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

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Summary

Background Adults hospitalised to a non-intensive care unit (ICU) ward with moderately severe community-acquired pneumonia are frequently treated with broad-spectrum antibiotics, despite Dutch guidelines recommending narrow-spectrum antibiotics. Therefore, we investigated whether an antibiotic stewardship intervention would reduce the use of broad-spectrum antibiotics in patients with moderately severe community-acquired pneumonia without compromising their safety.

Methods In this cross-sectional, stepped-wedge, cluster-randomised, non-inferiority trial (CAP-PACT) done in 12 hospitals in the Netherlands, we enrolled immunocompetent adults (≥18 years) who were admitted to a non-ICU ward and had a working diagnosis of moderately severe community-acquired pneumonia. All participating hospitals started in a control period and every 3 months a block of two hospitals transitioned from the control to the intervention period, with all hospitals eventually ending in the intervention period. The unit of randomisation was the hospital (cluster), and electronic randomisation (by an independent data manager) decided the sequence (the time of intervention) by which hospitals would cross over from the control period to the intervention period. Blinding was not possible. The antimicrobial stewardship intervention was a bundle targeting health-care providers and comprised education, engaging opinion leaders, and prospective audit and feedback of antibiotic use. The co-primary outcomes were broad-spectrum days of therapy per patient, tested by superiority, and 90-day all-cause mortality, tested by non-inferiority with a non-inferiority margin of 3%, and were analysed in the intention-to-treat population, comprising all patients who were enrolled in the control and intervention periods. This trial was prospectively registered at ClinicalTrials.gov, NCT02604628.

Findings Between Nov 1, 2015, and Nov 1, 2017, 5683 patients were assessed for eligibility, of whom 4084 (2235 in the control period and 1849 in the intervention period) were included in the intention-to-treat analysis. The adjusted mean broad-spectrum days of therapy per patient were reduced from 6·5 days in the control period to 4·8 days in the intervention period, yielding an absolute reduction of –1·7 days (95% CI –2·4 to –1·1) and a relative reduction of 26·6% (95% CI 18·0–35·3). Crude 90-day mortality was 10·9% (242 of 2228 died) in the control period and 10·8% (199 of 1841) in the intervention period, yielding an adjusted absolute risk difference of 0·4% (90% CI –2·7 to 2·4), indicating non-inferiority.

Interpretation In patients hospitalised with moderately severe community-acquired pneumonia, a multifaceted antibiotic stewardship intervention might safely reduce broad-spectrum antibiotic use.

Funding None.

Introduction

International guidelines recommend different empirical antibiotic treatments for patients with community-acquired pneumonia on the basis of disease severity. Community-acquired pneumonia can be classified as moderately severe on the basis of the need for hospital admission in a non-intensive care unit (ICU) ward (pragmatic classification); a pneumonia severity index of 3–4; or a confusion, urea, respiratory rate, blood pressure (CURB)-65 score of 2.[1] Empirical antibiotic treatments recommended for moderately severe community-acquired pneumonia include narrow-spectrum β-lactam monotherapy (eg, benzylpenicillin or amoxicillin),[2,3] β-lactam plus macrolide combination therapy,[4,5] and respiratory fluoroquinolone monotherapy.[5] One cluster-randomised study found that a strategy of preferred treatment with β-lactam monotherapy

Research in context

Evidence before this study

Antimicrobial stewardship aims to optimise antibiotic use without compromising patient outcomes. Using the search terms "antimicrobial stewardship" and "community-acquired pneumonia", we searched PubMed without language restrictions for studies published between database inception and Dec 1, 2020, evaluating the efficacy and safety of antimicrobial stewardship interventions for adult patients with non-severe community-acquired pneumonia. We excluded studies that only included children or patients with severe community-acquired pneumonia treated in intensive care units. Thus far, all studies evaluating the impact of antimicrobial stewardship interventions on patients with community-acquired pneumonia have been quasi-experimental or have not adequately evaluated the safety of the intervention. Concerns for safety might prevent the adoption of antimicrobial stewardship strategies into practice. To date, two randomised controlled trials have evaluated the efficacy of β-lactam monotherapy for community-acquired pneumonia. These trials showed non-inferior efficacy of β-lactam monotherapy compared with respiratory fluoroquinolone monotherapy in patients with mild-to-moderately severe community-acquired pneumonia. Despite these findings, confidence in narrow-spectrum β-lactam monotherapy is low in clinical practice, possibly due to fear of under-treating patients, resulting in low adherence to guideline recommendations.

Added value of this study

To our knowledge, this randomised trial was the first to evaluate the efficacy and safety of a multifaceted antimicrobial stewardship bundle based on proven effective stewardship interventions, comprising education, engaging opinion leaders, and audit and feedback of antibiotic use targeted towards health-care workers, in relation to patients with moderately severe community-acquired pneumonia. The intervention was intended to reduce the use of broad-spectrum antibiotics and increase the use of narrow-spectrum antibiotics.Our study built on evidence of the clinical safety of narrow-spectrum antibiotics for moderately severe community-acquired pneumonia. We found that the antimicrobial stewardship bundle reduced broad-spectrum antibiotic use in patients with moderately severe community-acquired pneumonia without compromising their safety.

Implications of all the available evidence

Our study adds to the already available evidence suggesting that antimicrobial stewardship interventions are efficacious in optimising antibiotic use. In addition, our results add to the existing evidence base regarding the efficacy of narrow-spectrum β-lactam monotherapy for patients with moderately severe community-acquired pneumonia, and thereby provide firm evidence to change clinical practice towards increased use of narrow-spectrum antibiotics, which will reduce antibiotic selective pressure for antimicrobial resistance.

