Antibiotic Review Kit for Hospitals (ARK-Hospital): a stepped wedge cluster randomised controlled trial

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Summary (398 words excluding funding)

Background: Strategies to reduce antibiotic overuse in hospitals depend on prescribers taking decisions to stop unnecessary antibiotics. There is limited evidence on how to support this. We evaluated a multifaceted behaviour change intervention (ARK) designed to reduce antibiotic use among adult acute/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 39 hospitals in 7 calendar-time blocks in the United Kingdom (25/September/2017-01/July/2019). Randomised implementation date was concealed until 12 weeks before implementation, when local preparations were designed to start. Co-primary outcomes were monthly antibiotic defined-daily-doses (DDD) per adult acute/medical admission (hospital-level, superiority) and all-cause 30-day mortality (patient-level, non-inferiority, margin 5%). Sites were eligible if they admitted non-elective medical patients, could identify an intervention "champion", and provide study data. Sites were followed for at least 14 months. Intervention effects were assessed using interrupted time series analyses within each site, estimating overall effects through random-effects meta-analysis, with heterogeneity across prespecified potential modifiers assessed using meta-regression. Trial registration: ISRCTN12674243.

Findings: Adjusted estimates showed reductions in total antibiotic DDDs per acute/medical admission (-4.8% per year, 95% CI: -9.1%,-0.2%) following the intervention. Among 7,160,421 acute/medical admissions, there were trends towards -2.7% (95% CI: -5.7%,+0.3%) immediate and +3.0% (95% CI: -0.1%,+6.2%) sustained changes in adjusted 30-day mortality. Site-specific mortality trends were unrelated to the site-specific magnitude of antibiotic reduction (Spearman's ρ=0.011, p=0.949). Whilst 90-day mortality odds appeared to increase (+3.9%, 95% CI: +0.5%,+7.4%), this was attenuated excluding admissions after COVID-19 onset (+3.2%, 95% CI:-1.5%,+8.2%). There was no evidence of intervention effects on length-of-stay (p>0.4).

Interpretation: The weak, inconsistent intervention effects on mortality are likely explained by the post-implementation onset of the COVID-19 pandemic. The ARK intervention resulted in sustained, safe reductions in antibiotic use among adult acute/medical inpatients.

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Research in context

Evidence before this study

Acutely ill patients often need to receive antibiotics before full diagnostic information is available. Consequently, reducing overuse of antibiotics in hospitals requires prescribers to review and where appropriate, stop, unnecessary antibiotic prescriptions. Evidence-based tools to support prescribers stop unnecessary antibiotics are very limited.

We searched PubMed, with no language or date restrictions, on 31/January/2022 for clinical studies focused on improving antibiotic use for hospitalised adults using the terms "anti-bacterial agents therapeutic use" AND "antibiotic stewardship". Among the 427 studies found, the great majority were uncontrolled evaluations of different approaches to education, decision support and feedback. These included one before-after study, which found no impact of unsupported clinician-led prescription review. Three small, hospital-level cluster-randomised trials were identified. One evaluated different approaches to feedback, one compared different hospital specialties and one found intense feedback to be effective. All were small and none considered clinical outcomes or sustainability. There is a need for research to deliver proven interventions ready for implementation into clinical practice.

Added value of this study

We evaluated a multifaceted "Antibiotic Review Kit" (ARK) intervention to support prescribers to appropriately stop antibiotics at clinical review. ARK comprises a prescription decision-aid supported by a brief online training tool, guidance on implementation (including regular data collection and feedback) and a patient information leaflet. We found that the intervention was associated with a sustained reduction in hospital-level antibiotic use overall, and specifically of oral and narrow-spectrum, and WHO Access and Watch, antibiotics. Weak trends were observed for 30-day mortality in opposite directions for immediate and sustained impact. Although there was some evidence of a sustained increase in 90-day mortality after the intervention, this was only seen when analyses included patients admitted after the start of the COVID-19 pandemic, and there was no association between the site-specific magnitude of antibiotic reductions and site-specific mortality trends. There was also no evidence of impact on hospital length-of-stay or admission to intensive care units. Taken together, we conclude that these mortality effects were unrelated to the intervention.

