# Prophylactic antibiotics after acute stroke for reducing pneumonia in patients with dysphagia (STROKE-INF): a prospective, cluster-randomised, open-label, masked endpoint, controlled clinical trial

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## Summary

**Background** Post-stroke pneumonia is associated with increased mortality and poor functional outcomes. This study assessed the effectiveness of antibiotic prophylaxis for reducing pneumonia in patients with dysphagia after acute stroke.

**Methods** We did a prospective, multicentre, cluster-randomised, open-label controlled trial with masked endpoint assessment of patients older than 18 years with dysphagia after new stroke recruited from 48 stroke units in the UK, accredited and included in the UK National Stroke Audit. We excluded patients with contraindications to antibiotics, pre-existing dysphagia, or known infections, or who were not expected to survive beyond 14 days. We randomly assigned the units (1:1) by computer to give either prophylactic antibiotics for 7 days plus standard stroke unit care or standard stroke unit care only to patients clustered in the units within 48 h of stroke onset. We did the randomisation with minimisation to stratify for number of admissions and access to specialist care. Patient and staff who did the assessments and analyses were masked to stroke unit allocation. The primary outcome was post-stroke pneumonia in the first 14 days, assessed with both a criteria-based, hierarchical algorithm and by physician diagnosis in the intention-to-treat population. Safety was also analysed by intention to treat. This trial is closed to new participants and is registered with isrctn.com, number ISRCTN37118456.

**Findings** Between April 21, 2008, and May 17, 2014, we randomly assigned 48 stroke units (and 1224 patients clustered within the units) to the two treatment groups: 24 to antibiotics and 24 to standard care alone (control). 11 units and seven patients withdrew after randomisation before 14 days, leaving 1217 patients in 37 units for the intention-to-treat analysis (615 patients in the antibiotics group, 602 in control). Prophylactic antibiotics did not affect the incidence of algorithm-defined post-stroke pneumonia (71 [13%] of 564 patients in antibiotics group *vs* 52 [10%] of 524 in control group; marginal adjusted odds ratio [OR] 1·21 [95% CI 0·71–2·08], p=0·489, intraclass correlation coefficient [ICC] 0·06 [95% CI 0·02–0·17]. Algorithm-defined post-stroke pneumonia could not be established in 129 (10%) patients because of missing data. Additionally, we noted no differences in physician-diagnosed post-stroke pneumonia between groups (101 [16%] of 615 patients *vs* 91 [15%] of 602, adjusted OR 1·01 [95% CI 0·61–1·68], p=0·957, ICC 0·08 [95% CI 0·03–0·21]). The most common adverse events were infections unrelated to post-stroke pneumonia (mainly urinary tract infections), which were less frequent in the antibiotics group (22 [4%] of 615 *vs* 45 [7%] of 602; OR 0·55 [0·32–0·92], p=0·02). Diarrhoea positive for *Clostridium difficile* occurred in two patients (<1%) in the antibiotics group and four (<1%) in the control group, and meticillin-resistant *Staphylococcus aureus* colonisation occurred in 11 patients (2%) in the antibiotics group and 14 (2%) in the control group.

**Interpretation** Antibiotic prophylaxis cannot be recommended for prevention of post-stroke pneumonia in patients with dysphagia after stroke managed in stroke units.

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## Introduction

Post-stroke pneumonia occurs in 10% of patients after an acute stroke, and is associated with a trebled increase in mortality.[1–3] Dysphagia, which occurs in 50–55% of patients after a stroke, is an important risk factor for post-stroke pneumonia; the prevalence of post-stroke pneumonia in patients with dysphagia is 16–19%, compared with 2–8% prevalence in those without dysphagia.[4] Prophylactic antibiotics might decrease the risk of post-stroke penumonia,[5] mortality, and disability in such patients but could also increase antibiotic-related infections.[6]

Pooled data from 506 stroke patients[5] showed a 14% reduction in all infections with prophylactic antibiotics but their effectiveness in reducing post-stroke pneumonia, mortality, and disability was equivocal. Findings from the Preventive Antibiotics in Stroke Study (PASS)[7] showed a significant reduction in infections with

## Research in context

### Evidence before this study

We searched PubMed, Embase, ClinicalTrials.gov, and ISRCTN.org for trials of any design of prophylactic or preventive antibiotics in patients with acute stroke (any setting). We identified one observational study, and two completed randomised clinical trials and three in progress, which showed that first, post-stroke pneumonia was common and associated with high mortality, and second, effectiveness of prophylactic antibiotics was equivocal. Our updated search of the scientific literature in October, 2014, showed five completed trials pooled in a Cochrane meta-analysis (published in 2012), which showed that preventive antibiotics reduced infections (relative risk [RR] 0·58, 95% CI 0·43–0·79) but had little effect on mortality (0·85, 0·47–1·51) and dependence (0·67, 0·32–1·43). Since the review, the Preventive Antibiotics in Stroke Study (PASS) in 2538 patients showed that intravenous ceftriaxone given for 4 days reduced infections but did not improve functional outcomes at 3 months (published in 2015). In addition to the study reported in this paper, a trial is in progress (STRAWINSKI [NCT01264549]), comparing procalcitonin-guided antibiotic treatment with standard care in 230 patients. This study has completed recruitment but the findings have not yet been reported.