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was non-inferior to strategies with fluoroquinolone monotherapy or β-lactam plus macrolide combination therapy for 90-day mortality.[6] However, in this study, β-lactam monotherapy mainly consisted of broad-spectrum β-lactams such as third-generation cephalosporins, despite Dutch guidelines recommending narrow-spectrum β-lactams.[1] Next to narrow-spectrum β-lactams, doxycycline is considered a first-line treatment for patients with mild community-acquired pneumonia and those treated in ambulatory care. Although doxycycline's spectrum of antibacterial activity is broader than that of narrow-spectrum β-lactams, it is still not active against most Gram-negative bacteria.[1] Antimicrobial stewardship might improve guideline adherence and reduce the use of broad-spectrum β-lactam antibiotics for the empirical treatment of patients with moderately severe community-acquired pneumonia.[7] However, high-quality evidence for equivalence in the clinical effectiveness of narrow-spectrum and broad-spectrum β-lactam monotherapy is sparse,[8,9] and larger trials are needed to evaluate the safety of such an antimicrobial stewardship programme.[10] Therefore, we investigated whether the implementation of a multifaceted antimicrobial stewardship intervention reduced broad-spectrum antibiotic use in patients with moderately severe community-acquired pneumonia without compromising their safety.

Methods

Study design and participants

The Community-Acquired Pneumonia increasing Protocol adherence by Antibiotic stewardship in a stepped-wedge Clustered-randomized Trial (CAP-PACT) was an investigator-initiated, stepped-wedge, cluster-randomised, non-inferiority, antimicrobial stewardship trial done in two university hospitals, seven teaching hospitals, and three non-teaching hospitals in the Netherlands. Any Dutch acute care hospital was eligible and a convenience sample was approached for study participation. Participating hospitals were: University Medical Centre Utrecht (Utrecht), Tergooi Hospital (Hilversum), Diakonessenhuis Utrecht (Utrecht), Langeland Hospital (Zoetermeer), Maxima Medisch Centrum (Veldhoven), Catharina Hospital (Eindhoven), Amphia Hospital (Breda), ZGT Hospital (Almelo), Erasmus Medical Centre (Rotterdam), Medisch Spectrum Twente Hospital (Enschede), Noordwest Ziekenhuisgroep (Alkmaar), and Wilhelmina Hospital (Assen). All Dutch hospitals have specialised antimicrobial stewardship teams responsible for implementing antimicrobial stewardship interventions, consisting of at least a clinical microbiologist, an infectious disease specialist, and a hospital pharmacist. Before study initiation, none of the participating hospitals had an active antimicrobial stewardship intervention focused

on the treatment of patients with community-acquired pneumonia.

Consecutively admitted adult patients aged 18 years or older who were receiving antibiotic therapy for a working diagnosis of community-acquired pneumonia and were admitted to a non-ICU ward (and were therefore classified as having moderately severe disease) were eligible for inclusion. Patients were not eligible if they had recently (≤14 days) resided in a nursing home or long-term care facility, were recently (≤14 days) admitted to an acute care hospital for 2 or more days, were known to have cystic fibrosis, or had an immunodeficiency. Immunodeficiencies were defined as having HIV infection (with a last CD4 cell count of <300 cells per μL), having received cytotoxic chemotherapy or radiotherapy in the previous 3 months, being on chronic (>3 months) haemodialysis, having received a solid organ or bone marrow transplant, or receiving immunosuppressive therapy. Corticosteroid therapy was considered as immunosuppressive only when dosage was high (>0·5 mg/kg per day) and prolonged (>14 days).

The study was reviewed by the ethics review board of the University Medical Centre Utrecht (reference number 15/100), and local antimicrobial stewardship teams provided written or oral consent to participate in the study. The need to obtain individual patient consent was waived because the implemented stewardship intervention promoted best practice as described in the national Dutch guidelines,[1] the intervention was aimed at health-care providers rather than individual patients, and anonymised routinely collected data were used. Data are reported according to Consolidated Standards for Reporting Trials guidelines of stepped-wedge cluster-randomised trials and non-inferiority trials.[11]

Randomisation and masking

The coordinating investigators approached hospitals for enrolment. All participating hospitals started in a control period and every 3 months a block of two hospitals transitioned from the control to the intervention period, with all hospitals eventually ending in the intervention period (appendix p 24). The unit of randomisation was the hospital (cluster), and electronic randomisation (by an independent data manager) decided the sequence (the time of intervention) by which hospitals would crossover from the control period to the intervention period. Randomisation was done electronically by an independent data manager after recruitment of all hospitals. Allocation to the different times of intervention implementation was concealed for treating physicians. Because of the nature of the trial design, blinding was not possible, and not deemed necessary because of the use of objective outcome measures.

See Online for appendix

Procedures

Imaging (mostly chest x-rays) was done as part of the work-up to set the working diagnosis of community-acquired pneumonia. Testing for the causative pathogen of the community-acquired pneumonia was not protocolised but was instead done according to local standards of care. Local standards of care always consisted of routinely performing blood cultures and sputum cultures, but not all hospitals routinely performed urinary antigen testing. Dutch national guidelines[1] encourage the performance of blood cultures, sputum cultures, and *Legionella* spp and pneumococcal urine antigen tests. PCR testing for atypical and viral pathogens is not routinely done, except for seasonal influenza. Dosing of antibiotics was according to local protocols. Generally, amoxicillin was administered either intravenously at 1000 mg every 6 h or orally at 500 mg or 750 mg every 8 h, and benzylpenicillin was administered intravenously at 1 million units every 4 h or 6 h.

The antimicrobial stewardship intervention was a multifaceted bundle based on previous stewardship interventions that have proven to be effective,[12] with the intention to increase the use of benzylpenicillin and amoxicillin by way of performing pneumococcal urinary antigen testing to reduce broad-spectrum antibiotic use in the treatment of community-acquired pneumonia.[12] The bundle consisted of (1) education, (2) engaging local opinion leaders, and (3) prospective audit and feedback of antibiotic use. The bundle also involved the use of a pragmatic classification of disease severity.

Educational activities were targeted at physicians in pulmonary and internal medicine departments and consisted of clinical lessons, electronic (e)-learning, and educational attributes. Clinical lessons, in which national community-acquired pneumonia guidelines were addressed by use of case-based discussions and feedback, with antibiotic prescribing data of the respective hospitals anonymously benchmarked against other participating hospitals, were given at month 0 of the intervention period and then every 6 months until study completion. At month 0 of the intervention period, physicians in the participating hospitals were invited to complete e-learning consisting of case-based questions about the community-acquired pneumonia guidelines. Invites to complete e-learning were sent periodically every 3–4 months to reach new employees. In addition, educational attributes—in the form of posters and pocket cards summarising the community-acquired pneumonia guidelines—were distributed at month 0 of the intervention period.