Implications of all available evidence

The ARK intervention is safe and effective in reducing antibiotic use among adult acute/medical hospital admissions. The tools used are now freely available for adoption into practice.

Introduction

The impact of antimicrobial resistance (AMR) on global public health is comparable to malaria and HIV, with an estimated 4.95 million deaths in 2019[1]. AMR places increased demands on healthcare systems, with substantial economic consequences.[2] Human antibiotic consumption is a major driver of AMR[3], with greater use driving resistance at both a population-level and an individual patient-level.[4] Although antibiotic use varies widely between and within healthcare systems, there is no evidence that clinical outcomes are influenced by this wide variation, e.g. between acute hospitals in England.[5]

Antimicrobial stewardship (AMS) aims to minimise resistance selection by ensuring antibiotics are only prescribed when clinically indicated and that narrow-spectrum agents are used whenever appropriate.[6] However, translating AMS research into practice is hampered by poor quality evidence, in particular 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 AMS strategies, such as avoiding or delaying antibiotics in respiratory tract infection, can be safe and effective.[9,10] In contrast, hospital AMS interventions that enable better prescribing are more acceptable and can reduce overuse and length-of-stay without compromising mortality.[11] The need to ensure 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 hours.[12] In the United States, the analogous term "antibiotic timeouts" is used, but revised Centers for Disease Control and Prevention (CDC) guidance in 2019[13] prioritised pharmacist-led audit and feedback to prescribers, as evidence is lacking that prescriber-led reviews reduce overall consumption.[14]

After introducing "Start Smart, then Focus" in 2011, antibiotic consumption in English hospitals continued to rise year-on-year until the COVID-19 pandemic in 2020.[15] This was despite financial incentives to reduce hospital prescribing, first through a Commissioning for Quality and Innovation (CQUIN) in 2016-18[16] and then its incorporation into the National Health Service (NHS) Standard Contract for acute hospitals. Although high rates of prescription review were achieved,[17] anecdotally, the great majority of review decisions were to adjust, rather than stop antibiotics.

The Antibiotic Review Kit (ARK) Hospital programme aimed to develop and evaluate a multifaceted behaviour change intervention to safely reduce antibiotic use in acute/general medical inpatients. ARK created a four-component intervention to help prescribers take appropriate decisions to stop or continue antibiotics at prescription review comprising: a novel prescribing decision aid, an online training tool supporting decision aid use, guidance for implementing audit and feedback, and a patient leaflet.[18,19] Here we report the immediate and sustained impact of the intervention on hospital-level antibiotic consumption and patient-level clinical outcomes.

Methods

Study Design
Following a feasibility evaluation at one acute NHS hospital,[20] the ARK intervention was evaluated at 39 hospitals (three pilot sites, 36 main trial sites) across all United Kingdom (UK) nations using a stepped-wedge cluster randomised controlled trial.[21] A cluster design was essential to avoid contamination from healthcare professionals moving between teams within a hospital. A stepped-wedge design was essential given the limited number of UK secondary care organisations that could be randomised. Fidelity of intervention implementation was assessed using eight pre-defined criteria (**Table 1**).

The ARK tools are freely available through the British Society for Antimicrobial Chemotherapy (BSAC) at: antibioticreviewkit.org.uk. 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 since electronic health records were pseudonymised and no personal identifiable data was collected other than date of death.

Participants
The unit of observation was a hospital organisation offering services for non-elective medical admissions (see **Supplementary Methods**). Sites were approached through professional networks and the Society for Acute Medicine. Eligible sites needed to admit adult general/medical inpatients, have a local 'champion' 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 most often used to admit adult general medicine inpatients (**Figure S1**; rationale in[21]).

Randomisation and masking
Sites were randomised using a computer-generated list by the Trial Statistician (ASW) in seven blocks of six sites, to implement every 1-2 weeks excluding over holidays or where the funder requested a pause on randomisation (**Figure S2**). To avoid contamination, complete information about the intervention and allocation sequence was concealed until the point of randomisation when sites were told that their randomised implementation date was 12 weeks in the future, ensuring all sites had 12 weeks for implementation preparation.