### Added value of this study

Published studies include 30–40% of patients with mild strokes and no dysphagia, for whom the risk of aspiration and the benefit of prevention are low. Many studies did not control either for the quality of stroke unit care (known to reduce post-stroke pneumonia) or allow for the variations in local antibiotic policies (which determine choice of agent in clinical settings). Only PASS assessed the incidence of *Clostridium difficile* diarrhoea, an important issue in antibiotic stewardship. Detection bias in previous studies was minimised by masked adjudication to reduced false-positive diagnoses of post-stroke pneumonia. This method does not adjust for false-negative disease missed on initial assessment. Finally, the confounding effect of higher mortality on length-of-stay comparisons was not adjusted in previous studies. This study included only patients at high risk of aspiration managed on specialist stroke units. It allowed for local antibiotic policies to be followed rather than prescribe a specific antimicrobial. A criteria-driven algorithm for diagnosis of post-stroke pneumonia applied to the whole dataset masked to allocation, thus minimising both false-positive and false-negative diagnoses. Comparisons of admissions to hospital were undertaken with death as a competing risk. The study showed that prophylactic antibiotics do not reduce post-stroke pneumonia, mortality, or dependence but might increase the length of hospital stay and poor outcomes in patients after acute stroke with dysphagia who are managed on specialist stroke units.

### Implications of all the available evidence

Evidence is against the routine use of antibiotics for prophylaxis against post-stroke pneumonia and suggests judicious use in stroke patients managed on stroke units, even if at high aspiration risk.

ceftriaxone but no effect on functional outcome scores. These studies were heterogeneous in size; some included patients with mild strokes and low risk of post-stroke pneumonia, some were not controlled for quality of stroke care (which is known to reduce post-stroke pneumonia[8]), and only PASS has assessed the incidence of *Clostridium difficile* toxin (CDT)-positive diarrhoea. Existing guidelines do not lend support to the use of prophylactic antibiotics in patients who have had a stroke.[9] Therefore, the aim of our study was to assess the effectiveness of prophylactic antibiotics for reducing incidence of post-stroke pneumonia, mortality, and admissions to hospital, and improving functional outcome in patients after acute stroke with dysphagia.

## Methods

### Study design and participants

In this prospective, multicentre, cluster-randomised, open-label controlled trial with masked endpoint assessment (STROKE-INF), we randomly assigned 48 UK stroke units (1:1) to give patients either prophylactic antibiotics for 7 days plus standard stroke unit care or standard stroke unit care only. We invited stroke units to complete the Expression of Interest forms through the National Institute for Health Research (NIHR) Stroke Research Network (SRN) trials office. Patients in selected units or their next of kin were approached by SRN research coordinators to check their eligibility and provide patient information sheets before consent. Units were eligible if they were accredited and included in the UK National Stroke Audit.[10] We purposely chose a cluster-randomised trial design to minimise between-group contamination of an open intervention in the same setting. Patients were eligible if they were aged older than 18 years, had a confirmed diagnosis of new stroke (ischaemic or haemorrhagic) with onset of symptoms within 48 h at recruitment, and were unsafe to swallow because of impaired consciousness, failed bedside swallow test, or presence of a nasogastric tube. We excluded those with contraindications to antibiotics, pre-existing dysphagia, pyrexia, known infection at admission, use of antibiotics within the past 7 days, pregnancy, or those who were not expected to survive beyond 14 days. Patients or their next of kin provided written informed consent or assent, respectively. The study was approved by the UK Medicines and Healthcare products Regulatory Agency (EudraCT number 2007-004298-24) and the National Research Ethics Committee (08/H0803/1).

### Randomisation and masking

We did the randomisation using a minimisation algorithm,[11] stratifying centres for number of stroke admissions per year and proportion admitted directly to specialist care. Randomisation was computer generated and done away from the trial office.

Patients, research staff obtaining data, and statisticians undertaking analyses of the outcome data were unaware of stroke unit allocation. Baseline data were obtained by Clinical Research Network staff who were not involved in patient care. Detection bias for the primary outcome between groups was minimised by a criteria-based algorithm for diagnosis of post-stroke pneumonia, applied blind to the whole dataset. Mortality and functional status at 90 days were assessed by trial office researchers masked to allocation. The statistical analysis plan was written without knowledge of outcome data.

### Procedures

All patients received recommended care for dysphagia.[9] Antibiotic choice at intervention centres conformed to local antibiotic policy, but amoxicillin or co-amoxiclav, together with clarithromycin for 7 days were recommended if no restrictions applied.[12] Antibiotics were initiated within 48 h of symptom onset at a dose and by a route according to local guidelines. Physicians were allowed to treat suspected infections with additional antibiotics.

Patient characteristics were recorded on enrolment. We assessed stroke severity with the National Institutes of Health Stroke Scale (NIHSS), scores ranging from 0 (no neurological deficit or stroke) to 42 (severe deficit), at baseline and 14 days or discharge. Dysphagia-trained nursing staff assessed swallowing using the standard bedside swallowing assessment test consisting of measuring levels of consciousness, oromotor function, and consumption of water or food.[13] Respiratory rate, temperature, chest symptoms and signs, white blood cell counts, and C-reactive protein were recorded at baseline, 2, 4, 7, 10, and 14 days by the treating clinician. Local guidelines for investigations were adhered to for suspected post-stroke pneumonia. We assessed mortality, functionality, and quality of life on day 90, and physician-diagnosed new pneumonia from day 15 to day 90. Stroke severity was measured at baseline, day 7, and day 14 (or at discharge if earlier than 14 days). We measured liver and renal enzymes (and did other laboratory tests) at baseline, 2, 7, 10, and 14 days.

Patients in hospitals in the UK are routinely screened for meticillin-resistant *Staphylococcus aureus* (MRSA) and CDT if they develop diarrhoea. We defined *C difficile* infection as diarrhoea in combination with a positive CDT test and ascertained the diagnosis with hospital infection surveillance records for 1 month after intervention. We defined MRSA colonisation as new positive isolates between hospital admission and discharge.

