Impact of point-of-care c-reactive protein testing intervention on non-prescription dispensing of antibiotics for respiratory tract infections in private community pharmacies in Nigeria: a cluster randomized controlled trial

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MAIN MANUSCRIPT

Title
Impact of point-of-care c-reactive protein testing intervention on non-prescription dispensing of antibiotics for respiratory tract infections in private community pharmacies in Nigeria: a cluster randomized controlled trial

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Abstract

Objectives
To ascertain if access to c-reactive protein (CRP) test kits – and staff training on how to use them in RTI management – in private community pharmacies (PCPs) can reduce non-prescription antibiotic dispensing for respiratory tract infection (RTI).

Methods
A parallel cluster randomized controlled trial was conducted in Nigeria. The clusters – which were equally the participating units – were PCPs with blood testing experience. Stratified block randomization was done. PCPs were stratified by the baseline value of the primary outcome. PCPs were not blinded. Intervention PCPs were provided with CRP kits and trained on how to use them to make decisions regarding non-prescription antibiotic dispensing for RTI. Control PCPs received no intervention. The primary outcome was the non-prescription antibiotic dispensing rate for RTI. Data were collected by blinded simulated clients who visited each PCP 30 times before and after the intervention without prescriptions. Analyses were by intention-to-treat.

Results
Twenty PCPs were randomized, 1:1. Ten PCPs were analysed in each arm. Each PCP contributed 30 data points to the multiple imputation analysis where antibiotic dispensing decreased by 15.66% (209/300 [intervention] vs 256/300 [control]) in the adjusted analysis (OR = 0.279, CI = 0.107 – 0.726; p-value = 0.0090) and 16% (208/300 [intervention] vs 256/300 [control]) in the crude analysis (OR = 0.299, CI = 0.098 – 0.911; p-value = 0.034).

Conclusions
Access to CRP kits – and staff training on how to use them in RTI management – in PCPs reduced non-prescription antibiotic dispensing for RTI.
Funding
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Trial registration
PACTR202111611256940
Introduction

Many bacteria in Nigeria have developed resistance to antibiotics [1] (Musa et al., 2020). This results in severe illnesses from infections and higher healthcare costs. The inappropriate use of antibiotics is one of the factors that facilitate the spread of resistant bacteria [2,3] (Odenholt et al., 2003; Riedel et al., 2007).

Respiratory tract infection (RTI) is caused by viruses and bacteria, however, a majority of cases are caused by viruses [4] (Ieven et al., 2018). It is often difficult to immediately distinguish viral and bacterial RTI in the absence of specialized diagnostic tools [5] (Whaley et al., 2013). Consequently, clinicians, in the absence of such tools, are usually tempted to recommend antibiotics to patients with RTI in an attempt to not miss a potentially serious bacterial RTI [6] (Horwood et al., 2016). This practice is problematic considering that patients with viral RTI will not benefit from antibiotics and such unnecessary use of antibiotics facilitates the spread of antibiotic resistance [3] (Riedel et al., 2007).

According to the Federal House of Representatives of Nigeria, there is a shortage of primary healthcare centres in Nigeria, with less than 20% of the 30,000 primary healthcare centres in Nigeria functioning [7] (Baiyewu, 2021). Consequently, private community pharmacies (PCPs) – rather than primary healthcare centres – routinely provide primary healthcare services [8] (Ihekoronye and Osemene, 2020). In Nigeria, staff of PCPs include pharmacists and pharmacy assistants. The pharmacists have Bachelor of Pharmacy and/or Doctor of Pharmacy degrees. They manage PCPs. Pharmacy assistants are well-trained by pharmacists to assist in the day-to-day running of PCPs. They are supervised by pharmacists. PCPs provide consultation services to patients, and then dispense medications accordingly or refer them to hospitals [8] (ibid.). This role played by PCPs is very important as it ensures that primary healthcare is not completely absent in many communities in Nigeria. However, it has its demerits – one of the most important is that it could encourage the
unnecessary use of antibiotics, as antibiotics are frequently dispensed to patients without prescriptions.

Accordingly, most patients in Nigeria with RTI receive their treatments in PCPs [8] (ibid.). In their study to assess the non-prescription dispensation of antibiotics to patients with RTI by PCPs in Nigeria, Akpan et al. [9] (2021) found that antibiotics were recommended to 68% of such patients.

Plasma C-reactive protein (CRP) rises well above normal when there is a bacterial infection [10] (Hjortdahl et al., 1991) and thus plasma CRP level can be used to identify bacterial RTI. CRP testing is effective at reducing the unnecessary use of antibiotics for RTI without exposing patients to risks [11] (Do et al., 2016).

This study aimed to ascertain if providing PCPs in Nigeria with CRP test kits and training them on how to use them accordingly in the management of RTI has the potential to improve their objective assessment of antibiotic needs in patients with RTI without prescriptions and reduce their dispensation of antibiotics to such patients. Table 1 shows the research in context.
Methodology

Study design

This trial was a parallel cluster randomized controlled trial. The clusters were PCPs. Cluster randomization was used because clusters were the targets of the intervention. The trial was conducted in Awka, Nigeria. There are over 60 PCPs in Awka. The trial started on January 21, 2022, and ended on July 23, 2022.