Procedures
The intervention comprised: 1) a decision aid 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 either "possible" or "probable", and then stopping or finalising the prescription if a clear indication for ongoing antibiotic treatment could be established at 48-72h review; 2) online training to motivate and support decision aid use; 3) implementation guidance, including audit and feedback tools; and 4) a patient leaflet.[18,19]

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. Study data was collected from February 2016 to October 2020 to facilitate pre- and post-implementation outcome assessment, with at least 14 months' follow-up in all sites (time periods for co-primary outcomes in **Figure S2**).

Co-primary outcomes
The trial had two co-primary outcomes: (1) antibiotic defined daily doses (DDDs) per adult acute/general medical admission (superiority), and (2) all-cause mortality within 30 days of admission (in/out of hospital) (non-inferiority, relative margin 5%). 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.

Secondary outcomes
Secondary antibiotic (superiority) outcomes were total antibiotic DDDs per acute/general medical bed-day, and DDDs/admission for specific antibiotic groups including carbapenems, parenteral and oral administration, broad-spectrum and narrow-spectrum, and the UK Health Security Agency's interpretations of Access, Watch, and Reserve (AWaRe) from the World Health Organisation's Essential Medicines List[22] (**Table S1**). Piperacillin/tazobactam and quinolones were considered in exploratory analyses. Admissions, rather than bed-days, were used as the main denominator because bed-days may be influenced by non-medical reasons for prolonged hospital stays. Although the protocol specified patient-level antibiotic outcomes (i.e. days on antibiotics and antibiotic-days per admission/bed-day, antibiotic restart after discontinuation for >48 hours)[21], only four sites had both the electronic prescribing systems and IT resources required to provide this data so these outcomes could not be analysed (**Figure S3**). Secondary non-inferiority outcomes were 90-day mortality, admission to an intensive care unit (ICU), 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.

All outcomes were assessed using pseudonymised electronic health records from adult (≥16 years) acute/general medical admissions (see **Supplementary Methods** for details including data cleaning, summarised for 30-day mortality in **Figure S4**), bulk antibiotic dispensing on the wards that implemented ARK, and *C. difficile* test results. Date of death within 90 days of admission (in/out of hospital) was obtained by sites through linkage with national registries.

Statistical analysis
An interrupted time series analysis estimated the intervention's immediate impact ('step change') and sustained impact on year-on-year trends post- versus pre-implementation within each site, using the randomised implementation date following intention-to-treat (ITT). The ITT approach was modified to exclude 7 sites withdrawing after randomisation but before implementation, from whom no data was collected. Overall intervention effects were then estimated using random effects meta-analysis, using meta-regression to assess heterogeneity in effects across prespecified potential effect modifiers. With a minimum 36 sites, the stepped-wedge cluster-randomised design had >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] See **Supplementary Methods** for further details.

Monthly antibiotic DDDs per admission were modelled using negative binomial regression, and binary outcomes per admission using logistic regression. Length-of-stay (days) was modelled using 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/colonisation using subhazard regression. Length-of-stay ≥48 hours was considered in an exploratory analysis using logit models. All models included a robust variance adjustment by patient.

Since the COVID-19 pandemic profoundly affected both primary and secondary outcomes, all models included a binary indicator for March-June 2020 unless otherwise noted. Sensitivity analyses excluded admissions after February 2020, including 12 sites with <12 months post-implementation data as a result. Antibiotic models additionally adjusted for seasonal effects by including day of year as a sin() + cos() function to ensure smooth risk changes day-to-day. Non-antibiotic models also adjusted for individual admission-level covariates, regardless of statistical significance (based on[23]): 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 (weekend versus weekday), admission day of year and time of day (and its interaction with admission day of the week), and number of overnight admissions and any previous overnight complex (>1 consultant episode, excluding episodes in the emergency department and rehabilitation) admission in the past year. Ethnicity was missing for median 8.8% admissions (IQR: 4.5-18.4%) per site so was not adjusted for. See **Supplementary Methods** for further details.

All analyses used Stata/MP 17. The Data Monitoring Committee reviewed outcome data three times during the trial, using a Haybittle-Peto statistical rule for early stopping. The trial was registered as ISRCTN12674243.