### Outcomes

The primary outcome was post-stroke pneumonia, determined by a statistician masked to allocation, using a criteria-based hierarchical algorithm. Additionally, a diagnosis of pneumonia made by the local treating physician was also recorded as a co-primary outcome. The algorithm was derived from criteria for pneumonia from the Centres for Disease Control and Prevention[14] that assess eight clinical or laboratory findings at six timepoints (baseline, 2, 7, 10, and 14 days) for (1) patient's temperature of at least 37·5°C or higher on two consecutive measurements or one measurement of 38·0°C or higher and (2) a respiratory rate of 20 breaths per min or more, or cough and breathlessness, or purulent sputum, and (3) a white blood cell count that is higher than $11{\cdot}0\times10^9$/L, or chest infiltrates on radiograph, or positive sputum culture or microbiology, or positive blood culture.

Secondary clinical endpoints included NIHSS score at 14 days, death at 14 and 90 days, functional outcome at 90 days defined by the modified Rankin Scale (mRS) which ranges from 0 (no symptoms) to 6 (death), CDT-positive diarrhoea, MRSA colonisation, health-related quality of life measured at 90 days with the five domains of the European Quality of Life (EuroQoL) scale, physician-diagnosed new pneumonia at baseline, 2, 7, 10, and 14 days, length of stay in hospital, and time to death.

As well as being outcomes, physician-diagnosed post-stroke pneumonia, CDT diarrhoea, and MRSA colonisation were serious adverse events that required obligatory reporting to the trial office. We also recorded stroke extension, gastrointestinal bleed, cardiac events, increased liver or renal enzymes, and transfer to intensive care as serious adverse events.

### Statistical analysis

In a pooled analysis of 881 patients,[4] post-stroke pneumonia occurred in 87 (22%) of 400 patients with dysphagia and in 29 (6%) of 491 without dysphagia. We calculated that ten clusters of 40 patients each would give 80% power to detect an absolute difference between 22% and 10%, with an intraclass correlation coefficient (ICC) of 0·05.[15] We recalculated the sample size to decrease cluster size, and increase the number of centres because of slow recruitment. We set a recruitment target of 1450 to allow an attrition rate of 25%; the actual attrition rate was 3%, which needed 1200 participants. Results from a post-hoc power analysis suggest that, taking into account the actual missing rate, reported ICC, and average cluster size, this study would have been powered to detect an absolute difference between control and treatment groups of 10·5%, with 80% power and a two-sided 5% type I error.

Primary and safety analyses were intention to treat. We used a generalised mixed model with post-stroke pneumonia as the primary outcome to account for patients nested within centres; details for the calculation of post-stroke pneumonia are provided in the appendix. A fixed

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contrast for treatment effect was included to establish the mean treatment effectiveness for the antibiotics group versus the control group. Other patient-level covariates included age, sex, baseline NIHSS score, premorbid mRS score, stroke type, previous strokes, thrombolysis, chronic lung disease, and smoking. Centre-level covariates were the number of admissions for stroke per year and quartile ranking of the centre in the 2012 national stroke audit, which took into consideration casemix and quality of care.[16] To account for missingness, all outcome data (primary and secondary) was included by multiple imputation via chained equations under the assumption of missingness at random. 25 imputations of data were generated and combined with Rubin's rules. Variables in the imputation model included all variables in the primary analysis model because no others were identified as predictive of missingness. We did sensitivity analyses to check the effect of missingness on the results. We used the marginal (or population) odds ratio (OR) because population estimates are more likely to show the true effect of treatment.[17] The ICC was calculated with 95% CIs.

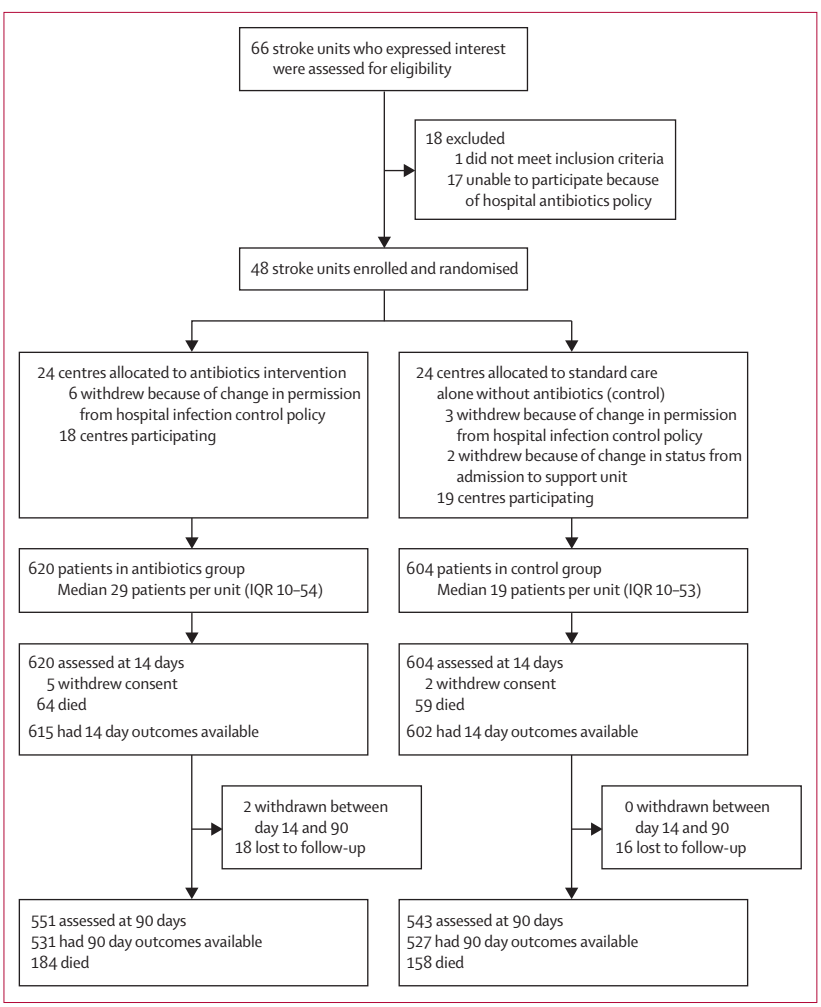


***Figure 1:*** **Trial profile**

We used similar methods and prognostic variables to analyse secondary outcomes. We assessed all-cause mortality as a binary outcome. The mRS was dichotomised to good (0–2) and poor outcome (3–6), and