Local opinion leaders were identified with the help of the local antibiotic stewardship teams and were actively involved in the study and stewardship activities. Local opinion leaders were members of the local antibiotic stewardship team, internal medicine specialists, or pulmonary medicine specialists with expertise on antimicrobial prescribing. They were asked to encourage guideline-adherent treatment throughout the intervention period (eg, during handover meetings).

Prospective audit and feedback were implemented throughout the whole intervention period by the local

antimicrobial stewardship team. On weekdays, all patients admitted to non-ICU wards with moderately severe community-acquired pneumonia on the previous day were actively identified (audit) and the responsible physicians were contacted by a member of the local antimicrobial stewardship team to recommend switching treatment to benzylpenicillin or amoxicillin monotherapy if the treatment they had initiated was not consistent with the guideline recommendation (feedback). The audit and feedback were done at least once per patient, unless the patient was treated according to guidelines, in which case no feedback was given. If, for any reason, treatment could not be switched, physicians were recommended to conduct a pneumococcal urine antigen test to facilitate de-escalation if the test result was positive. Guideline-adherent reasons for not prescribing benzylpenicillin or amoxicillin monotherapy included having risk factors for *Legionella* spp infection (eg, being treated for >48 h with a β-lactam antibiotic without clinical effect, recent travel abroad, or a proven link with a *Legionella* spp outbreak). Recommendations were done by telephone and were registered in electronic health records, as were reasons for physicians not accepting recommendations.

Data were collected by trained research nurses using standardised methodology. We also used anonymised data (eg, on baseline demographics, comorbidities, and severity of illness scores [CURB-65 and pneumonia severity index]) available from electronic health records. Vital status at day 90 was derived from the municipal records database if not evident from medical records.

Outcomes

The co-primary outcomes were broad-spectrum days of therapy per patient and 90-day all-cause mortality. Days that patients received antibiotic treatment were classified as narrow-spectrum days of therapy if amoxicillin, benzylpenicillin, or doxycycline monotherapy was given and as broad-spectrum days of therapy if any other antibiotic regimen was administered. Doxycycline monotherapy was defined as narrow-spectrum therapy, as the Dutch national guidelines recommend it to be equivalent to amoxicillin for mild community-acquired pneumonia.[1] Secondary outcomes were narrow-spectrum days of therapy, total days of therapy, 30-day all-cause mortality, length of hospital stay, hospital readmissions within 30 days of hospital admission, ICU admissions, complications, *Clostridioides difficile*-associated disease, and antibiotic switches. Outcomes were locally assessed by trained research nurses using standardised methodology for data collection.

Statistical analysis

The analysis of broad-spectrum days of therapy per patient was a superiority analysis to show a change in broad-spectrum antibiotic use, and the analysis of 90-day mortality was a non-inferiority analysis. The required sample size was largest for the all-cause 90-day mortality co-primary outcome. Assuming an all-cause 90-day mortality of 10%, a non-inferiority margin of 3%, a one-sided alpha of 0·05, and taking into account the stepped-wedge design, a total of 4464 patients were required for 80% power to detect non-inferiority.[13] Our primary analyses were done in the intention-to-treat population, which comprised all patients who were enrolled in the control and intervention periods, by use of mixed effects logistic regression models including a random intercept and a random slope per hospital and time as a fixed effect, and are reported as risk differences.[14] We adjusted the models for the following potential confounders (as fixed effects): pneumonia severity index score, smoking status (current smoker, past smoker, or never smoker), chronic obstructive pulmonary disease (COPD), diabetes, and pre-treatment with antibiotics within the preceding 14 days. For 90-day mortality, we calculated 90% CIs to test one-sided for non-inferiority at the 5% significance level, and we also calculated 95% CIs. Intracluster correlations were calculated for the co-primary outcomes. Survival was plotted by use of a Kaplan–Meier curve.

As secondary analyses, we did an as-treated analysis and a complier average causal effect (CACE; comprising all patients who were enrolled in the control and intervention periods) analysis, both aiming to estimate the difference in mortality between patients empirically treated with narrow-spectrum versus broad-spectrum antibiotics. The CACE analysis was used—with randomisation as an instrumental variable—to estimate the

For the **municipal records database** see https://www.government.nl/topics/personal-data/personal-records-database-brp