Role of the funding source
The funder had no role in study design, data collection, analysis, interpretation, or report writing and the decision to publish.

Results

Three pilot sites implemented the intervention between 25 September 2017 and 20 November 2017; 43 further sites were randomised to implement between 12 February 2018 and 1 July 2019, of whom 7 withdrew before implementation and were excluded from analyses as no data were collected (**Figure S3**).

Thirteen sites were classed as large (>850 beds available, median: 991), 14 medium (551-850 beds, median: 670) and 12 small (≤550 beds, median: 487) (**Table 1**). Sites were distributed across the UK, with the largest number (n=13) in the South of England. The Champion was a Microbiologist in 19 sites, was trained jointly in Microbiology and Acute Medicine or Infectious Diseases in 3, in Acute Medicine alone in 7, and was a Pharmacist in 10. At implementation, prescribing was paper-based in 25 sites and electronic in 14 (6 Cerner™, 3 JAC™, 5 other). Twenty-one (54%) sites implemented the decision aid with a "hard stop" to the initial prescription unless revised by 72 hours, 9 (23%) as a "soft stop" highlighting the need to stop or finalise within 72 hours, and 9 (23%) did neither.

Antibiotic use in the 12 months before randomised implementation varied very widely, both in total DDDs/admission (median: 2.9, IQR: 2.1-4.7, range: 0.4-11.3) and specific agents, classes, and AWaRe categories (**Table 1**, **Figure S5**). Access antibiotics accounted for 30.7-85.2% of total DDDs, Watch for 4.8-44.1%, and Reserve for 0.3-5.7%.

Intervention adherence

Site champions named a median 19 (IQR: 14-34, range: 5-72) people as essential for doing the online training; median 78% (IQR: 63-90%) completed the training by 12 weeks, with 16 (41%) sites below the ≥70% target (**Figure 1A**). The total number of staff completing training also varied substantially, with median 24 (IQR: 15-41) staff trained per 100 acute beds and 12 (31%) sites achieving <20 (**Figure 1B&C**) by 12 weeks although this fell to 9 (23%) overall. Actual implementation was delayed at 9 sites, by median 7.4 weeks after the randomised date (IQR: 6.1-13, range: 5.3-25), typically because of delays implementing the decision aid into prescribing processes. Sites achieved a median 6 (IQR: 5-7, range: 2-8) of the eight implementation fidelity criteria (**Table 1**); 9 (25%) sites achieved ≤4.

Post-implementation audit data were available for 37 sites, of which 31 provided baseline audit data. Through 12 weeks following randomised implementation, a median 51.6% (IQR: 31.4-75.9%) of audited antibiotic prescriptions were categorised using the decision aid at the initial prescription (**Figure 1D**). At 12 weeks a median 89.9% (IQR: 80.8-96.5%) of audited prescriptions were reviewed versus 91.0% (IQR: 78.6-95.8%) at baseline (Wilcoxon matched-pairs p=0.209), with greater increases in sites with lower baseline rates (**Figure 1E**) A median 16.2% (IQR: 12.8-23.3%) were stopped at 'review and revise' versus 12.7% (IQR: 5.4-21.4%) at baseline (p=0.006), again with greater increases in sites with lower baseline rates (**Figure 1F**).

Total DDD per acute/general medical admission (co-primary outcome)

Sites contributed a median 23 months (range: 14-37) of antibiotic data post-implementation (**Figure S2**). Adjusting for the impact of COVID-19 and interrupted time series trends (shown by site in **Figure S6**), the intervention was associated with a -1.0% immediate change in total antibiotic DDDs/admission (95% CI: -4.0%,+2.1%) and a sustained -4.8% reduction per year subsequently (95% CI: -9.1%,-0.2%) (**Figures 2&3**), with little association between the immediate and longer-term intervention effects across sites (Spearman's rho: -0.088, p=0.599,

Figure S7). There was substantial heterogeneity in trajectories of DDDs/admission pre- and post-intervention (**Figure S8)**. Intervention effects were similar unadjusted (**Figure 2**) and excluding all follow-up from March 2020 (**Table S2**).

