feedback element, so it is perhaps not surprising that rates of audit completion were generally higher before implementation than afterwards. Notably, among individual intervention components, implementing the decision aid into the prescribing process and greater uptake of the online learning were both associated with greater reductions in antibiotic use than were not implementing these elements of the intervention, suggesting that these are key elements in achieving sustained change.

The ARK intervention focuses on decisions to stop rather than decisions to start antibiotics, because this approach has the potential to reduce overall use without withholding empirical antibiotics from patients with acute illness. Nevertheless, we considered it important to evaluate whether introducing ARK was associated with excess mortality. Beginning in March, 2020, when 12 of 39 sites were still within 12 months of implementation, the COVID-19 pandemic was associated with substantial increases in mortality among acute hospital admissions (appendix pp 51–127). Adjusting for this effect, in most of the main models and through sensitivity analysis excluding these 12 sites, we identified no clear evidence of associations between the intervention and 30-day or 90-day mortality. Notably, implementing the decision aid with a hard stop of antibiotic prescriptions at 72 h if not revised was associated with decreased risk of death over time, despite prescribers reporting anxiety that hard stops could compromise clinical outcomes.²⁷ This decrease might be explained by clinicians placing a greater emphasis on prescription reviews at sites that introduced hard stops, improving patient management more broadly. Furthermore, we found no evidence that

sites that achieved greater reductions in antibiotic DDDs per admission had larger increases in mortality than did sites with smaller reductions in antibiotic DDDs per admission (figure 6).

Our study has important limitations. First, there are intrinsic limitations of the cluster-randomised design. Although we included over a quarter of all acute hospitals in the UK health system, we cannot reliably exclude imbalance, particularly of time-dependent factors, as emphasised by the onset of the COVID-19 pandemic during the postimplementation period. There could be imbalance in other time-dependent organisational changes (eg, staffing, clinical or stewardship practice, or case-mix), which might have changed antibiotic consumption at individual sites. We do not have data for antibiotic resistance rates, which might have varied between sites over time and are generally lower in the UK than in many other countries.

Second, although sites were robustly randomised with respect to the timing of intervention implementation, they might not be a random sample of UK acute hospitals. It is plausible that only sites with well constituted antimicrobial stewardship teams volunteered, and other sites might not see the same effect, particularly as effect was associated with some aspects of intervention fidelity. Alternatively, the intervention effect could be greater at sites with weaker stewardship teams.

Third, we measured antibiotic consumption indirectly from dispensing data to clinical areas, as individual-level antibiotic data could be provided by only four sites. This method means that we cannot explore mechanisms through which the intervention reduced antibiotic use. However, our mortality analysis included over 7 million admissions, so there was no ability to collect individual prescribing data other than electronically. Although richer data at the individual-patient level would have allowed more detailed exploration, collecting consent and antibiotic use data from the number of patients needed to conduct a robust analysis would be infeasible. Furthermore, stewardship interventions, such as ARK, are made at the organisation level and, as such, organisation-level antibiotic use is an appropriate outcome.

Fourth, it is probable that not all prescribing decisions in the patient population analysed were subject to the intervention (eg, outlying surgical patients). Conversely, some patients for whom prescribing decisions were not subject to the intervention might have been included in analysis. These inclusions and exclusions are because acute general medical inpatients are not easily identified in electronic admission data, and we had to infer this population from specialty codes, which are used slightly differently across sites. Importantly, both these effects, and low implementation fidelity at some sites, would be expected to dilute the observed effect of the intervention on antibiotic use, suggesting that antibiotic reductions might have been even greater in targeted patients and in sites with high implementation fidelity.

In terms of potential clinical harms from the intervention, analysing routinely available electronic health records, we identified no consistent evidence of effect on mortality, admission to critical care, length of stay, or readmission. Although we cannot exclude the possibility of other harms related to shorter antibiotic treatment, our overall findings make substantial increases in treatment failure and recurrence unlikely. Equally, we were not able to measure potential direct benefits from reduced antibiotic treatment, but it is a reasonable assumption that reductions in antibiotic exposure will reduce antibiotic-associated harms, including resistance.