| | Antibiotics group (n=615) | Control group (n=602) |
|---|---|---|
| Age (years) | 77·7 (11·9) | 78·0 (12·2) |
| Missing data | 0 | 1 (0·2%) |
| Sex | | |
| Male | 265 (43%) | 258 (43%) |
| Female | 347 (56·5%) | 343 (56·8%) |
| Missing data | 3 (0·5%) | 1 (0·2%) |
| Type of stroke | | |
| Ischaemic | 546 (89%) | 545 (91%) |
| Haemorrhagic | 69 (11%) | 56 (9%) |
| Missing data | 0 | 1 (0·2%) |
| Thrombolysis | 192 (31%) | 205 (34%) |
| Missing data | 0 | 3 (0·5%) |
| Nasogastric tube | 164 (27%) | 134 (22%) |
| Missing data | 0 | 0 |
| Score on National Institutes of Health Stroke Scale* | 15 (9–20) | 14 (9–20) |
| Missing data | 1 (0·2%) | 3 (0·5%) |
| Comorbidities | | |
| Hypertension | 433 (70%) | 404 (67%) |
| Diabetes | 105 (17%) | 97 (16%) |
| Atrial fibrillation | 227 (37%) | 221 (37%) |
| Chronic obstructive pulmonary disease | 48 (8%) | 40 (7%) |
| Previous strokes | 176 (29%) | 176 (29%) |
| Missing data | 0 | 1 (0·2%) |
| Current smoker | 96 (16%) | 88 (15%) |
| Missing data | 18 (3%) | 10 (2%) |
| Premorbid score of 0–2 on the modified Rankin Scale before onset of stroke† | 490 (80%) | 498 (83%) |
| Missing data | 9 (1%) | 9 (1%) |
| Antibiotic use on days 0–7 after stroke | | |
| Any antibiotic at least once | 602 (98%) | 207 (34%) |
| Any antibiotic at least three times | 536 (87%) | 62 (10%) |
| Co-amoxiclav or amoxicillin, plus clarithromycin | 477 (78%) | 1 (0·2%) |
| Co-amoxiclav alone | 53 (9%) | 41 (7%) |
| Amoxicillin alone | 36 (6%) | 9 (1%) |
| Amoxicillin plus metronidazole | 22 (4%) | 29 (5%) |
| Cephalosporins | 14 (2%) | 4 (0·7%) |
| Other antibiotics‡ | 81 (13%) | 123 (20%) |
| Missing data | 0 | 0 |

Data are mean (SD), n (%), or median (IQR). *Maximum score (worst outcome) is 42 (severe stroke). †Maximum score (worst outcome) is 6 (death). ‡Includes second-line antibiotics for post-stroke pneumonia; ie, tazocin (piperacillin with tazobactam), gentamicin, meropenem, and vancomycin, and antibiotics for urinary tract infections and other infections; ie, trimethoprim, ciprofloxacin, doxycycline, and flucloxacillin.

***Table 1:*** **Baseline patient characteristics of the intention-to-treat population**

we assessed mRS shift using ordinal regression of the entire range (0–6) and checked it by fitting a marginal model and applying Brant's parallel regression test.[18] NIHSS score at 14 days was assessed with a baseline adjusted linear mixed model. We assessed group differences in length of hospital stay and time to death using Fine and Gray's cumulative incidence curve model adjusted for clustering,[19] with death or discharge as competing risk. For the logistic and ordinal regressions we included a random intercept for each centre to allow