There was no evidence that immediate effects on total DDDs/admission at implementation and on year-on-year trends post- versus pre-intervention were associated with overall implementation fidelity (per unit higher -0.5%, 95% CI: -2.7%,+1.7%; and -1.4%, 95% CI: -4.9%,+2.3%, respectively) (**Figure 3**). Reductions in total DDDs/admission at implementation were greater among sites with processes for ongoing audit and feedback in place by implementation (by -16.6%, 95% CI: -28.5%,-2.8%), and among sites that submitted post-implementation audit data within 4 weeks following implementation (by -8.3%, 95% CI: -15.1%,-1.0%), with the latter explained by the former in multivariable models (**Table S3**). There was also marginal evidence of greater sustained reductions in total DDDs/admission among sites that introduced ARK categories into the prescribing process by implementation (by -11.5%, 95% CI: -22.9%,+1.7%) and among sites with greater uptake of the online learning by implementation (by -9.9% if ≥20 people/100 acute beds, 95% CI: -19.7%,+1.1%). Medium-sized sites also tended to have greater reductions in DDDs at implementation (by -7.4%, 95% CI: -14.6%,+0.5%), with weak evidence for increases subsequently (by +14.6, 95% CI: +0.1%,+31.3%) (**Table S3**).

Secondary antibiotic outcomes
Adjusted models showed no evidence of an immediate impact on total antibiotic DDDs/bed-day (-0.4%, 95% CI: -3.2%,+2.5%), with marginal evidence of reductions subsequently (by -4.2% per year, 95% CI: -8.3%,+0.1%) (**Figures 2, S9**); similar to effects on total DDD/admission (co-primary outcome). At implementation, rates of broad-spectrum and Watch DDDs/admission dropped significantly (-6.3%, 95% CI: -9.5%,-3.0% and -9.5%, 95% CI: -13.2%,-5.6%, respectively), as did quinolones (-15.5%, 95% CI: -21.9%,-8.5%), whereas Access DDDs/admission increased slightly (+4.4%, 95% CI: +0.3%,+8.8%) (**Figures 2, S10, S11**). There was no evidence of immediate effects on other secondary antibiotic outcomes at implementation, nor on piperacillin-tazobactam DDDs/admission (**Figure 2**).

However, there were sustained reductions in year-on-year trends for most antibiotic DDD/admission groups, including narrow-spectrum (-5.2%, 95% CI: -9.4%,-0.9%) (**Figures 2, 10**), Watch (-11.0%, 95% CI: -17.1%,-4.5%), Access (-5.3%, 95% CI: -10.0%,-0.4%) (**Figure S11**), oral antibiotics (-6.4%, 95% CI: -11.2%,-1.4%) (**Figure S12**) and quinolones (-13.8%, 95% CI: -22.5%,-4.0%, **Figure S13**). There was no evidence of long-term effects on broad-spectrum (-2.6%, 95% CI: -8.5%,+3.6%), parenteral (-0.9%, 95% CI: -5.2%,+3.6%), or antibiotics considered Access or Watch depending on indication (+1.0, 95% CI: -5.2%,+7.6%), nor on piperacillin-tazobactam (+0.6%, 95% CI: -14.9%,+18.8%, **Figure S13**). In contrast, year-on-year trends in DDDs/admissions increased faster post- versus pre-implementation for carbapenems (+12.3%, 95% CI: +2.3%,+23.2%) (**Figure S13**) with a similar trend for Reserve antibiotics (+7.3%, 95% CI: -1.5%,+17.0%) (**Figure S11**), but from very low levels and with wide confidence bounds (**Table 1**, **Figure S5**).