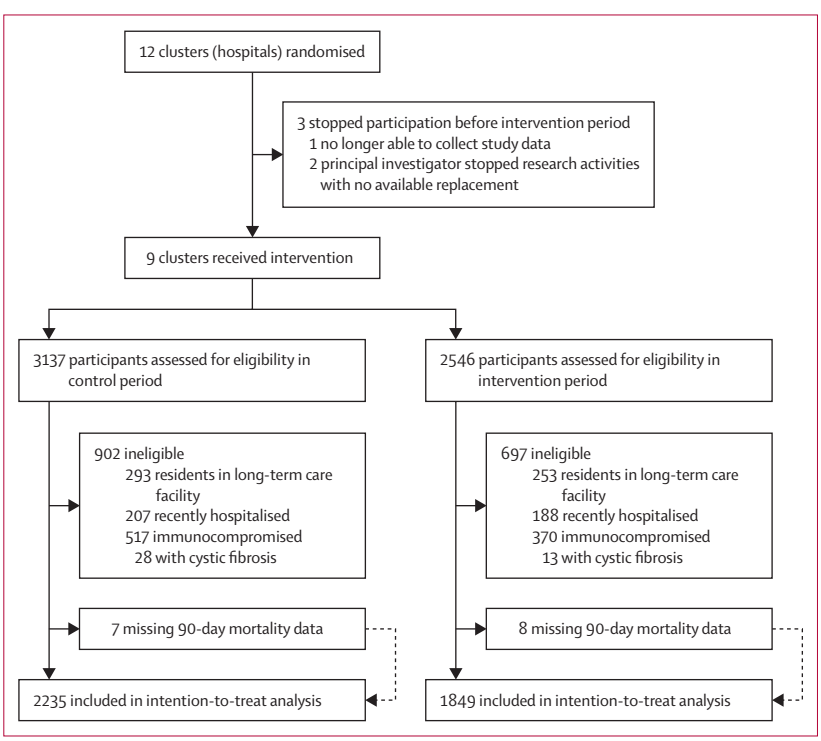

Figure 1: **Trial profile**

	Hospitalised in control period (n=2235)	Hospitalised in intervention period (n=1849)
Age, years	73 (63–81)	74 (64–82)
Sex		
Female	1047 (46·8%)	874 (47·3%)
Male	1188 (53·2%)	975 (52·7%)
Antibiotic use 2 weeks before admission	742 (33·2%)	569 (30·8%)
Smoking status		
Current smoker	512/1881 (27·2%)	412/1494 (27·6%)
Past smoker	725/1881 (38·5%)	626/1494 (41·9%)
Never smoker	396/1881 (21·1%)	264/1494 (17·7%)
Not currently smoking but history unknown	248/1881 (13·2%)	192/1494 (12·9%)
Medical speciality admitted to		
Internal medicine	416 (18·6%)	349 (18·9%)
Pulmonology	1731 (77·4%)	1426 (77·1%)
Other	88 (3·9%)	74 (4·0%)
Comorbidities		
COPD or asthma	962 (43·0%)	880 (47·6%)
Cardiovascular disease	300 (13·4%)	259 (14·0%)
Diabetes	389 (17·4%)	315 (17·0%)
Malignancy	239 (10·7%)	185 (10·0%)
Pneumonia severity index score	89 (70–112)	91 (72–113)
Risk class I	101 (4·5%)	73 (3·9%)
Risk class II	473 (21·2%)	357 (19·3%)
Risk class III	581 (26·0%)	493 (26·7%)
Risk class IV	823 (36·8%)	722 (39·0%)
Risk class V	257 (11·5%)	204 (11·0%)
CURB-65 score	2 (1–2)	2 (1–2)
Radiologically confirmed disease	1689 (75·6%)	1377 (74·5%)
Blood culture	1602 (71·7%)	1387 (75·0%)
Sputum culture	888 (39·7%)	784 (42·4%)
Pneumococcal urinary antigen test	965 (43·2%)	1173 (63·4%)
Legionella spp urinary antigen test	1297 (58·0%)	1255 (67·9%)

Data are median (IQR), n (%), or n/N (%). COPD=chronic obstructive pulmonary disease. CURB-65=confusion, urea, respiratory rate, blood pressure-65.

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

intention to treat adjusted for non-compliance,[15] and estimated the effect of the intervention if all patients were treated with narrow-spectrum antibiotics. We changed our planned analysis method from negative binomial models to linear regression models after statistical review because days of therapy are better modelled as continuous data than as count data, but still report results from the negative binomial regression method.

We analysed 30-day mortality with similar methods to our analysis of 90-day mortality. Narrow-spectrum days of therapy, total days of therapy, complications, and *C difficile*-associated disease were only descriptively reported.

As Fine and Gray competing events models do not allow random effects, the length of hospital stay was analysed by use of mixed effects Cox proportional hazards models while setting the follow-up duration to the maximum length of stay for patients who died in the hospital. ICU admissions, hospital readmissions, and antibiotic switches were analysed by use of mixed effects logistic regression. Missing data were imputed by multiple imputation, except for data on respiratory rate, heart rate, and confusion at admission, which were assumed to be normal when not documented in medical charts. No transition period was used because the treatment effect of the audit and feedback was assumed to be immediate. Pre-specified sensitivity analyses included a subgroup analysis of our co-primary outcomes in only patients with radiologically confirmed community-acquired pneumonia, and an analysis of our co-primary outcomes in which doxycycline was considered broad-spectrum. Post-hoc, we analysed empirical antibiotic specifications prescribed to patients with COPD or asthma, those treated with antibiotics 2 weeks before hospital admission, and those admitted during influenza seasons (appendix p 20). All analyses were done by use of R, version 3.5.1. This trial was prospectively registered at ClinicalTrials.gov, NCT02604628, where the detailed statistical analysis plan was published before database lock. Data monitoring was done by the coordinating investigators. There was no formal data monitoring committee.

Role of the funding source

There was no funding source for this study.

Results

11 hospitals included patients from internal medicine and pulmonary departments and one hospital included patients from the pulmonary department only. Three of 12 randomised hospitals stopped participation before they entered the intervention period and data from these hospitals were not used for our analysis. Between Nov 1, 2015, and Nov 1, 2017, 5683 participants with community-acquired pneumonia were admitted to a non-ICU ward, of whom 4084 (71·9%; 2235 admitted during the control period and 1849 admitted during the intervention period) were included in the intention-to-treat analysis (figure 1). The baseline characteristics of patients admitted during the control period were similar to those of patients admitted during the intervention period (table 1). The most commonly identified (proven or possible) pathogens were *Streptococcus pneumoniae* (488 [11·9%] of 4084 patients), followed by *Haemophilus influenza* (285 [7·0%]), and *Staphylococcus aureus* (97 [2·4%]), with no differences in pathogens detected between patients admitted during the control and intervention periods (appendix pp 4–5).

We initially aimed to give clinical lessons every 6 months. However, during the trial, they were given more frequently due to the absences of doctors or logistical reasons. In the intervention period, 54 clinical lessons were given,

with a mean interval of 90 days (SD 43), and 235 physicians completed the e-learning (appendix p 6). Recommendations after audit and feedback were not required for 1258 (68·0%) of 1849 patients, mostly because they had already been treated with narrow-spectrum antibiotics at hospital admission (appendix pp 6–8). Of the 591 patients eligible for feedback, the local antibiotic stewardship teams made 330 recommendations to switch antibiotics, of which 197 (59·7%) were accepted. The most common reasons for not accepting their recommendations were that patients had COPD (11 [8%] of 133 rejections), patients had severe pneumonia (pneumonia severity index score of 5, CURB-65 score of 3–5, or clinical deterioration; nine [7%]), or suspicions of a resistant pathogen (nine [7%]). Another less common reason for rejection was when patients were perceived to have hospital-acquired pneumonia, even if they did not fulfil our predefined exclusion criterion of being recently (≤14 days) admitted to an acute care hospital (eg, if the patients were admitted to hospital >14 days before index presentation; appendix pp 6–8). Across the nine hospitals, adherence to completing the e-learning ranged from one physician completing the e-learning (2%) of 48 invited to complete the e-learning to 49 completers (72%) of 68 invitees, and the mean attendance per clinical lesson ranged from 10·5% (SD 5·0) to 52·7% (8·4; appendix p 23).