Participants

The trial clusters – PCPs – were also the participating units in this trial. A PCP was considered eligible to be included in the study if it is experienced with blood testing – ascertained by checking if it provides malaria and/or typhoid blood test services. This was to include PCPs that could adapt to the intervention procedure within the timeframe available for the trial. The inclusion criteria originally stated in the protocol, including the presence of a PCP in the database of the pharmacist council of Nigeria (PCN) and the regular presence of a pharmacist registered with PCN in a PCP, were not assessed because they could not be efficiently evaluated. These changes to the inclusion criteria were made before the first PCP was recruited. In the first instance, an eligibility assessment of PCPs was done by a member of the research team. They presented as a client to PCPs and asked pharmacy staff whether they provide malaria and typhoid test services. They told pharmacy staff that they would return for the test(s), where necessary. Following the assessment, PCPs that met the inclusion criteria were approached by the principal investigator and relevant details were verbally provided to their managers. If a manager did not provide consent, another eligible PCP was approached. Two written consent forms were given to the managers, who provided consent, to sign. The consent forms were equally signed by the principal investigator who then left with one copy.
Randomization and masking

Eligible PCPs were randomly assigned to the intervention and control arms on a 1:1 basis leveraging the stratified block randomization technique. This technique, rather than the block randomization originally stated in the protocol, was used to ensure that PCPs were uniformly distributed between the study arms with respect to the baseline value of the primary outcome. The decision to use this technique was made before the first PCP was recruited. The statistical analysis plan was updated accordingly to reflect this change. The stratification variable was based on the percentage of encounters (visits) in which an antibiotic was dispensed by PCPs at baseline (details of how this information was collected are in the “Outcomes” section). It had three strata – low, moderate, and high. PCPs that dispensed antibiotics in < 70%, 70% - 89%, and ≥ 90% of visits at baseline were respectively categorized into the low (four PCPs), moderate (ten PCPs), and high (six PCPs) strata. Each stratum had a separate list. The random sequence for each stratum (consisting of 1s and 2s) was generated using Research Randomizer [12] (Urbaniak and Plous, 2013) and coded (specifying which number represented intervention) by an individual who was not part of the trial team. Two sets of random numbers (two numbers per set), five sets of random numbers (two numbers per set), and three sets of random numbers (two numbers per set) were respectively generated for the low, moderate, and high strata. By following the random sequence after it was shared with the research team, PCPs within the list of each stratum were assigned 1 or 2 sequentially. The code (specifying which number represented intervention) was shared with the trial team after the assignments had been finalised. PCPs were not masked to treatment assignment. The simulated clients who collected data were masked.

Interventions

PCPs in the intervention arm were provided with CRP test kits (the kits were specially produced for the trial by Zhuhai Encode Medical Engineering Co., Ltd, China) and other test materials, and their staff were trained on how to use the kits and how to use test results to distinguish viral and bacterial
aetiologies in patients with suspected RTI without prescriptions in order to make more effective decisions regarding antibiotic dispensation. The CRP test kits were semi-quantitative in nature. The cost of a single CRP test kit was 0.75 USD. The test involves using finger prick blood to assess the level of CRP in the blood. Each test takes just over 5 minutes. It has been shown that CRP concentrations > 30 mg/L in patients with RTI are of great importance in the identification of RTI that should be managed with antibiotics [13] (van Vugt et al., 2013). This is best interpreted as – among patients with RTI, those with CRP concentrations of > 30 mg/L are likely to have bacterial RTI, while those with CRP concentrations of ≤ 30 mg/L are likely to have viral RTI. Other studies suggest that it is not unusual for many patients with viral RTI to have CRP concentrations > 30 mg/L, albeit patients with viral RTI are unlikely to have CRP concentrations > 100 mg/L [10,14] (Hjortdahl et al., 1991; Putto et al., 1985). Considering these – regarding managing patients with suspected RTI without prescriptions, pharmacy staff were advised to not dispense antibiotics to patients with CRP concentrations < 30 mg/L, to use their clinical judgment to come to a decision when patients have CRP concentrations ≥ 30 mg/L but < 100 mg/L, and to dispense antibiotics when patients have CRP concentrations ≥ 100 mg/L. They were not discouraged from using their professional judgment where necessary, regardless of CRP test results.

Training, which included practical demonstration, was carried out in each PCP by a pharmacist and a medical laboratory technician. The training was delivered, by the same professionals, in the same way across the board. The staff of PCPs were provided with training materials. They were asked to charge no more than 400 NGN (approximately 1 USD) per CRP test in order to ensure that low-income patients were not excluded. They were followed up regularly throughout the post-intervention period and any problems they had were addressed. PCPs in the control arm received no intervention.
Outcomes

The primary outcome was the rate at which antibiotics were dispensed to patients with RTI without prescriptions – that is, the proportion of visits in which antibiotics were dispensed. The secondary outcome was the rate at which a medical test for identifying bacterial RTI was conducted to inform decisions regarding non-prescription antibiotic dispensation to patients with RTI – that is, the proportion of visits in which relevant tests were conducted.