30-day mortality (co-primary outcome)
Sites contributed a median 23 months (range: 15-37) all-cause 30-day mortality (in/out of hospital) data post-implementation (**Figure S2**). Analysis included 7,160,421 admissions (**Table S4**); 314,313 (4.4%) 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%,+0.3%)

immediate change in 30-day mortality odds and a +3.0% (95% CI: -0.1%,+6.2%) sustained change post- versus pre-implementation (**Figures 2&4**). Sites with larger immediate mortality reductions tended to have larger sustained increases post- versus pre-implementation (Spearman rho: -0.28, p=0.082, **Figure S14**). This suggests the weak overall effects could be an artefact from the individual interrupted time series (**Figure S6**), given the substantial heterogeneity in trajectories of 30-day mortality pre- and post-intervention (**Figure S15**), potentially related to the electronic data submitted (**Table S5**). There was no evidence that effects on 30-day mortality were associated with implementation fidelity (immediate effect +1.3% per unit higher, 95% CI: -6.8%,+3.3%; and change in year-on-year trend post- versus pre-implementation -0.1%, 95% CI: -2.1%,+1.9%, respectively) (**Figure 4**). Intervention effects on unadjusted 30-day mortality were relatively similar (**Figure 3**), as were effects excluding all follow-up from March 2020 (**Table S2**).

There was weak evidence for greater sustained reductions in 30-day mortality among sites that introduced the ARK categories into the prescribing process by implementation (-7.2%, 95% CI: -14.6%,+0.8%), among sites implementing a hard stop versus no soft/hard stop (-8.2%, 95% CI: -15.0%,-0.9%), and among sites implementing in July-September versus January-March (-10.3%, 95% CI: -19.0%,-0.8%) (**Table S3**).

There was no evidence that sites with greater reductions in antibiotic DDDs/admission had larger immediate (Spearman's ρ: 0.044, p=0.795) or sustained (Spearman's ρ: 0.011, p=0.949) increases in 30-day mortality trends (**Figure 5**).

Other secondary clinical outcomes
Mortality within 90 days of admission was 8.1% overall (range: 4.6%,12.5% by site) and adjusted models showed weak evidence for an immediate -3.1% (95% CI: -6.5%,+0.5%) decline in 90-day mortality odds and evidence of a sustained year-on-year increase of +3.9% (95% CI: +0.5%,+7.4%) (**Figure S16**). However, there was no evidence of association after excluding admissions from the onset of the COVID-19 pandemic in March 2020 (-3.9%, 95% CI: -8.3%,+0.7%, and +3.2%, 95% CI: -1.5%,+8.2%, respectively) (**Table S2**).

Admission to critical care was uncommon (1.6% overall, range: 0.4%,4.2%) and there was no evidence of an immediate (+2.3%, 95% CI: -1.9%,+6.7%) or sustained implementation effect (-5.9%, 95% CI: -12.8%,+1.6%) (**Figures 2, S17**). Similarly, there was no evidence of association between length-of-stay (median 8.5 hours, IQR: 3.1-89.2) and the ARK intervention at implementation (-0.3% relative change in subhazard ratio, 95% CI: -1.0%,+0.5%) or year-on-year post- versus pre-implementation (+0.1%, 95% CI: -0.8%,1.1%) (**Figure S18**). An exploratory analysis of the percentage of admissions with length-of-stay >48h (32.6% overall, range: 23.1%,51.3%) also showed no immediate (+0.3%, 95% CI: -2.6%,+3.2%) or sustained (-1.2%, 95% CI: -5.5%,+3.2%) implementation effect (**Table S2, Figure S18**). Emergency readmission to hospital (any specialty) was 13.6% across sites (range: 8.7%,26.4%), with no evidence of an immediate (-0.1%, 95% CI: -2.6%,+2.5%) or sustained implementation effect (-1.5%, 95% CI: -4.6%,+1.6%) (**Figure S19**). Detection of *C. difficile* infection and colonisation within 90 days of admission was low (0.2%, range: 0.1%,0.6% and 0.5%, range: 0.2%,1.1%, respectively). There was no evidence of an intervention effect on *C. difficile* infection and colonisation within 90 days of admission at implementation (-4.6%, 95% CI: -16.6%,+9.0%; and -5.6%, 95% CI; -16.9%,+7.2%, respectively) or post- versus pre-implementation (+5.8%, 95% CI: -8.1%,+21.9%; and -6.9%, 95% CI: -17.5%,5.0%, respectively) (**Figure S20**).

Discussion

Here, we have evaluated the ARK intervention,[18,20] which aimed to safely reduce antibiotic consumption in adult acute/medical hospital admissions, in a stepped-wedge cluster-randomised trial.