The most commonly prescribed empirical antibiotic regimens in the control and intervention periods, respectively, were narrow-spectrum antibiotics (640 [28·6%] of 2235 *vs* 840 [45·4%] of 1849), broad-spectrum β-lactam monotherapy (712 [31·9%] of 2235 *vs* 454 [24·6%] of 1849), and β-lactam plus fluoroquinolone combination therapy (561 [25·1%] of 2235 *vs* 393 [21·3%] of 1849; appendix pp 10–11). Overall narrow-spectrum antibiotic use mostly consisted of amoxicillin (1293 [87·4%] of 1480), followed by doxycycline (139 [9·4%]) and benzylpenicillin (48 [3·2%]).

The median broad-spectrum days of therapy per patient were 6 (IQR 2–9) in the control period and 3 (0–8) in the intervention period, and the adjusted relative reductions in broad-spectrum days of therapy per hospital ranged from 16·7% to 39·3% (appendix p 9). The median total days of therapy per patient were 8 days (IQR 7–10) in the control period and 8 days (7–11) in the intervention period (figure 2). The adjusted mean broad-spectrum days of therapy per patient was reduced from 6·5 days in the control period to 4·8 days in the intervention period, with an adjusted absolute difference of –1·7 days (95% CI –2·4 to –1·1) and an adjusted relative reduction of 26·6% (95% CI 18·0–35·3). The crude absolute difference was –1·3 days (95% CI –2·1 to –0·5) and, when adjusted for design and time, the absolute difference was –1·8 days (–2·9 to –0·8). The crude relative reduction was 20·8% (95% CI 20·6–20·9) and, when adjusted for design and time, the relative reduction was 28·1% (27·9–28·2). The median broad-spectrum days of therapy per patient differed per hospital and over time (appendix pp 25–26)—the median narrow-spectrum days of therapy per patient

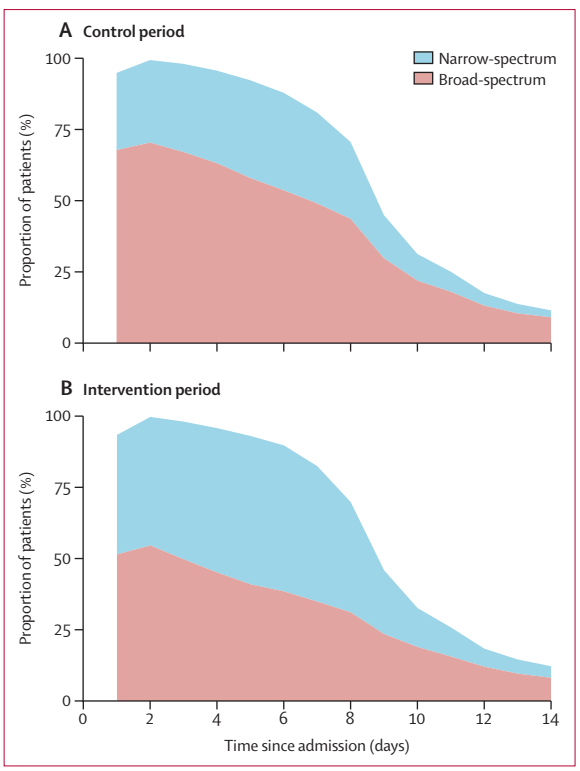

Figure 2: **Proportion of patients receiving narrow-spectrum versus broad-spectrum antibiotics**
(A) Patients admitted during the control period. (B) Patients admitted during the intervention period.

were 0 days (IQR 0–6) in the control period and 5 days (0–8) in the intervention period. Results were similar when we used mixed effects negative binomial regression, as predefined in the statistical analysis plan (appendix p 22). The intracluster correlation for broad-spectrum days of therapy was 0·02.

90-day all-cause mortality was 10·9% (242 of 2228 patients died) in the control period and 10·8% (199 of 1841 patients died) in the intervention period (figures 3, 4). In the intention-to-treat analysis, the adjusted risk difference in 90-day all-cause mortality was 0·4% (90% CI –2·7 to 2·4). Non-inferiority was met because the upper limit of the CI was less than the pre-specified non-inferiority margin of 3% (figure 3). The intracluster correlation for 90-day all-cause mortality was 0·007. Results were similar in the as-treated and CACE analyses (appendix p 12). Our pre-specified sensitivity analyses in patients with radiologically confirmed community-acquired pneumonia or when doxycycline was considered broad-spectrum yielded similar results to our main analysis (appendix p 13).

30-day all-cause mortality, the median length of hospital stay, and the proportions of hospital readmissions, complications, *C difficile*-associated disease, patients switching from intravenous to oral antibiotics, patients switching from oral to intravenous antibiotics,

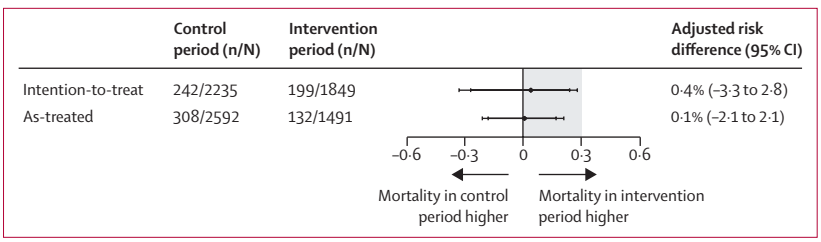

Figure 3: **Forest non-inferiority plot for 90-day all-cause mortality**
The diamonds represent the adjusted risk difference. To allow for one-sided testing of non-inferiority, 90% CIs were calculated (inner confidence bars); 95% CIs are also provided (outer confidence bars). CIs within the grey-shaded area are non-inferior.