Data were collected by simulated clients who were students of Nnamdi Azikiwe University, Nigeria, recruited by the research team. The simulated clients were trained on what the data collection entailed. The training was fundamentally delivered twice – shortly after the simulated clients were recruited and a few days before data collection started. Each training consisted of a 2-hour lecture. The simulated clients were provided with training materials. Following the second training, they were engaged in a 6-hour role play in which some members of the research team acted as pharmacy staff while the simulated clients acted as patients with RTI. Any mistakes made by them were corrected by members of the research team. On the day that each simulated client would collect data, the research team member who supervised the data collection discussed essential parts of the data collection protocol with them.

At baseline, 30 simulated clients collected data over 30 data collection days – on each data collection day, just one simulated client visited and collected data from the 20 PCPs under the supervision of a member of the research team who monitored each visit from a distance. Similarly, post-intervention, 30 simulated clients collected data over 30 data collection days – on each data collection day, just one simulated client visited and collected data from the 20 PCPs under the supervision of a member of the research team who monitored each visit from a distance. The PCPs did not anticipate the visits by the simulated clients. Male and female simulated clients mostly collected data on alternate data collection days. On their data collection day, each simulated client was told the symptoms of RTI to complain about. They complained of the same symptoms across all
the 20 PCPs. The symptoms complained of over the 30 days of data collection at baseline and post-intervention can be found in the appendix. These symptoms were developed leveraging the common symptoms of RTI as documented in the literature [15,16,17] (Altiner et al., 2009; Kuchar et al., 2015; National Health Service UK, 2021).

After presenting their symptoms without any prescriptions, they asked the pharmacy staff what the best treatments for their symptoms were. They did not request any particular treatments. They did not admit to having any other symptoms outside what they had been told to complain about. They also did not admit to already visiting a doctor or taking any medications. They noted if relevant medical tests were ordered by pharmacy staff to determine suitable treatments and memorized any drugs they recommended. To aid memorization, they mostly memorized the brand names of drugs – these were subsequently categorized as antibiotic or non-antibiotic by a pharmacist. To ensure good simulation, they paid for tests ordered and/or drugs recommended by pharmacy staff. On visits where the budget for drugs was exceeded, they told pharmacy staff that they would return at a later time to purchase recommended drugs. At the end of each visit, they recorded the data collected on a structured data collection form held by the member of the research team who supervised them.

**Statistics**

The number of PCPs included in this trial and the number of visits assessed in each PCP at baseline and post-intervention was based on the recommendations of the World Health Organization [18] (1993) regarding the number of facilities and visits to be assessed when evaluating the impact of interventions on drug use practices in healthcare facilities. According to the recommendation, there should be at least ten healthcare facilities in the intervention arm and ten healthcare facilities in the control arm, and data should be collected from at least thirty clinical visits/encounters in each of the healthcare facilities at baseline and post-intervention.

Missing post-intervention data were multiply imputed in R (version 4.2.1) using the jomoImpute function of the mitml package (version 0.4.3) [19] (Grund et al., 2021). For the multiple imputation
regarding the adjusted analysis – the multiple imputation model included the primary and secondary outcome variables as target variables; treatment status, stratification, and simulated client gender variables as fixed effect predictor variables; and PCP identification variable as a cluster indicator variable. The difference in the multiple imputation regarding the crude analysis was that the fixed effect predictor variable was just the treatment status variable. Regarding missing baseline data, missing primary outcome data were multiply imputed using jomoImpute, with the primary outcome variable as the target variable and the PCP identification variable as the cluster indicator variable. In every case of multiple imputation, 20 imputations were generated because this number of imputations is adequate [20] (Schafer and Graham, 2002). Convergence was assessed using the potential scale reduction factor.

Analyses were by intention-to-treat. Relevant frequencies were computed using SPSS Statistics 24. Relevant percentages were then computed accordingly. For the adjusted analysis – using the glmer function of the lme4 package (version 1.1.30) in R [21] (Bates et al., 2015), generalized linear mixed-effects model (GLMM) based on random intercept; with the treatment status, stratification, and simulated client gender variables as fixed effects, and PCP identification variable as a random effect; was used to ascertain if there was a significant difference in the rate at which antibiotics were dispensed in the intervention and control arms after the intervention. The difference in the crude analysis was that the fixed effect was just the treatment status variable. The random effect was used to account for any correlation in the data repeatedly collected from each PCP. The stratification variable was taken into account because not doing so could lead to wrong p-values and confidence intervals [22] (Kahan and Morris, 2012). Analysis was based on the multiply imputed dataset – multiple imputation analysis, and also based on the original dataset with missing data – complete case analysis.
Results

Sixty-four PCPs were assessed for eligibility. Forty-one did not meet the inclusion criteria.