Despite its limitations, the cluster-randomised approach that we adopted allowed us to capture both the organisation-level effects of the intervention on antibiotic consumption and the patient-level effects on clinical outcomes. Our findings are entirely consistent with the three, much smaller, previous trials of hospital stewardship interventions, which showed the importance of intervention co-design with practitioners,²⁸ practitioner education, and clinically relevant audit and feedback to clinicians.^{29,30} Our findings are also consistent with conclusion of the most recent Cochrane review that stewardship interventions can reduce unnecessary antibiotic use safely.¹¹ Our approach to intervention design and evaluation addresses many of the limitations that have prevented the translation of previous research findings into hospital practice.^{7,8} Crucially, the wider ARK-Hospital programme has delivered practice-ready materials for implementation, which are freely available. Acute hospital providers should consider embedding the ARK-Hospital toolkit in their staff training, prescribing processes, and stewardship work to reduce antibiotic overuse in acute general medical inpatients and protect these patients from antibiotic-related harms.

Contributors

TEAP, ASW, LY, and MJL conceived the research. ELAC, KS, SW, MSa, AK, FM, KSH, DWC, LV, SH LY, TEAP, and ASW conceived and developed the intervention. ML-S, RA, SB, PC, GC-B, SD, ME, RF, KJF, VG-A, SG, CG, KG, CH, DH, TH, SI, AJ, NJ, PK, GK, DMac, CM, DMaw, BM, MM, RM, SN, AN, JN, JO, AP, RP, NP, DP, ES, MSI, BS, CW, IW, MD, and MJL conducted the trial. EPB conducted the statistical analysis. EPB and ASW accessed and verified all the data. ASW, EPB, and MJL wrote the first draft. All authors reviewed and approved the final manuscript. All authors had full access to the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

MJL, DWC, LY, TEAP, and ASW declare funding from the National Institute for Health Research (NIHR) for the ARK-Hospital programme. ASW is an NIHR Senior Investigator. All other authors declare no competing interests.

Data sharing

The de-identified patient-level electronic health records (on over 7 million admissions) and hospital-level antibiotic use data used for this analysis was obtained from individual hospital organisations without permission for onward data sharing. It can be accessed either directly from the participating organisations or through the trial team if the participating organisations provide permission. De-identified patient-level admission data can also be accessed directly through an application to NHS Digital. All enquiries should be sent to Prof Martin J Llewelyn

(m.j.llewelyn@bsms.ac.uk or Prof Sarah Ann Walker (sarah.walker@ndm.ox.ac.uk). The full protocol is available on <http://www.arkstudy.ox.ac.uk/ark-for-healthcare-professionals>. The statistical analysis plan is available by emailing Prof Martin J Llewelyn or Prof Sarah Ann Walker.