| | Antibiotics group | Control group | Differences between groups | | Adjusted differences between groups | |
|---|---|---|---|---|---|---|
| | | | Odds ratio (95% CI) | p value | Adjusted odds ratio (95% CI)* | p value |
| **Primary outcome of post-stroke pneumonia at 14 days** | | | | | | |
| Algorithm diagnosed | 71/564 (13%) | 52/524 (10%) | 1·35 (0·79–2·29) | 0·269 | 1·21 (0·71–2·08) | 0·489 |
| Physician diagnosed† | 101/615 (16%) | 91/602 (15%) | 1·03 (0·66–1·61) | 0·889 | 1·01 (0·61–1·68) | 0·957 |
| **Secondary outcomes** | | | | | | |
| Score on National Institutes of Health Stroke Scale at 14 days‡ | 11·7 (8·1) | 10·1 (7·7) | 1·69 (0·47–2·91)§ | 0·007 | 1·3 (0·6–2·01)§ | 0·001 |
| All-cause mortality at 14 days | 62/596 (10%) | 56/587 (10%) | 1·05 (0·67–1·64) | 0·846 | 0·95 (0·62–1·44) | 0·796 |
| All-cause mortality at 90 days | 184/595 (31%) | 158/586 (27%) | 1·2 (0·93–1·54) | 0·164 | 1·22 (0·9–1·64) | 0·204 |
| Score of 0–2 on the modified Rankin Scale at 90 days | 109/595 (18%) | 121/586 (21%) | 0·89 (0·66–1·2) | 0·436 | 0·87 (0·6–1·24) | 0·448 |
| Score on the modified Rankin Scale at 90 days | | | | | | |
| 0 (no symptoms at all) | 14/595 (2%) | 20/586 (3%) | .. | .. | .. | .. |
| 1 (no disability despite symptoms) | 38/595 (6%) | 40/586 (7%) | .. | .. | .. | .. |
| 2 (slight disability) | 57/595 (10%) | 61/586 (10%) | .. | .. | .. | .. |
| 3 (moderate disability needing some help) | 79/595 (13%) | 89/586 (15%) | .. | .. | .. | .. |
| 4 (severe disability needing help with daily living) | 110/595 (18%) | 117/586 (20%) | .. | .. | .. | .. |
| 5 (severe disability, bed bound, and incontinent) | 113/595(19%) | 101/586 (17%) | .. | .. | .. | .. |
| 6 (death) | 184/595 (31%) | 158/586 (27%) | .. | .. | .. | .. |
| CDT-positive diarrhoea† | 2/615 (0·3%) | 4/602 (0·7%) | 0·49 (0·04–3·33) | 0·45 | .. | .. |
| MRSA colonisation† | 11/615 (2%) | 14/602 (2%) | 0·76 (0·31–1·82) | 0·55 | .. | .. |
| EuroQoL at 90 days | | | | | | |
| Problems with mobility¶ | 289/411 (70%) | 296/428 (69%) | 1·05 (0·74–1·48) | 0·794 | 1·08 (0·77–1·52) | 0·657 |
| Problems with self-care¶ | 292/411 (71%) | 299/428 (70%) | 1·03 (0·75–1·4) | 0·872 | 1·06 (0·75–1·50) | 0·749 |
| Problems with usual activities¶ | 349/409 (85%) | 364/424 (86%) | 0·96 (0·62–1·49) | 0·857 | 0·96 (0·62–1·49) | 0·854 |
| Pain or discomfort¶ | 217/405 (54%) | 207/418 (50%) | 1·21 (0·87–1·69) | 0·255 | 1·09 (0·80–1·47) | 0·593 |
| Anxiety or depression¶ | 211/398 (53%) | 214/415 (52%) | 1·02 (0·77–1·34) | 0·893 | 1·06 (0·80–1·42) | 0·673 |
| New pneumonia from 15 to 90 days¶ | 56/339 (17%) | 56/396 (14%) | 1·05 (0·7–1·58) | 0·81 | 1·03 (0·65–1·62) | 0·905 |
| Time to hospital discharge (days) | 26 (12–55) | 19 (9–43) | 0·81 (0·66–1·03)‖ | 0·081 | 0·82 (0·65–1·02)‖ | 0·074 |
| Time to death (days) | 24 (9–64); 34·2 (64·6) | 26 (8–64); 39·6 (40·0) | 1·30 (1·00–1·70)‖ | 0·051 | 1·33 (1·01–1·75)‖ | 0·045 |
| **Serious adverse events** | | | | | | |
| Infections unrelated to post-stroke pneumonia | 22/615 (4%) | 45/602 (7%) | 0·55 (0·32–0·92) | 0·02 | .. | .. |
| Urinary tract infections | 15/615 (2%) | 39/602 (6%) | .. | .. | .. | .. |
| Others | 7/615 (1%) | 6/602 (1%) | .. | .. | .. | .. |
| Systemic events | | | | | | |
| CT-confirmed stroke extension | 23/615 (4%) | 22/602 (4%) | 1·03 (0·54–1·96) | 0·98 | .. | .. |
| Other neurological events including intracranial haemorrhage | 14/615 (2%) | 12/602 (2%) | 1·15 (0·49–2·78) | 0·84 | .. | .. |
| Gastrointestinal bleed | 5/615 (0·8%) | 6/602 (1%) | 0·81 (0·2–3·23) | 0·77 | .. | .. |
| Cardiac (MI, HF, pulmonary oedema) | 15/615 (2%) | 11/602 (2%) | 1·35 (0·57–3·23) | 0·55 | .. | .. |
| Raised hepatic or renal enzymes | 8/615 (1%) | 7/602 (1%) | 1·11 (0·35–3·7) | 0·89 | .. | .. |
| Transfer to intensive care | 6/615 (1%) | 4/602 (0·7%) | 1·47 (0·35–7·14) | 0·75 | .. | .. |
| Miscellaneous | 6/615 (1%) | 8/602 (1%) | 0·73 (0·21–2·33) | 0·60 | .. | .. |

Data are n/N (%), mean (SD), or median (IQR). ..=not applicable. EuroQoL=European Quality of Life scale. CDT=*Clostridium difficile* toxin. MRSA=meticillin-resistant *Staphylococcus aureus*. MI=myocardial infarction. HF=heart failure. *Adjusted for age, sex, premorbid score on the modified Rankin Scale (mRS), severity and type of stroke, thrombolysis, chronic lung disease, smoking, and centre characteristics. †Also counted as a serious adverse event. ‡Maximum score (worst outcome) is 42 (severe stroke). §Mean difference between scores on the National Institutes of Health Stroke Scale (NIHSS) from linear mixed models with treatment and treatment-by-day interaction, adjusted for baseline NIHSS score, age, sex, premorbid mRS score, severity and type of stroke, thrombolysis, chronic lung disease, smoking, centre characteristics, random effects of patient (repeated measures across day 7 and day 14), and stroke unit. ¶EuroQoL score categories for patients reporting moderate or severe problems versus no problems. ‖Hazard ratio from the cumulative incidence curve model of time to event (death or hospital discharge as a competing risk) in patients receiving antibiotic prophylaxis compared with control patients.