In our final model adjusting for COVID-19, the ARK intervention resulted in average reductions in antibiotic use of 4.8% per year. That the intervention changed prescribing over time rather than suddenly might be expected, given the different components, including training in using the novel decision aid, and audit and feedback to re-enforce learning.[24] It may also reflect increasing acceptance that completion of arbitrary antibiotic courses may not reduce risk of resistance.[25] Although the trial was powered to detect a 15% immediate reduction associated with the intervention, the impact observed is potentially clinically very 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 impact from behaviour change interventions in antibiotic stewardship, it is notable that this reduction was seen over a median 23 months (range: 14-37). Of note, consistent reductions were seen in Access and Watch, narrow-spectrum and oral antibiotics, but not in broad-spectrum or Reserve classes. Since the intervention was targeted at acute/general medical admissions it is unsurprising its impact was seen in narrow-spectrum and Access agents, which are typically used as first-line or for de-escalation. The significant increase in carbapenem use post-intervention could suggest a "squeezing the balloon" effect in which reduced use of one set of agents increases use of others. This seems unlikely because the differences measured are relative and the absolute increases are very small (**Figure S5E**). Furthermore, use of these agents 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 in specific situations or when microbiology has identified a specific pathogen, and we may simply have observed an increase that the intervention would not be expected to affect.

We found no overall relationship between fidelity of implementation and its impact. This may be because complex interactions between intervention elements and the implementation setting are difficult to measure quantitatively in a large-scale trial, or because our fidelity criteria averaged across important and less important components. The ARK audit tools were designed to support frequent, light-touch feedback to prescribers, sometimes called "hand-shake 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 pre-intervention to generate baseline data for the intervention's feedback element so it is perhaps not surprising that rates of audit completion were on the whole higher pre-implementation. It is noteworthy that 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, 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 acutely ill patients. Nevertheless, we considered it important to evaluate whether introducing ARK was associated with excess mortality. Beginning in March 2020 when 12/39 sites were still within 12 months of implementation, the COVID-19 pandemic

was associated with substantial increases in mortality among acute hospital admissions (**Figure S6**). Adjusting for this effect, both in the main models and through sensitivity analysis excluding these 12 sites, we found no clear evidence of associations between the intervention and 30-day or 90-day mortality, with weak trends towards decreased risk of death at intervention implementation and towards increased risk of death over time, likely reflecting some residual confounding from COVID-19. Notably, implementing the decision aid with a "hard stop" of antibiotic prescriptions at 72 hours if not revised, was associated with **decreased** risk of death over time. This is intriguing given that, anecdotally, prescribers reported anxiety that "hard stops" could compromise clinical outcomes.[27] It may 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/admission had larger increases in mortality (**Figure 5**).

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 highlighted by the onset of the COVID-19 pandemic during the post-implementation period. There could be imbalance in other time-dependent organisational changes (e.g. staffing, clinical or stewardship practice, case-mix) which may have changed antibiotic consumption at individual sites. We lack data on antibiotic resistance rates may have varied between sites over time and are generally lower in the UK than many other countries.

Second, although sites were robustly randomised with respect to the timing of intervention implementation, they may 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 experience the same impact, particularly as impact was associated with some aspects of intervention fidelity. Alternatively, the intervention impact 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 only be provided by four sites. This means 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. While richer individual-patient level data would have allowed more detailed exploration, the number of patients needed to collect this robustly would be infeasible with individual-participant consent and current electronic data systems in the NHS. Furthermore, stewardship interventions such as ARK are made at the organisation level and as such, organisation-level antibiotic use are appropriate outcomes.

Fourth, it is likely that not all prescribing decisions in the patient population analysed were subject to the intervention (e.g. outlying surgical patients). Conversely, some patients for whom prescribing decisions were not subject to the intervention may have been included in analysis. This is 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 the lack of implementation fidelity in some sites, would be expected to dilute the observed impact of the intervention on antibiotic use, suggesting that antibiotic reductions may have been even greater in targeted patients and in sites with better implementation.