Acknowledgments

The trial was funded by the NIHR under its Programme Grants for Applied Research Programme (reference number RP-PG-0514-20015). ASW and LY are NIHR Senior Investigators. ASW, DWC, TEAP, MJL, and LSJR are supported by the NIHR Biomedical Research Centre, Oxford, UK. LY is partly supported by NIHR Applied Research Collaboration-West and NIHR Health Protection Research Unit for Behavioural Science and Evaluation, University of Bristol, Bristol UK. The ARK online tool was developed using the LifeGuide software, which was partly funded by the NIHR Biomedical Research Centre, Southampton, UK. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care. We thank the ARK-Hospital Team for their work delivering the trial at their respective hospital sites. The programme steering committee consisted of Alison Holmes (chair, Imperial College London, London, UK); Philip Gothard (University College Hospital, London, UK); Karla Hemming (University of Birmingham, Birmingham, UK); Cliff Gorton (Oxford, UK). The data monitoring committee consisted of Neil French (chair, Liverpool University, Liverpool, UK); Tom Rogers (Trinity College, Dublin, Ireland); James Lewis (Cardiff University, Cardiff, UK). The hospital team consisted of Sath Nag, Richard Bellamy, Debbie Lockwood (South Tees Hospitals NHS Foundation Trust, Middlesbrough, UK); Neil Powell (Royal Cornwall Hospitals NHS Trust, Truro, UK); Cassandra Watson, Priya Khanna, Elizabeth Fleet, Kam Cheema, Amit Amin, Alastair McGregor, G Gopal Rao, Mushtaqur Rahman, Sunder Chita, (London North West University Healthcare NHS Trust, Harrow, UK); Alison Johnson, Sue Vaughan (Wye Valley NHS Trust, Hereford, UK); Stuart Bond, Jade Lee-Milner (Mid Yorkshire Hospitals NHS Trust, Wakefield, UK); Mandy Slatter, Jane Liu, Belen Espina (Royal United Hospitals Bath NHS Foundation Trust, Bath, UK); Charlotte Makanga (Betsi Cadwaladr University Health Board, Bangor, UK); Mariyam Mirfenderesky, Semra Ali, Salih Hassan, Roxanne Forbes (North Middlesex University Hospital NHS Trust, London, UK); Kevin Frost (Airedale NHS Foundation Trust, Keighley, UK); Ruth McEwen, Ildiko Kustos, Joy Nicholls, Alice Rafferty (Countess of Chester Hospital NHS Foundation Trust, Chester, UK); Geraldine Conlon-Bingham, Sara Hedderwick, Cara McKeating, Peter McKee, Lisa Lennon, Orla McGivern, Jessie McNally, Toni Donnelly, Roger Stewart, Diarmuid McNicholl, Eoghan McCloskey, Wendy Baird, Donna Muckian, Martin Brown (Southern Health and Social Care Trust, Craigavon, UK); David Price, Kathy Gillespie, Andrew Heed, Matthew Lowery (Newcastle Upon Tyne Hospitals NHS Foundation Trust, Newcastle-upon-Tyne, UK); Stephen Glass, Amy Dalton, Doreen Flower, Christopher Parokkaren (East Kent Hospitals University NHS Foundation Trust, Ashford, UK); John Northfield, Prithwiraj Chakrabarti (Milton Keynes Hospital NHS Foundation Trust, Milton Keynes, UK); Veronica Garcia-Arias, Consuelo Amigo-Vaquero, Patrick Doyle, Paul Flattery, Sarah Short (Frimley Health NHS Foundation Trust, Frimley, UK); Gloria Kiapi, Laura Gonzalez, Sally Tipping, Mark Hackett (Great Western Hospitals NHS Foundation Trust, Swindon, UK); Amanda Pegden, Umi Quinn, Caroline Duffin, Sawsan Awad (Chesterfield Royal Hospital NHS Foundation Trust, Chesterfield, UK); Elizabeth Sheridan, Samantha Ruston, Craig Prescott (Poole Hospital NHS Foundation Trust, Poole, UK); Bernie McCullagh, Peter Yew, Frederick McIlwaine (South Eastern Health And Social Care Trust, Belfast, UK); Nicola Jones, Louise Dunscombe, Mridula Rajwani (Oxford University Hospitals NHS Foundation Trust, Oxford, UK); Jena O'Driscoll, Claire Brandish, Beeyean Ng, Jose Pereira (Buckinghamshire Healthcare NHS Trust, Stoke Mandeville, UK); Damien Mack, Stephanie Harris, Alan Hunter, Marisa Lanzman, Indran Balakrishnan, Rachel Moores, Lucy Lamb, Penny Smith, Christof Stigone (Royal Free London NHS Foundation Trust, London, UK); Rosemary Fok, Suzanne Price, Robert Tilley, Austin Hunt, Neha Maasala, Anna Kampa, John Siewruk (University Hospitals Plymouth NHS Trust, Plymouth, UK); Damian Mawer, Anita Chalmers, Melissa Cochran, Stephen Waring, Jawwad Azam,