***Table 2:*** **Primary, secondary, and safety endpoints**

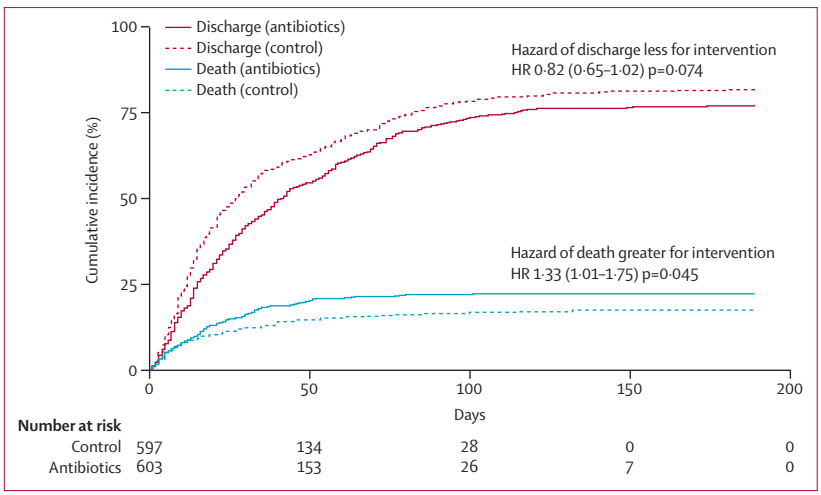


***Figure 2:*** **Cumulative incidence of time to hospital discharge and time to death**
HR=hazard ratio.

for differential statistical dependencies for patients within centres versus between centres.

We did subgroup analyses for the primary outcome as specified in the protocol. These included assessment of the effectiveness of antibiotic prophylaxis according to age (<80 years *vs* ≥80 years), baseline stroke severity on the NIHSS scale (0–5, 6–15, 16–25, 26–42), thrombolysis, pre-morbid stroke mRS (0–2 *vs* 3–5) and centre ranking (higher or lower than the national median). We did sensitivity analyses using more liberal thresholds for temperature, and also using physician-defined post-stroke pneumonia, which takes into account subjective patient assessment. We analysed antibiotic use in both groups to assess crossover of intervention and analysed outcomes in patients receiving 1, 3, or more than 3 days of antibiotics in both groups. Baseline characteristics and outcomes were summarised by treatment group. Analyses were done with R version 3.0[20] of Stata software (StataCorp 2009. Stata Statistical Software Release 11. College Station, TX, USA). Trial data were verified against source data by a monitor from the King's Healthcare Partners Clinical Trials Office. This trial is registered with isrctn.com, number ISRCTN37118456.

### 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. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Results

Between April 21, 2008, and May 17, 2014, we randomly assigned 48 stroke units (and 1224 patients clustered within the units) to the two treatment groups: 24 to antibiotics and 24 to standard care alone (control; figure 1). 11 units and seven patients withdrew after randomisation before 14 days (withdrawn patients did not receive any treatment), leaving 1217 patients in 37 units for the intention-to-treat analysis (615 in the antibiotics group and 602 in the control group). No patients were lost to follow-up at the primary endpoint; two patients in the antibiotic group withdrew consent and 16 (3%) in the control group and 18 (3%) in the antibiotic group were not contactable for the 90 day follow-up.

Baseline demographic characteristics, risk factor profiles, and stroke severity are in table 1. 1216 (>99%) of 1217 patients had a definitive stroke diagnosis, 1091 (90%) of whom had cerebral infarction and 125 (10%) had cerebral haemorrhage. Thrombolytic therapy was given to 397 (36%) of 1091 patients with cerebral infarction. The median NIHSS score at randomisation was 15 (IQR 9–20) and 298 (25%) patients had nasogastric tubes. Prophylactic antibiotics were given to nearly all those in the antibiotics group, most of whom received the recommended regimen. 144 (24%) of 602 patients in the control group received any antibiotic at least once in the first week for proven infections and 63 (10%) for pyrexia of undefined cause (table 1).

At 14 days, post-stroke pneumonia was diagnosed by algorithm in 123 (11%) of 1088 patients (table 2). A definitive diagnosis could not be established in 129 (10%) patients because of missing data (appendix). No significant differences were apparent between any of the subcomponents of the algorithm (appendix). Prophylactic antibiotics did not reduce the incidence of algorithm-diagnosed post-stroke pneumonia, even after we adjusted the results for patient, stroke, and centre characteristics (marginal adjusted OR 1·21 [95% CI 0·71–2·08], p=0·489; ICC 0·06 [95% CI 0·02–0·17]; table 2). The incidence of physician-diagnosed post-stroke pneumonia at 14 days was higher (occurring in 192 [16%] of 1217 patients), but again no differences were noted between the two treatment groups (marginal adjusted OR 1·01 [95% CI 0·61–1·68], p=0·957; ICC 0·08 [95% CI 0·03–0·21]; table 2). We assessed the agreement between post-stroke pneumonia diagnosed by algorithm and diagnosed by physician in the 1088 patients with data available. Post-stroke pneumonia was judged absent or present by both in 885 (81%) patients, present on algorithm only in 75 (7%), and present on physician diagnosis only in 128 (12%) (agreement: actual 0·81, expected 0·76; κ 0·22 [95% CI 0·14–0·29]).

Sensitivity analyses with more liberal criteria for temperature, physician-defined post-stroke pneumonia, duration of antibiotic use, and different outcome assumptions for the 10% of patients missing a diagnosis did not show significant differences in outcomes between patients in the control group and the antibiotics group (appendix).