Recruitment of PCPs took place from January 21, 2022, to February 17, 2022. Three PCPs that met the inclusion criteria were excluded because their managers did not provide consent. Twenty PCPs that met the inclusion criteria were included in the trial and randomized. Ten PCPs were randomly assigned to each of the intervention and control arms. They were all treated accordingly. None of the PCPs that were randomized withdrew. The trial ended on July 23, 2022, when post-intervention data collection was completed. In 5 of the 600 visits (0.83%) at baseline, no data were collected. For the control arm, in 7 of the 300 (2.33%) visits post-intervention, no data were collected. For the intervention arm, in 1 of the 300 visits (0.33%) post-intervention, no data were collected. These were mostly because the concerned PCPs were closed or did not have relevant drugs in stock when simulated clients visited. Please see figure 1 for more information.

The simulated clients that collected data at baseline and post-intervention mostly had similar demographic characteristics (table 2). PCPs in the intervention and control arms had similar characteristics with respect to the baseline value of the outcomes (table 3).

Regarding the primary outcome in the adjusted analysis (table 4) – in the multiple imputation analysis, antibiotics were dispensed to simulated clients in 209/300 (69.67%) and 256/300 (85.33%) visits in the intervention and control arms respectively (odds ratio = 0.279, 95% confidence interval = 0.107 – 0.726; p-value = 0.0090; absolute reduction in antibiotic dispensation = 15.66%). Regarding the primary outcome in the crude analysis (table 4) – in the multiple imputation analysis, antibiotics were dispensed to simulated clients in 208/300 (69.33%) and 256/300 (85.33%) visits in the intervention and control arms respectively (odds ratio = 0.299, 95% confidence interval = 0.098 – 0.911; p-value = 0.034; absolute reduction in antibiotic dispensation = 16%).

Regarding the secondary outcome (table 5) – in the multiple imputation analysis, medical tests for identifying bacterial RTI (CRP tests) were conducted on simulated clients in 65/300 (21.67%) and
0/300 (0%) visits in the intervention and control arms respectively. Based on the complete case analysis, antibiotics were not subsequently dispensed in 28/64 (43.75%) of the visits in which CRP tests were conducted.

**Discussion**

This is the first study to assess the impact of access to CRP test kits, and staff training on how to use them in RTI management, on the non-prescription dispensation of antibiotics for RTI in PCPs—a situation that is largely seen in many resource-limited settings [9,23,24] (Akpan et al., 2021; Chen et al., 2020; Zawahir et al., 2022). Previous studies that assessed the impact of access to CRP test kits—and staff training on how to use them in RTI management—in PCPs [25,26] (Sim et al., 2021; Wakeman et al., 2018) focused on how the rate at which patients subsequently visit a general practitioner with the hope of receiving an antibiotic prescription got affected.

This study shows that access to CRP test kits—and staff training on how to use them in RTI management—in PCPs reduces the non-prescription dispensation of antibiotics for RTI; as there was an absolute reduction—in the non-prescription dispensation of antibiotics—of 15.66% and 16%, based on the multiple imputation regarding the adjusted analysis and crude analysis respectively.

Before making treatment decisions; PCPs in the intervention arm conducted CRP tests on simulated clients in 21.40% of visits and 21.67% of visits, based on the complete case analysis and multiple imputation analysis respectively. No such tests were conducted in the control arm. The results of the CRP tests (that is, viral or bacterial or uncertain) were not explicitly assessed. However, considering that the simulated clients were healthy adults, they were all expected to have CRP levels of <30 mg/L (and hence the CRP tests should suggest that they require no antibiotics). Antibiotics were not dispensed in 43.75% of the visits in which CRP tests were conducted, based on the complete case analysis.
Although the percentage of visits in which CRP tests were conducted is not quite high, the observed uptake of CRP testing suggests that CRP testing in PCPs is feasible. At the end of the trial, key pharmacy staff in the intervention arm were interviewed to ascertain any challenges they had regarding CRP testing. This will be reported separately and will, hopefully, provide insight into strategies that could be used to improve the uptake of CRP testing in future interventions of this kind.

The findings of this trial are similar to that of a trial conducted in Vietnam, a resource-limited setting, to assess the impact of access to CRP test kits – and staff training on how to use them in RTI management – in primary healthcare centres on antibiotic use for RTI. In the trial, Do et al. [11] (2016) reported that access to CRP test kits – and staff training on how to use them in RTI management – reduced antibiotic prescribing for RTI by 20%. This suggests that access to CRP test kits – and staff training on how to use them in RTI management – is as effective in reducing healthcare practitioners’ offer of antibiotics for RTI in PCPs as it is in primary healthcare centres in resource-limited settings.

Given that PCPs play an important role in the unnecessary use of antibiotics for RTI in resource-limited settings as they frequently dispense antibiotics to patients with RTI without prescriptions [9,23,24] (Akpan et al., 2021; Chen et al., 2020; Zawahir et al., 2022), an intervention of this nature has the potential to improve antibiotic use for RTI and therefore reduce the spread of antibiotic resistance when implemented in such settings. If economic analysis shows that the cost of implementing this intervention in resource-limited settings is manageable, then – all things being equal – its implementation by relevant stakeholders in such settings is recommended; as this would be very helpful in the fight against antibiotic resistance.