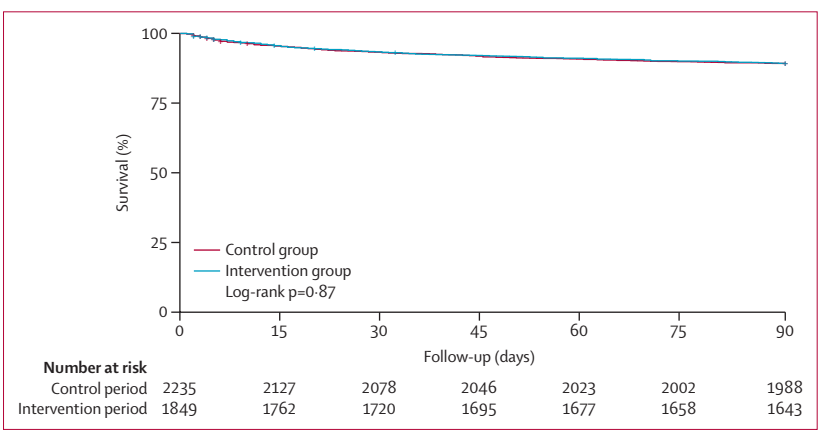

Figure 4: **Kaplan–Meier curve of survival with time**

and patients switching from narrow-spectrum to broad-spectrum antibiotics were similar between patients admitted during the control period and patients admitted during the intervention period (table 2; appendix p 15). ICU admissions occurred more frequently in the control period (94 [4·2%] of 2235 patients) than in the intervention period (38 [2·1%] of 1849 patients; table 2). More patients switched from broad-spectrum to narrow-spectrum antibiotics in the intervention period (413 [41·3%] of 1000) than in the control period (421 [26·4%] of 1592; table 2). Time to switch from broad-spectrum to narrow-spectrum antibiotics was lower in the intervention period than in the control period (table 2). For 30-day all-cause mortality, the results from the as-treated analysis were similar to those from the intention-to-treat analysis, but the results from the CACE analysis were hard to interpret because of wide CIs (appendix p 14).

In post-hoc analyses, we found that prescribed antibiotic regimens for patients with COPD or asthma (appendix pp 16–17) and for those admitted during influenza seasons (appendix pp 20–21) were similar to those of the total patient population (appendix pp 10–11). By contrast, in patients who were treated with antibiotics in the 2 weeks before hospital admission, there was no reduction in empirical broad-spectrum antibiotic use (appendix pp 18–19).

Discussion

In this stepped-wedge, cluster-randomised trial, a multifaceted antimicrobial stewardship intervention based on education on local guidelines and audit and feedback resulted in a 26·6% adjusted relative reduction in the mean days of broad-spectrum antibiotic use in patients hospitalised with moderately severe community-acquired pneumonia without compromising patient all-cause mortality at day 90 after hospital admission.

The stewardship intervention bundle contained elements that are considered effective in optimising antibiotic use.[7,12] One meta-analysis found that the proportion of guideline-adherent prescriptions increased from 43% to 58% after the implementation of antimicrobial stewardship interventions, corresponding to a relative increase of 25·9%.[7] Compared with this result, our bundle was equally as efficacious. However, heterogeneity was large between hospitals, with reductions in prescribing broad-spectrum antibiotics ranging from 16·7% to 39·3%. This heterogeneity in the intervention's effect might have resulted from different barriers for prescribing narrow-spectrum antibiotics between hospitals. Therefore, although the components of our bundle are evidence-based, identifying barriers to guideline-adherent prescribing and tailoring the intervention to the specific setting on the basis of behavioural change theory might be a more efficient use of resources.[16] Future perspectives of antimicrobial stewardship in patients with community-acquired pneumonia might change with the increasing availability of point-of-care molecular testing. Finding a causative pathogen more often and earlier enhances opportunities for streamlining antibiotic therapy, and antimicrobial stewardship intervention bundles should consider this.

The optimal empirical treatment for moderately severe community-acquired pneumonia is still subject to debate. Thus far, two cluster-randomised trials have investigated the effects of empirical coverage for atypical pathogens on patient outcome.[6,17] In a multicentre, non-inferiority, randomised controlled trial, β-lactam monotherapy was inferior to β-lactam–macrolide combination therapy for time to clinical stability in the treatment of patients with moderately severe community-acquired pneumonia.[17] In this study, patients who were randomly assigned to β-lactam monotherapy had a 7·6% higher absolute risk than patients who were assigned to the combination therapy of not being clinically stable at day 7, but there were no significant differences in 30-day or 90-day mortality between the two groups.[17] In another multicentre, cluster-randomised, crossover trial, a strategy of preferred empirical treatment with β-lactam monotherapy was non-inferior to β-lactam–macrolide combination therapy and fluoroquinolone monotherapy for 90-day mortality.[6]

This equipoise is also reflected in international guideline recommendations for the empirical treatment of moderately severe community-acquired pneumonia. US[5] and UK[4] guidelines recommend β-lactam–macrolide

	Hospitalised in control period (n=2235)	Hospitalised in intervention period (n=1849)	Unadjusted estimates (95% CI)	Adjusted estimates (95% CI)
30-day all-cause mortality	154 (6·9%)	123 (6·7%)	RD –0·3 (–1·8 to 1·3)	RD –1·1 (–3·5 to 1·1)
Length of hospital stay, days	5 (3–8)	5 (3–8)	HR 1·0 (1·0 to 1·1)	HR 1·1 (1·0 to 1·3)
Intensive care unit admissions	94 (4·2%)	38 (2·1%)	OR 0·5 (0·3 to 0·7)	OR 0·3 (0·2 to 0·6)
Hospital readmissions	243/2150 (11·3%)	203/1778 (11·4%)	OR 1·0 (0·8 to 1·2)	OR 1·2 (0·8 to 1·7)
Antibiotic switches				
From broad-spectrum to narrow-spectrum	421/1592 (26·4%)	413/1000 (41·3%)	OR 2·0 (1·7 to 2·3)	OR 2·1 (1·5 to 2·8)
From narrow-spectrum to broad-spectrum	148/643 (23·0%)	195/848 (23·0%)	OR 1·0 (0·8 to 1·3)	OR 1·0 (0·7 to 1·5)
From intravenous to oral	1469/1818 (80·8%)	1262/1506 (83·8%)	OR 1·2 (1·0 to 1·5)	OR 1·3 (0·9 to 1·8)
From oral to intravenous	44/417 (10·6%)	26/342 (7·6%)	OR 0·7 (0·4 to 1·2)	OR 0·7 (0·3 to 1·8)
Time until switch from broad-spectrum to narrow-spectrum antibiotics, days	3 (2–4)	3 (2–4)	HR 1·8 (1·5 to 2·0)	HR 1·7 (1·4 to 2·1)

Data are n (%), n/N (%), or median (IQR), unless otherwise specified. We adjusted for design, time, and confounding variables (pneumonia severity index, smoking status, chronic obstructive pulmonary disease, diabetes, and antibiotics pre-treatment). HR=hazard ratio. OR=odds ratio. RD=risk difference.