All-cause mortality occurred in 118 (10%) of 1183 patients at 14 days and 342 (29%) of 1181 patients at 90 days; we noted no differences in mortality rates between treatment groups. There were no differences in the percentage of patients with good functional outcomes (mRS 0–2) but

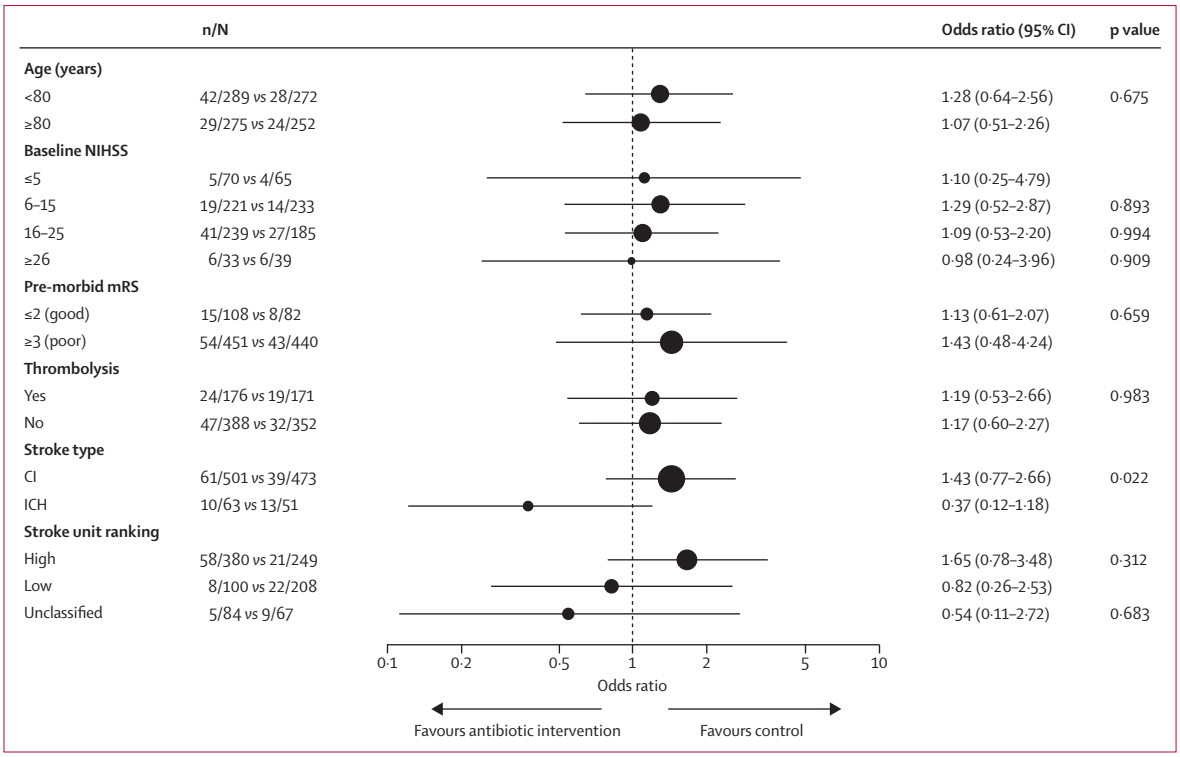


***Figure 3:*** **Treatment effect on the primary outcome stratified by subgroups**
p value is for interaction. NIHSS=National Institute of Health Stroke Scale score. mRS=modified Rankin Scale. CI=cerebral infarction. ICH=intracerebral haemorrhage. Stroke unit ranking=higher or lower than the national median in the 2012 National Stroke Audit. Unclassified=centres which did not submit data for the audit. The size of the circle denoting the point estimate shows the size of the subgroup.

the distribution of mRS scores shifted towards worse outcomes at 90 days in the intervention group (adjusted OR 1·26 [95% CI 1·01–1·57], p=0·039; table 2). We noted a significant association between physician-diagnosed post-stroke pneumonia and worse functional outcome at 90 days (p=0·001) but not for algorithm-diagnosed post-stroke pneumonia (appendix). NIHSS score at 14 days was slightly but significantly higher in the antibiotics group than in the control group (adjusted difference 1·4 [95% CI 0·6–2·1], table 2; p=0·001). No between-group differences were noted for the outcomes of CDT-positive diarrhoea, MRSA colonisation, EuroQoL scores at 90 days, or chest symptoms from 15–90 days (table 2). Results from the competing risks analyses of cumulative incidence of death and length of hospital stay suggested that patients in the antibiotics group were significantly more likely to die throughout follow-up than patients in the control group (p=0·045; figure 2). Patients in the antibiotics group had longer stays in hospital than control patients, but this difference was not significant (table 2, figure 2).

Treatment effect for the incidence of algorithm-defined post-stroke pneumonia at 14 days did not differ significantly in the predefined subgroups of age, premorbid functional status, baseline stroke severity, thrombolysis, or performance ranking of stroke units (figure 3). There was a significant interaction between prophylactic antibiotic use and the type of stroke, suggesting a tendency for patients who have had a haemorrhagic stroke to benefit from the treatment; however, the OR in both the cerebral infarction group and the intracerebral haemorrhage group was not significantly different from 1. No interaction was noted between intervention and thrombolysis for functional outcome at 90 days (appendix).

Few adverse events occurred in both treatment groups (table 2). Prophylactic antibiotics significantly reduced the number of non-post-stroke pneumonia infections compared with control (p=0·02; table 2), especially urosepsis. The incidence of CDT-positive diarrhoea and MRSA colonisation and systemic serious adverse events were low and equal in both groups.

## Discussion

We have shown that antibiotic prophylaxis did not reduce post-stroke pneumonia or mortality in patients after acute stroke with dysphagia managed in stroke units. Additionally, prophylactic antibiotics might increase the length of hospital stay and poor outcomes in these patients.