Regarding generalisability – antibiotic dispensation for RTI in children was not captured as all the simulated clients were adult, university students who were the only population group readily available to work as simulated clients within the resources available for the study. This may limit the
generalizability of the findings of this study to the paediatric population. Additionally, it may be that PCPs that fail to meet the inclusion criteria differ significantly – with respect to blood testing experience – from those that were included in the study, thereby threatening the generalizability of the findings of this study to them. However, this is unlikely to be the case. Malaria and typhoid tests were preferentially used to assess blood testing experience solely because the concerned conditions are not sensitive as to make the individual who assessed eligibility uncomfortable. Most PCPs that fail to meet the inclusion criteria are likely to be equally experienced with blood testing by virtue of offering other blood test services, including blood glucose test which is routinely offered by PCPs in Nigeria [8] (Ihekoronye and Osemene, 2020).

Regarding limitations – this study did not investigate what would happen if patients without prescriptions directly request to be given antibiotics for their RTI rather than merely complain about their RTI symptoms. This could be addressed in future trials. In addition, although pharmacy staff did not anticipate the visits by the simulated clients, it is not possible to say with certainty that there was no Hawthorne effect. Therefore, this effect may have contributed to some of the effects observed in this study.

Access to CRP test kits – and staff training on how to use them in RTI management – in PCPs in Nigeria improved the objective assessment of antibiotic needs in patients with RTI without prescriptions and reduced the dispensation of antibiotics to such patients. All things being equal; if economic analysis shows that the cost of implementing this intervention in resource-limited settings is manageable, its implementation by relevant stakeholders in such settings is recommended – as this would help reduce the burden of antibiotic resistance.
Registration

The trial was prospectively registered at the Pan African Clinical Trials Registry. Its registration number is PACTR202111611256940.

Trial protocol

The study protocol will be available to researchers who request it from the corresponding author.

Declaration of interests

The authors declare no competing interests.

Acknowledgment

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Ethical approval

This study was approved by the research ethics committee of Chukwuemeka Odumegwu Ojukwu University Teaching Hospital, Awka, Nigeria. Assigned Number: COOUTH/CMAC/ETH.C/VOL.1/FN:04/136.

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https://doi.org/10.1007/5584_2015_110.


https://doi.org/10.1136/bmj.e5840.


CONSORT CHECKLIST, INCLUDING CONSORT FLOWCHART

Title and abstract

1a – Title (page 1)
Impact of point-of-care c-reactive protein testing intervention on non-prescription dispensing of antibiotics for respiratory tract infections in private community pharmacies in Nigeria: a cluster randomized controlled trial

1b – Abstract (pages 2 & 3)

Trial design
A parallel cluster randomized controlled trial was conducted in Awka, Nigeria. The clusters were private community pharmacies (PCPs).

Methods

Participants
The clusters were also the participating units. PCPs with blood testing experience were included in the trial.

Interventions
PCPs in the intervention arm were provided with c-reactive protein (CRP) kits and trained on how to use them to make decisions regarding non-prescription dispensing of antibiotics to respiratory tract infection (RTI) patients. Those in the control arm received no intervention.

Objective
To ascertain if access to c-reactive protein (CRP) test kits – and staff training on how to use them in RTI management – in private community pharmacies (PCPs) can reduce non-prescription antibiotic dispensing for respiratory tract infection (RTI).
**Outcome**

The primary outcome was the rate of non-prescription antibiotic dispensation to RTI patients. Data were collected by blinded simulated clients who visited each PCPs 30 times before and after the intervention without prescriptions.

**Randomization**

Stratified block randomization was done. PCPs were stratified by the baseline value of the primary outcome.

**Blinding**

PCPs were not blinded. The simulated clients who collected data were blinded.

**Results**

**Number randomized**

Twenty PCPs were randomized on a 1:1 basis.

**Number analysed and outcome**

Analyses were by intention to treat. Ten PCPs were analysed in each arm. Each PCP contributed 30 data points to the multiple imputation analysis where antibiotic dispensing decreased by 15.66% (209/300 [intervention] vs 256/300 [control]) in the adjusted analysis (OR = 0.279, CI = 0.107 – 0.726; p-value = 0.0090) and 16% (208/300 [intervention] vs 256/300 [control]) in the crude analysis (OR = 0.299, CI = 0.098 – 0.911; p-value = 0.034).

**Harm**

Not applicable

**Conclusions**

Access to CRP kits – and staff training on how to use them in RTI management – in PCPs reduced non-prescription antibiotic dispensing for RTI.
Introduction

Background and objectives

2a – Background and rationale (pages 4 – 6)

Many bacteria in Nigeria have developed resistance to antibiotics [1] (Musa et al., 2020). This results in severe illnesses from infections and higher healthcare costs. The inappropriate use of antibiotics is one of the factors that facilitate the spread of resistant bacteria [2,3] (Odenholt et al., 2003; Riedel et al., 2007).

Respiratory tract infection (RTI) is caused by viruses and bacteria, however, a majority of cases are caused by viruses [4] (Ieven et al., 2018). It is often difficult to immediately distinguish viral and bacterial RTI in the absence of specialized diagnostic tools [5] (Whaley et al., 2013). Consequently, clinicians, in the absence of such tools, are usually tempted to recommend antibiotics to patients with RTI in an attempt to not miss a potentially serious bacterial RTI [6] (Horwood et al., 2016). This practice is problematic considering that patients with viral RTI will not benefit from antibiotics and such unnecessary use of antibiotics facilitates the spread of antibiotic resistance [3] (Riedel et al., 2007).