Sachin Thakur, Alexander Brightmore, Melanie Bootland, Tina Leake, Joseph Suich, Fiori Massimo (York and Scarborough Teaching Hospital NHS Foundation Trust, York, UK); Tim Hills, Sam Vickers, Liz Hart, Terence Ong, Carolyne Chee, Pete Eddowes, Adrian Jones, Chamira Rodrigo, Bethan Walsh, Sue Bowler, Annette Clarkson, Shanika Cruz, Robin Allan, Raj Shah, Cheermy Relloso (Nottingham University Hospitals NHS Trust, Nottingham, UK); Robert Porter, Hazel Parker, Hannah Burnett, Sally Tipping, Maximilian Gilbert, Steve Westlake (Royal Devon and Exeter NHS Foundation Trust, Exeter, UK); Samantha Dymond, Jack Houlton, Duncan Kaye, Rebecca Langley (Northern Devon Healthcare NHS Trust, Barnstaple, UK); Rebecca Alexander, Kate Armitage, Rashmi Dube, Richard Cowan, Helen Dunn, Ahmed Mohamed, Greg Morris, Naveen Aggarwal, Rachel Hodson, Steve Yeomans, Ben Prudon, Richard Thomas (North Tees and Hartlepool NHS Foundation Trust, Stockton on Tees, UK); Immo Weichert, Gillian Urwin, Holly Gissing (East Suffolk and North Essex Hospital NHS Foundation Trust, Ipswich, UK); D Harvey, A Wilson (Wirral University Teaching Hospital NHS Foundation Trust, Upton, UK); Phil Coles, Julie Harris, Charlotte Richards (Swansea Bay Health Board, Swansea, UK); Parmjit Kang, Mike Cooper, Kate Willmer, Jaspreet Kaur, Phillip Thomas, Atul Gulati, Tariq Aljemali, Sian Rowley, Jayne Lawrence, Lucy Stelfox, Daniel Rosamond, Alison Walker, Rebecca Brady (The Royal Wolverhampton NHS Trust, Wolverhampton, UK); Clare Hamson, Jan Forlow (North Cumbria Integrated Care NHS Foundation Trust, Carlisle, UK); Shabnam Iyer, Andy Walden, Wajid Rafai, Varun Nelatur (Royal Berkshire NHS Foundation Trust, Reading, UK); Bruce Stewart, Amy Lee, Martin Dachsels, Daniel Woosey (Surrey and Sussex Healthcare NHS Trust, Redhill, UK); Cairine Gormley, Gerard Glynn, Christopher Armstrong, Emer Teague (Western Health and Social Care Trust, Londonderry, UK); David Farren, Eileen Dorgan, Salah Elshibly, Naomi Baldwin, Fidelma Magee, Fiona Gilmore, Oonagh McCourt, Andrew Currie, Gareth Lewis, Ronan Donnelly, Eunice Minford, James Gray, Joy Cuthbertson, Karen Darragh, Wilma Williamson, Cynthia Thompson, Laura Davidson, Alastair Thompson (Northern Health and Social Care Trust, Antrim, UK); Katherine Gray, Rosalyn Ward (Southport and Ormskirk Hospital NHS Trust, Southport, UK); Morgan Evans, Alison Cockburn, Carol Philip, Esperanza Palenzuela, Rachel McKinney (Western General Hospital, Edinburgh, UK)

References

- 1 Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet* 2022; **399**: 629–55.
- 2 Shrestha P, Cooper BS, Coast J, et al. Enumerating the economic cost of antimicrobial resistance per antibiotic consumed to inform the evaluation of interventions affecting their use. *Antimicrob Resist Infect Control* 2018; **7**: 98.
- 3 Holmes AH, Moore LS, Sundsfjord A, et al. Understanding the mechanisms and drivers of antimicrobial resistance. *Lancet* 2016; **387**: 176–87.
- 4 Costelloe C, Metcalfe C, Lovering A, Mant D, Hay AD. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. *BMJ* 2010; **340**: c2096.
- 5 Budgell EP, Davies T, Donker T, et al. Impact of hospital antibiotic use on patient-level risk of death among 36,124,372 acute and medical admissions in England. *J Infect* 2022; **84**: 311–20.
- 6 Davey P, Sneddon J, Nathwani D. Overview of strategies for overcoming the challenge of antimicrobial resistance. *Expert Rev Clin Pharmacol* 2010; **3**: 667–86.
- 7 Schweitzer VA, van Heijl I, van Werkhoven CH, et al. The quality of studies evaluating antimicrobial stewardship interventions: a systematic review. *Clin Microbiol Infect* 2019; **25**: 555–61.
- 8 Schweitzer VA, van Werkhoven CH, Rodriguez Baño J, et al. Optimizing design of research to evaluate antibiotic stewardship interventions: consensus recommendations of a multinational working group. *Clin Microbiol Infect* 2020; **26**: 41–50.
- 9 Little P, Moore M, Kelly J, et al. Delayed antibiotic prescribing strategies for respiratory tract infections in primary care: pragmatic, factorial, randomised controlled trial. *BMJ* 2014; **348**: g1606.