Post-stroke pneumonia in this study was measured in two different ways: first, by the masked application of predefined criteria applied to the whole patient group giving a frequency of 11% at 14 days, and second, by physician diagnosis, which identified this infection in

16% of patients at 14 days. These rates are less than those reported in the scientific literature, even in studies that used standard criteria.[21] Although algorithms might underdiagnose post-stroke pneumonia, findings from studies[22] show that inter-rater reliability for diagnosing this disorder is also low among clinicians (κ 0·3), even with standardised criteria. Many physicians use fever and severe stroke as the main criteria, thus overdiagnosing incidence of post-stroke pneumonia.[23] An algorithm-based approach to diagnosis might increase accuracy but needs validation against other diagnostic measures. This study and others[21–23] suggest that the true incidence is uncertain because of obscure presentation and an absence of adequate clinical methods for accurate and definitive diagnosis after stroke.

Antibiotic prophylaxis did not reduce post-stroke pneumonia, 90 day mortality, or functional disability. Sensitivity analyses or analyses with prespecified subgroups did not show benefits of prophylactic antibiotics. The most likely explanation is that prophylactic antibiotics do not add to existing preventive measures such as positioning, regular suction, swallowing techniques, modified diets, and early initiation of antibiotics in patients with suspected post-stroke pneumonia in specialist stroke units.[8] Crossover of treatment might be another reason—a low threshold for antibiotics in stroke patients might occur in real-world practice but can confound the benefit of prophylactic antibiotics. However, analyses based on antibiotics use in both groups did not change our findings. Prophylaxis is unlikely to have an effect if post-stroke pneumonia is a marker of stroke severity rather than an independent determinant of outcome as reported in some studies.[24] Post-stroke pneumonia might also be a respiratory syndrome resulting from complex bacterial, chemical, and immunological causes that might not be prevented by antibiotics alone.[7] Prophylactic antibiotic use seemed to be associated with a reduced incidence of post-stroke pneumonia in patients who had had a haemorrhagic stroke—however, this finding needs to be interpreted with care because, with the small numbers, the OR in both the stroke type groups (cerebral infarction and intracerebral haemorrhage) did not differ from 1.

Antibiotic prophylaxis was associated with longer hospital stay than for controls. Long stays in hospital or poor functional outcome could result from antibiotic-related infections,[25] but less than 1% of patients developed *C difficile* diarrhoea in this study. This low frequency is similar to the proportion of 0·2% noted with antibiotic intervention in the PASS study,[7] and is unlikely to have resulted from under-reporting because of ascertainment against mandatory *C difficile* surveillance records at centres. Possible explanations for the low incidence include: a delay in discharge until completion of the prophylactic antibiotic regimen, although delay was not a protocol requirement; delays in diagnosis of post-stroke pneumonia because prophylactic antibiotics might have masked early symptoms; false perceptions of adequacy of continued antibiotic treatment—second-line antibiotics were started in all cases of physician-diagnosed post-stroke pneumonia in controls but in only 81% of patients on prophylactic antibiotics (table 1); or breakthrough infections in the intervention group, which were more virulent or resistant to common antibiotics. These explanations should be interpreted cautiously because the total doses of antibiotics given to each patient, microbiology of post-stroke pneumonia, and infection with multidrug-resistant organisms other than MRSA were not recorded and are a limitation of the study.

Our study has other limitations. For example, selection bias, especially in a cluster-randomised trial, could result from patients at increased risk of post-stroke pneumonia being recruited preferentially to the antibiotic intervention group. However, we noted no differences in baseline characteristics between groups. Variations in the antimicrobial range of antibiotics allowed by the hospitals could have compromised the effectiveness of prophylaxis. The study replicated mainstream practices to make the findings generalisable and, despite variations, nearly 80% of the stroke units assigned to antibiotics used those recommended by the protocol. Open-intervention allocation can influence physician diagnosis of post-stroke pneumonia and other outcomes. This detection bias has been minimised by use of masked adjudication in previous studies. Although this method eliminates false-positive diagnoses of post-stroke pneumonia, it cannot include false-negative disease missed in reporting. On one hand, the algorithm method was applied to the whole masked dataset and did not have this limitation. On the other hand, the algorithm missed a diagnosis of post-stroke pneumonia in 10% of patients. If the frequencies suggested a substantial but smaller than expected difference in rates of disease occurrence between the groups, absence of power (type II error) could be an issue. However, the difference of 2·7%, in favour of the control group, suggests that 10% missing outcomes would not have changed the outcome of the study. Post-hoc power analyses show that, even after accounting for missingness, the study was sufficiently powered to detect an absolute difference of 10·5% or higher. Differences in mortality might bias any length-of-stay comparisons; mortality data were adjusted with competing risk analysis. Lower than predicted rates of post-stroke pneumonia and unequal cluster sizes could reduce power and underestimate the effect of the antibiotic intervention. The design error for unequal clusters is 3·4 compared with 2·15 for equal clusters; therefore, a study of 1217 patients would have 86·2% power at the 5% level to detect a significant treatment effect.[26]

In conclusion, prophylactic antibiotics do not reduce incidence of post-stroke pneumonia in patients after stroke with dysphagia, managed in stroke units with

guidelines for reducing aspiration and early treatment of post-stroke pneumonia. The routine use of antibiotics for prophylaxis against post-stroke pneumonia cannot be recommended and should be used judiciously for treatment in patients after stroke who are managed on stroke units, even if they are at a high risk of aspiration.

#### Contributors

LK did the overall trial management. LK, MG, and DS conceived and designed the study; AP also contributed to the design. SI contributed to trial coordination. LK, SI, IR-M, and JH contributed to data acquisition. LK, SI, MG, AP, IR-M, and JH contributed to data interpretation. MS contributed to the design of the database and electronic case report forms, and collated and cleaned the data. IR-M and JH contributed to the study analysis plan and data analysis. LK, SI, AP, IR-M, and JH drafted the report. MG, MS, and DS commented on the draft.

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#### Declaration of interests

We declare no competing interests.

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