According to the Federal House of Representatives of Nigeria, there is a shortage of primary healthcare centres in Nigeria, with less than 20% of the 30,000 primary healthcare centres in Nigeria functioning [7] (Baiyewu, 2021). Consequently, private community (PC) pharmacies – rather than primary healthcare centres – routinely provide primary healthcare services [8] (Ihekoronye and Osemene, 2020). In Nigeria, staff of PCPs include pharmacists and pharmacy assistants. The
pharmacists have Bachelor of Pharmacy and/or Doctor of Pharmacy degrees. They manage PCPs. Pharmacy assistants are well-trained by pharmacists to assist in the day-to-day running of PCPs. They are supervised by pharmacists. PCPs provide consultation services to patients, and then dispense medications accordingly or refer them to hospitals [8] (ibid.). This role played by PCPs is very important as it ensures that primary healthcare is not completely absent in many communities in Nigeria. However, it has its demerits – one of the most important is that it could encourage the unnecessary use of antibiotics as antibiotics are frequently dispensed to patients without prescriptions.

Accordingly, most patients in Nigeria with RTI receive their treatments in PCPs [8] (ibid.). In their study to assess the non-prescription dispensation of antibiotics to patients with RTI by PCPs in Nigeria, Akpan et al. [9] (2021) found that antibiotics were recommended to 68% of such patients.

Plasma C-reactive protein (CRP) rises well above normal when there is a bacterial infection [10] (Hjortdahl et al., 1991) and thus plasma CRP level can be used to identify bacterial RTI. CRP testing is effective at reducing the unnecessary use of antibiotics for RTI without exposing patients to risks [11] (Do et al., 2016).
A cluster design was used because clusters (PCPs) were the targets of the intervention.

2b – Aims (page 5)

This study aimed to ascertain if providing PCPs in Nigeria with CRP test kits and training them on how to use them accordingly in the management of RTI has the potential to improve their objective assessment of antibiotic needs in patients with RTI without prescriptions and reduce their dispensation of antibiotics to such patients. Please see the table attachment for the research in context.

Methods

Trial design

3a – Description of trial design (pages 6 & 7)

This trial was a parallel cluster randomized controlled trial with an allocation ratio of 1:1. The clusters were PCPs in Awka, Nigeria.

3b – Changes to methods after trial commencement

Crude analysis was done in order for the impact of adjustments to be seen. Additionally, the gender of the simulated clients was included in the statistical models in order to account for any effects it may have on the outcomes.

Participants

4a – Eligibility criteria for participants (page 6)

The trial clusters – PCPs – were also the participating units in this trial. A PCPs was considered eligible to be included in the study if it is experienced with blood testing – ascertained by checking if it provides malaria and/or typhoid blood test services. An eligibility assessment of PCPs was done by a member of the research team. They presented as a client to PCPs and asked pharmacy staff
whether they provide malaria and typhoid test services. They told pharmacy staff that they would return for the test(s), where necessary.

4b – Settings and locations (page 6)

The trial was conducted in Awka, Nigeria. There are over 60 PCPs in Awka.

Interventions

5 – Interventions (pages 7 & 8)

PCPs in the intervention arm were provided with CRP test kits (the kits were specially produced for the trial by Zhuhai Encode Medical Engineering Co., Ltd, China) and other test materials, and their staff were trained on how to use the kits and how to use test results to distinguish viral and bacterial aetiologies in patients with suspected RTI without prescriptions in order to make more effective decisions regarding antibiotic dispensation. The CRP test kits were semi-quantitative in nature. The cost of a single CRP test kit was 0.75 USD. The test involves using finger prick blood to assess the level of CRP in the blood. Each test takes just over 5 minutes. It has been shown that CRP concentrations > 30 mg/L in patients with RTI are of great importance in the identification of RTI that should be managed with antibiotics [13] (van Vugt et al., 2013). This is best interpreted as – among patients with RTI, those with CRP concentrations of > 30 mg/L are likely to have bacterial RTI, while those with CRP concentrations of ≤ 30 mg/L are likely to have viral RTI. Other studies suggest that it is not unusual for many patients with viral RTI to have CRP concentrations > 30 mg/L, albeit patients with viral RTI are unlikely to have CRP concentrations > 100 mg/L [10,14] (Hjortdahl et al., 1991; Putto et al., 1985). Considering these, regarding managing patients with suspected RTI without prescriptions, pharmacy staff were advised to not dispense antibiotics to patients with CRP concentrations < 30 mg/L, to use their clinical judgment to come to a decision when patients have CRP concentrations ≥ 30 mg/L but < 100 mg/L, and to dispense antibiotics when patients have CRP concentrations ≥ 100 mg/L. They were not discouraged from using their professional judgment where necessary, regardless of CRP test results.
Training, which included practical demonstration, was carried out in each PCPs by a pharmacist and a medical laboratory technician. The training was delivered, by the same professionals, in exactly the same way across the board. The staff of PCPs were provided with training materials. They were asked to charge no more than 400 NGN (approximately 1 USD) per CRP test in order to ensure that low-income patients were not excluded. They were followed up regularly throughout the post-intervention period and any problems they had were addressed. PCPs in the control arm received no intervention.