Table 2: **Secondary outcomes in the intention-to-treat population**

combination therapy or respiratory fluoroquinolone monotherapy, whereas Swedish,[2] Danish,[3] and Dutch[1] guidelines recommend narrow-spectrum β-lactam monotherapy. The rationale for empirical treatment with narrow-spectrum β-lactam monotherapy is that the most common causative pathogen in community-acquired pneumonia, *S pneumoniae*, is susceptible to these antibiotics, and that the severity of disease allows escalation within 48 h to broader antibiotic therapy dependent on diagnostic testing or lack of clinical improvement. Thus far, two randomised controlled trials have evaluated the efficacy of narrow-spectrum β-lactams in patients with moderately severe community-acquired pneumonia.[8,9] One trial[9] compared moxifloxacin with amoxicillin in patients with mild-to-moderate suspected pneumococcal community-acquired pneumonia and clinical success rates were 86·5% (173 of 200 patients were cured) in the moxifloxacin group and 82·2% (171 of 208 patients were cured) in the amoxicillin group. In the other trial investigating the treatment of adult patients with community-acquired suspected pneumococcal pneumonia,[8] clinical cure rates were 83·6% (133 of 159 patients cured) in those treated with sparfloxacin and 84·7% (144 of 170 patients) in those treated with amoxicillin. Yet, in clinical practice, physicians are apparently reluctant to use narrow-spectrum β-lactams, as shown by the low adherence to current guideline recommendations in the control period of our study. Our findings provide further evidence that more patients with moderately severe community-acquired pneumonia can be safely empirically treated with narrow-spectrum antibiotics, which would contribute to the more prudent use of antibiotics.

The antimicrobial stewardship intervention reduced broad-spectrum antibiotic use and increased the frequency of diagnostic testing. Indeed, pneumococcal urine antigen testing was recommended as part of the audit and feedback, which might have concomitantly increased the frequencies that physicians obtained blood cultures and sputum cultures, and performed *Legionella* spp urine antigen testing due to increased awareness.

In our study, 1311 (32·1%) of 4084 patients were already being treated with antibiotics before hospital admission, which is similar to previous studies.[6] Dutch national guidelines[1] recommend adding atypical antibiotic coverage if patients do not clinically improve after 48 h or more of β-lactam therapy. Patients that were pre-treated with antibiotics were included in the audit and feedback. However, because prescribing broad-spectrum antibiotics and atypical coverage for these patients adheres to the guidelines, switching to narrow-spectrum antibiotics was not often recommended. In a post-hoc subgroup analysis of patients treated with antibiotics before admission, the antibiotic stewardship intervention did not reduce broad-spectrum antibiotic use.

Recommendations after audit and feedback were not required in 1258 (68·0%) of 1849 patients, mostly because they had already been treated with narrow-spectrum antibiotics. Of the remaining 591, recommendations were given for 330 (55·8%), of which 197 (59·7%) were accepted. The most common reasons for rejecting feedback were that patients had severe pneumonia (according to pneumonia severity index scores, CURB-65 scores, or clinical deterioration) or COPD, or there were suspicions of a resistant pathogen. Antimicrobial stewardship interventions to increase narrow-spectrum antibiotic use will most likely have a minimal effect for these patients.

The prevalence of ICU admission was significantly lower in the intervention period compared with the control period. It is not likely that patients in the intervention period were less severely ill at baseline because the other indicator for disease severity (ie, the pneumonia severity index score and the CURB-65 score) was similar between the control and intervention groups. The reason for this difference remains unclear and is probably not a direct effect of prescribing more narrow-spectrum antibiotics.

In a study in which different time periods are compared, seasonal differences between the control and intervention periods might influence the results because of a difference in the prevalence of respiratory pathogens. To account for this potential limitation and exclude seasonal imbalances as much as possible, our study was designed to last 2 years (from Nov 1, 2015, to Nov 1, 2017), with equal durations for the control and intervention periods. In addition, time was included in the model as a fixed effect to account for longer-term linear time effects.

A total of 4084 patients were included in the intention-to-treat analysis, whereas the a priori required sample size was 4464. Studies might be underpowered if their sample sizes are too small, producing results that have low precision and corresponding CIs that are too wide to draw any meaningful conclusions.[18] However, in our study, we were able to show a significant and clinically relevant reduction in broad-spectrum antibiotic use and non-inferiority for 90-day all-cause mortality with adequate precision, indicating that the study was sufficiently powered.

Our study has several limitations. First, because we implemented a multifaceted bundle of stewardship interventions, it was not possible to estimate the effect of the individual components. However, the approach reflects clinical practice, where stewardship interventions are usually implemented as bundles. Second, the nature of the intervention precluded a blinded evaluation, and, therefore, information bias cannot be excluded. To minimise the impact of information bias, we chose objective primary outcomes and used trained research nurses and standardised methodology for data collection. Third, in cluster-randomised, stepped-wedge designs, selection bias might occur if different types of patients are included in different study periods. Yet, the baseline characteristics of patients admitted during the control period or intervention period were similar and we adjusted for important prognostic confounding factors. Compared with individual patient randomisation, a cluster-randomised design has major advantages as it reduces contamination of the intervention and better reflects clinical practice where a stewardship bundle gets implemented.[10] As a result, the study design we used has high generalisability. Fourth, the inclusion of patients without radiologically confirmed community-acquired pneumonia might have diluted the effect to non-inferiority for mortality. However, the chosen study population (ie, those being treated for presumed community-acquired pneumonia) closely represents clinical practice. In addition, one study has shown that radiological infiltrates detected by CT scans are not apparent on chest x-rays in around 30% of patients with community-acquired pneumonia.[19] This finding implies that many patients with community-acquired pneumonia would be excluded if enrolment was based on chest x-ray results. Moreover, in our study, sensitivity analyses in a subset of patients with radiologically confirmed community-acquired pneumonia yielded similar results to our main analysis of the total cohort. Finally, our study was done in a setting with a low prevalence of antimicrobial resistance and atypical pathogens, which could limit its generalisability to settings with a higher prevalence of antimicrobial resistance and atypical pathogens. In the Netherlands, the prevalence of *S pneumoniae* that is intermediately resistant or resistant to benzylpenicillin is 6%.[20]

To conclude, a multifaceted antimicrobial stewardship intervention focused on education and audit and feedback reduced broad-spectrum antibiotic use by 26·6% and was non-inferior in 90-day all-cause mortality for immunocompetent patients hospitalised with moderately severe community-acquired pneumonia. These results indicate that more patients with moderately severe community-acquired pneumonia can be safely treated with narrow-spectrum antibiotics.