In terms of potential clinical harms from the intervention, analysing routinely available electronic health records, we found no consistent evidence of impact 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 we adopted allowed us to capture both the organisation-level impact of the intervention on antibiotic consumption and patient-level impact on clinical outcomes. Our findings are entirely consistent with the three, much smaller, previous trials of hospital stewardship interventions, which demonstrated the importance of intervention co-design with practitioners,[28] practitioner education and clinically relevant audit and feedback to clinicians.[29,30] They 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 through BSAC at antibioticreviewkit.org.uk. Acute hospital providers should embed 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.

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CONTRIBUTORS

TEAP, ASW, LY, MJL conceived the research. ELAC, KS, SW, MS, AK, FM, KSH, DC, LV, SH LY, TEAP and ASW conceived and developed the intervention. MLS, RA, SB, PC, GCN, SD, ME, RF, KJF, VGA, SG, CG, KG, CH, DH, TH, SI, AJ, NJ, PK, GK, DM, CM, DM, BMcC, MM, RMcE, SN, AN , JN, JO'D, AP, RP, NP, DP, ES, MS, 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.

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 Llewelyn (m.j.llewelyn@bsms.ac.uk or Prof Sarah 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 Profs Lllewelyn or Walker.

FIGURE LEGENDS

Figure 1: Intervention adherence through 12 weeks' implementation in terms of completing ARK training (A-C), using the decision aid (D), reviewing antibiotic prescriptions (E) and stopping antibiotics at 'review and revise' (F)

Note: panels show percentage of essential people completing ARK training (A), staff completing ARK training (B), staff completing training per 100 acute beds (C), percent antibiotic prescriptions categorised using the decision aid at the initial prescription (D), percent antibiotic prescriptions reviewed versus baseline (E), and percent antibiotic prescriptions stopped at 'review and revise' versus baseline (F). Sites are identified numerically by the order in which they were randomised to implement. 70% target for essential people completing ARK training and >20 staff per 100 acute beds are arbitrary but were pre-specified for the funder as part of trial agreements and as part of pre-specified fidelity criteria. Audit data was unavailable at 2/39 hospitals (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.

Figure 2: Impact of the ARK intervention: immediate effect at implementation (A) and effect on year-on-year trend post- versus pre-implementation (B)

Note: top part of each panel shows antibiotic primary (bold) and secondary outcomes, and bottom part shows clinical primary (bold) and secondary outcomes. Effects only adjusted for the effects of COVID-19 shown in grey, and fully adjusted effects (see Methods) in red where evidence of an association or otherwise in black. OR = Odds ratio (logistic regression), IRR = Incidence rate ratio (negative binomial regression), SHR = subhazard ratio (competing risks regression)

Figure 3: Total antibiotic DDDs/admission (co-primary endpoint); immediate effect at implementation, overall (A) and by implementation fidelity (B), effect on year-on-year trend post- versus pre-implementation, overall (C) and by implementation fidelity (D)

Note: sites identified numerically by the order in which they were randomised to implement, and ordered by the number of fidelity criteria achieved (Table S1). IRR = incidence rate ratio. The size of the symbols in all panels reflects the precision of each estimate (inverse of the within-hospital variance).

Figure 4: Adjusted 30-day mortality (co-primary endpoint); immediate effect at implementation, overall (A) and by implementation fidelity (B), effect on year-on-year trend post- versus pre-implementation, overall (C) and by implementation fidelity (D)

Note: sites identified numerically by the order in which they were randomised to implement, and ordered by the number of fidelity criteria achieved (Table S1). IRR = incidence rate ratio. The size of the symbols in all panels reflects the precision of each estimate (inverse of the within-hospital variance).

Figure 5: Comparison of intervention effects on 30-day mortality and total antibiotic DDDs/admission, immediate effect at implementation (A) and effect on year-on-year trend post- versus pre-implementation (B)

Table 1: Site characteristics

[1] See **Figure S3**; excludes site 3 which was not included in analyses of antibiotic use (see Supplmentary Methods); includes 2 sites that shared hospital-level DDDs due to limitations posed by local pharmacy information systems (sites 22 and 30)
[2] Antibiotics in this category may be considered either Access or Watch depending on indication. Since indication was unknown, they were analysed separately
[3] Not required for pilot sites: treated as achieved in analysis.
[4] Site 3 excluded from analyses of antibiotic use, see **Supplementary Methods**