**Outcomes**

**6a – Outcomes (pages 9 & 10)**

The primary outcome was the rate at which antibiotics were dispensed to patients with RTI without prescriptions – that is, the proportion of visits in which antibiotics were dispensed. The secondary outcome was the rate at which a medical test for identifying bacterial RTI was conducted to inform decisions regarding non-prescription antibiotic dispensation to patients with RTI – that is, the proportion of visits in which relevant tests were conducted.

Data were collected by simulated clients who were students of Nnamdi Azikiwe University, Nigeria, recruited by the research team. The simulated clients were trained on what the data collection entailed. The training was fundamentally delivered twice – shortly after the simulated clients were recruited and a few days before data collection started. Each training consisted of a 2-hour lecture. The simulated clients were provided with training materials. Following the second training, they were engaged in a 6-hour role play in which some members of the research team acted as pharmacy staff while the simulated clients acted as patients with RTI. Any mistakes made by them were corrected by members of the research team. On the day that each simulated client would collect data, the research team member who supervised the data collection discussed essential parts of the data collection protocol with them.
At baseline, 30 simulated clients collected data over 30 data collection days – on each data collection day, just one simulated client visited and collected data from the 20 PCPs under the supervision of a member of the research team who monitored each visit from a distance. Similarly, post-intervention, 30 simulated clients collected data over 30 data collection days – on each data collection day, just one simulated client visited and collected data from the 20 PCPs under the supervision of a member of the research team who monitored each visit from a distance. The PCPs did not anticipate the visits by the simulated clients. Male and female simulated clients mostly collected data on alternate data collection days. On their data collection day, each simulated client was told the symptoms of RTI to complain about. They complained of the same symptoms across all the 20 PCPs. The symptoms complained of over the 30 days of data collection at baseline and post-intervention can be found in the appendix. These symptoms were developed leveraging the common symptoms of RTI as documented in the literature [15,16,17] (Altiner et al., 2009; Kuchar et al., 2015; National Health Service UK, 2021).

After presenting their symptoms without any prescriptions, they asked the pharmacy staff what the best treatments for their symptoms were. They did not request any particular treatments. They did not admit to having any other symptoms outside what they had been told to complain about. They also did not admit to already visiting a doctor or taking any medications. They noted if relevant medical tests were ordered by pharmacy staff to determine suitable treatments and memorized any drugs they recommended. To aid memorization, they mostly memorized the brand names of drugs – these were subsequently categorized as antibiotic or non-antibiotic by a pharmacist. To ensure good simulation, they paid for tests ordered and/or drugs recommended by pharmacy staff. On visits where the budget for drugs was exceeded, they told pharmacy staff that they would return at a later time to purchase recommended drugs. At the end of each visit, they recorded the data collected on a structured data collection form held by the member of the research team who supervised them.

Please see the table attachment for the demographic characteristics of the simulated clients.
6b – Changes to outcomes after trial commencement

Not applicable

Sample size

7a – Sample size determination (page 10)

The number of PCPs included in this trial and the number of visits assessed in each PCPs at baseline and post-intervention was based on the recommendations of the World Health Organization [18] (1993) regarding the number of facilities and visits to be assessed when evaluating the impact of interventions on drug use practices in healthcare facilities. According to the recommendation, there should be at least ten healthcare facilities in the intervention arm and ten healthcare facilities in the control arm, and data should be collected from at least thirty clinical visits/encounters in each of the healthcare facilities at baseline and post-intervention.

7b – Interim analysis and stopping guidelines

Not applicable

Randomization

Sequence generation

8a – Method used to generate sequence (page 7)

The random sequence (consisting of 1s and 2s) was generated using Research Randomizer [12] (Urbaniak and Plous, 2013).

8b – Details of randomization (page 7)

Stratified block randomization was done. The stratification variable was based on the percentage of encounters (visits) in which an antibiotic was dispensed by PCPs at baseline (details of how this information was collected are in 6a above). It had three strata – low, moderate, and high. PCPs that dispensed antibiotics in < 70%, 70% - 89%, and ≥ 90% of visits at baseline were respectively
categorized into the low (four PCPs), moderate (ten PCPs), and high (six PCPs) strata. Each stratum had a separate list. Two sets of random numbers (two numbers per set), five sets of random numbers (two numbers per set), and three sets of random numbers (two numbers per set) were respectively generated for the low, moderate, and high strata.

Allocation concealment

9 – Mechanism used to implement sequence and approach to concealment (page 7)

By following the random sequence after it was shared with the research team, PCPs within the list of each stratum were assigned 1 or 2 sequentially. The code (specifying which number represented intervention) was shared with the trial team after the assignments had been finalised.