- 10 Royal College of General Practitioners. TARGET antibiotics toolkit hub. 2021. <https://elearning.rcgp.org.uk/course/view.php?id=553> (accessed Sept 14, 2022).
- 11 Davey P, Marwick CA, Scott CL, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database Syst Rev* 2017; 2: CD003543.
- 12 Ashiru-Oredope D, Sharland M, Charani E, McNulty C, Cooke J. Improving the quality of antibiotic prescribing in the NHS by developing a new antimicrobial stewardship programme: Start Smart—Then Focus. *J Antimicrob Chemother* 2012; 67 (suppl 1): i51–63.
- 13 Centers for Disease Control and Prevention. Core elements of antibiotic stewardship. 2019. <https://www.cdc.gov/antibiotic-use/core-elements/index.html> (accessed Sept 14, 2022).
- 14 Thom KA, Tamma PD, Harris AD, et al. Impact of a prescriber-driven antibiotic time-out on antibiotic use in hospitalized patients. *Clin Infect Dis* 2019; 68: 1581–84.
- 15 UK Health Security Agency. English surveillance programme for antimicrobial utilisation and resistance (ESPAUR) report 2020 to 2021. March 21, 2022. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1069632/espaur-report-2020-to-2021-16-Nov-FINAL-v2.pdf (accessed Sept 14, 2022).
- 16 NHS England. Antimicrobial resistance CQUIN 2020/2021. 2021. <https://www.england.nhs.uk/nhs-standard-contract/cquin/cquin-20-21/antimicrobial-resistance-cquin-2020-21> (accessed Sept 14, 2022).
- 17 Ashiru-Oredope D, Budd EL, Doble A, Cramp E, Hendrick A, Hopkins S. Development and implementation of a national antimicrobial stewardship surveillance system, with open access data sharing. *J Hosp Infect* 2021; 107: 16–22.
- 18 Santillo M, Sivyer K, Krusche A, et al. Intervention planning for antibiotic review kit (ARK): a digital and behavioural intervention to safely review and reduce antibiotic prescriptions in acute and general medicine. *J Antimicrob Chemother* 2019; 74: 3362–70.
- 19 Mowbray F, Sivyer K, Santillo M, et al. Patient engagement with antibiotic messaging in secondary care: a qualitative feasibility study of the ‘review and revise’ experience. *Pilot Feasibility Stud* 2020; 6: 43.
- 20 Cross ELA, Sivyer K, Islam J, et al. Adaptation and implementation of the ARK (antibiotic review kit) intervention to safely and substantially reduce antibiotic use in hospitals: a feasibility study. *J Hosp Infect* 2019; 103: 268–75.
- 21 Walker AS, Budgett E, Laskawiec-Szkonter M, et al. Antibiotic review kit for hospitals (ARK-Hospital): study protocol for a stepped-wedge cluster-randomised controlled trial. *Trials* 2019; 20: 421.
- 22 Budd E, Cramp E, Sharland M, et al. Adaptation of the WHO essential medicines list for national antibiotic stewardship policy in England: being AWaRe. *J Antimicrob Chemother* 2019; 74: 3384–89.
- 23 Walker AS, Mason A, Quan TP, et al. Mortality risks associated with emergency admissions during weekends and public holidays: an analysis of electronic health records. *Lancet* 2017; 390: 62–72.
- 24 Cosgrove SE, Seo SK, Bolon MK, et al. Evaluation of postprescription review and feedback as a method of promoting rational antimicrobial use: a multicenter intervention. *Infect Control Hosp Epidemiol* 2012; 33: 374–80.
- 25 Llewelyn MJ, Fitzpatrick JM, Darwin E, et al. The antibiotic course has had its day. *BMJ* 2017; 358: j3418.
- 26 Hurst AL, Child J, Pearce K, Palmer C, Todd JK, Parker SK. Handshake stewardship: a highly effective rounding-based antimicrobial optimization service. *Pediatr Infect Dis J* 2016; 35: 1104–10.
- 27 Llewelyn MJ, Nagg S, Garcia-Arias V, Jones N. It’s time to put a hard stop to antibiotic overprescribing in hospitals. March 6, 2019. <https://blogs.bmj.com/bmj/2019/03/06/its-time-to-put-a-hard-stop-to-antibiotic-overprescribing-in-hospitals> (accessed Sept 14, 2022).
- 28 Wathne JS, Kleppe LKS, Harthug S, et al. The effect of antibiotic stewardship interventions with stakeholder involvement in hospital settings: a multicentre, cluster randomized controlled intervention study. *Antimicrob Resist Infect Control* 2018; 7: 109.
- 29 Kallen MC, Hulscher MEJL, Elzer B, et al. A multicentre cluster-randomized clinical trial to improve antibiotic use and reduce length of stay in hospitals: comparison of three measurement and feedback methods. *J Antimicrob Chemother* 2021; 76: 1625–32.
- 30 Stenehjem E, Hersh AL, Buckel WR, et al. Impact of implementing antibiotic stewardship programs in 15 small hospitals: a cluster-randomized intervention. *Clin Infect Dis* 2018; 67: 525–32.