Contributors

VAS, IvH, JWD-Z, PDvdL, CHEB, JJO, CHvW, and MJMB conceived and designed the study. VAS, IvH, WGB, WR, KV, MJG, SUCS, AKvdB, WdB, HSMA, IO, JMMR-vdV, EME-D, FEA-E, and MBH were involved in the acquisition and interpretation of the data. VAS and IvH accessed and verified the underlying data. VAS, IvH, and CHvW statistically analysed the data. VAS, IvH, JWD-Z, PDvdL, CHEB, JJO, CHvW, and MJMB wrote the first draft of the manuscript. All authors critically reviewed, revised, and approved the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

CHvW reports grants from Pfizer; personal fees from Pfizer and MSD/Merck; non-financial support from BioMérieux and DA Volterra, outside the submitted work; and a patent issued for the prediction of clinical manifestations of gut microbiota. All other authors declare no competing interests.

Data sharing

Deidentified individual participant data will be available with Article publication upon requests directed to the corresponding author (V.A.Schweitzer-2@UMCUtrecht.nl) and, after approval of a proposal, can be shared through a secure online platform. The study protocol and statistical analysis plan are available with publication as part of the appendix.

References

1 Wiersinga WJ, Bonten MJ, Boersma WG, et al. Management of community-acquired pneumonia in adults: 2016 guideline update from the Dutch Working Party on Antibiotic Policy (SWAB) and Dutch Association of Chest Physicians (NVALT). *Neth J Med* 2018; **76:** 4–13.

2 Athlin S, Lidman C, Lundqvist A, et al. Management of community-acquired pneumonia in immunocompetent adults: updated Swedish guidelines 2017. *Infect Dis (Lond)* 2018; **50:** 247–72.

3 Fally M, Weinreich UM, Nielsen TL, Jensen J-US. Dansk Lungemedicinsk Selskab. Pneumoni—initial undersogelse og behandling. 2017. https://lungemedicin.dk/wp-content/uploads/2021/05/Pneumoni_2017.pdf (accessed Nov 18, 2019).

4 Lim WS, Baudouin SV, George RC, et al. BTS guidelines for the management of community acquired pneumonia in adults: update 2009. *Thorax* 2009; **64** (suppl 3)**:** iii1–55.

5 Metlay JP, Waterer GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med* 2019; **200:** e45–67.

6 Postma DF, van Werkhoven CH, van Elden LJ, et al. Antibiotic treatment strategies for community-acquired pneumonia in adults. *N Engl J Med* 2015; **372:** 1312–23.

7 Davey P, Marwick CA, Scott CL, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database Syst Rev* 2017; **2:** CD003543.

8 Aubier M, Verster R, Regamey C, Geslin P, Vercken JB. Once-daily sparfloxacin versus high-dosage amoxicillin in the treatment of community-acquired, suspected pneumococcal pneumonia in adults. *Clin Infect Dis* 1998; **26:** 1312–20.

9 Petitpretz P, Arvis P, Marel M, Moita J, Urueta J. Oral moxifloxacin vs high-dosage amoxicillin in the treatment of mild-to-moderate, community-acquired, suspected pneumococcal pneumonia in adults. *Chest* 2001; **119:** 185–95.

10 Schweitzer VA, van Werkhoven CH, Rodríguez 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.

11 Hemming K, Taljaard M, McKenzie JE, et al. Reporting of stepped wedge cluster randomised trials: extension of the CONSORT 2010 statement with explanation and elaboration. *BMJ* 2018; **363:** k1614.

12 Dellit TH, Owens RC, McGowan JE Jr, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin Infect Dis* 2007; **44:** 159–77.

13 Woertman W, de Hoop E, Moerbeek M, Zuidema SU, Gerritsen DL, Teerenstra S. Stepped wedge designs could reduce the required sample size in cluster randomized trials. *J Clin Epidemiol* 2013; **66:** 752–58.

14 Kleinman LC, Norton EC. What's the risk? A simple approach for estimating adjusted risk measures from nonlinear models including logistic regression. *Health Serv Res* 2009; **44:** 288–302.

15 Dunn G, Maracy M, Tomenson B. Estimating treatment effects from randomized clinical trials with noncompliance and loss to follow-up: the role of instrumental variable methods. *Stat Methods Med Res* 2005; **14:** 369–95.

16 Hulscher MEJL, Prins JM. Antibiotic stewardship: does it work in hospital practice? A review of the evidence base. *Clin Microbiol Infect* 2017; **23:** 799–805.

17 Garin N, Genné D, Carballo S, et al. β-Lactam monotherapy *vs* β-lactam-macrolide combination treatment in moderately severe community-acquired pneumonia: a randomized noninferiority trial. *JAMA Intern Med* 2014; **174:** 1894–901.

18 Goodman SN, Berlin JA. The use of predicted confidence intervals when planning experiments and the misuse of power when interpreting results. *Ann Intern Med* 1994; **121:** 200–06.

19 Claessens YE, Debray MP, Tubach F, et al. Early chest computed tomography scan to assist diagnosis and guide treatment decision for suspected community-acquired pneumonia. *Am J Respir Crit Care Med* 2015; **192:** 974–82.

20 Dutch Foundation of the Working Party on Antibiotic Policy. NethMap 2020. Consumption of antimicrobial agents and antimicrobial resistance among medically important bacteria in the Netherlands in 2019. June, 2020. https://swab.nl/exec/file/download/141 (accessed Feb 6, 2020).