Implementation

10a – Who generated the random sequence, who enrolled clusters, and who assigned clusters to interventions (pages 6 & 7)

The random sequence for each stratum (consisting of 1s and 2s) was generated and coded (specifying which number represented intervention) by an individual who was not part of the research team. The clusters were enrolled and assigned to treatment groups by the research team.

10b – Mechanism by which individual participants were included in clusters

The clusters – PCPs – were also the participating units in this trial.

10c – From whom consent was sought and was it before or after randomization (page 6)

Consent was sought before randomization. Following eligibility assessment, PCPs that met the inclusion criteria were approached by the principal investigator and relevant details were verbally provided to their managers. If a manager did not provide consent, another eligible PCPs was approached. Two written consent forms were given to the managers, who provided consent, to sign. The consent forms were equally signed by the principal investigator who then left with one copy.
Blinding

11a – Who was blinded (page 7)

The simulated clients who collected data were masked.

11b – Similarity of interventions

Not applicable

Statistical methods

12a – Statistical methods used to compare groups (pages 10 & 11)

Missing post-intervention data were multiply imputed in R (version 4.2.1) using the jomoImpute function of the mitml package (version 0.4.3) [19] (Grund et al., 2021). For the multiple imputation regarding the adjusted analysis – the multiple imputation model included the primary and secondary outcome variables as target variables; treatment status, stratification, and simulated client gender variables as fixed effect predictor variables; and PCPs identification variable as a cluster indicator variable. The difference in the multiple imputation regarding the crude analysis was that the fixed effect predictor variable was just the treatment status variable. Regarding missing baseline data, missing primary outcome data were multiply imputed using jomoImpute, with the primary outcome variable as the target variable and the PCPs identification variable as the cluster indicator variable. In every case of multiple imputation, 20 imputations were generated because this number of imputations is adequate [20] (Schafer and Graham, 2002). Convergence was assessed using the potential scale reduction factor.

Relevant frequencies were computed using SPSS Statistics 24. Relevant percentages were then computed accordingly. For the adjusted analysis – using the glmer function of the lme4 package (version 1.1.30) in R [21] (Bates et al., 2015), generalized linear mixed-effects model (GLMM) based on random intercept; with the treatment status, stratification, and simulated client gender variables as fixed effects, and PCPs identification variable as a random effect; was used to ascertain if there
was a significant difference in the rate at which antibiotics were dispensed in the intervention and control arms after the intervention. The difference in the crude analysis was that the fixed effect was just the treatment status variable. The random effect was used to account for any correlation in the data repeatedly collected from each PCPs. The stratification variable was taken into account because not doing so could lead to wrong p-values and confidence intervals [22] (Kahan and Morris, 2012).

Analysis was based on the multiply imputed dataset – multiple imputation analysis, and also based on the original dataset with missing data – complete case analysis.

12b – Additional analyses

Not applicable

Results

Participant flow

13a and 13b – Trial profile (page 12, figure attachment)

Ten PCPs were randomly assigned to each of the intervention and control arms. They were all treated accordingly. None of the PCPs that were randomized withdrew. In 5 of the 600 visits (0.83%) at baseline, no data were collected. For the control arm, in 7 of the 300 (2.33%) visits post-intervention, no data were collected. For the intervention arm, in 1 of the 300 visits (0.33%) post-intervention, no data were collected. These were mostly because the concerned PCPs were closed or did not have relevant drugs in stock when simulated clients visited.

Recruitment

14a – Dates defining the periods of recruitment and follow-up (page 12)

Sixty-four PCPs were assessed for eligibility. Forty-one did not meet the inclusion criteria.

Recruitment of PCPs took place from January 21, 2022, to February 17, 2022. Three PCPs that met the inclusion criteria were excluded because their managers did not provide consent. Twenty PCPs
that met the inclusion criteria were included in the trial and randomized. The trial ended on July 23, 2022.

**14b – Why the trial ended (page 12)**

The trial ended because the post-intervention data collection was completed.

**Baseline data**

**15 – Table showing baseline characteristics (table attachment)**

**16, 17a, and 17b – Main results (pages 11, 12 & 13, table attachment)**

Analyses were by intention-to-treat.

Regarding the primary outcome in the adjusted analysis (table 4) – in the multiple imputation analysis, antibiotics were dispensed to simulated clients in 209/300 (69·67%) and 256/300 (85·33%) visits in the intervention and control arms respectively (odds ratio = 0·279, 95% confidence interval = 0·107 – 0·726; p-value = 0·0090; absolute reduction in antibiotic dispensation = 15·66%). Regarding the primary outcome in the crude analysis (table 4) – in the multiple imputation analysis, antibiotics were dispensed to simulated clients in 208/300 (69·33%) and 256/300 (85·33%) visits in the intervention and control arms respectively (odds ratio = 0·299, 95% confidence interval = 0·098 – 0·911; p-value = 0·034; absolute reduction in antibiotic dispensation = 16%).

Regarding the secondary outcome (table 5) – in the multiple imputation analysis, medical tests for identifying bacterial RTI (CRP tests) were conducted on simulated clients in 65/300 (21·67%) and 0/300 (0%) visits in the intervention and control arms respectively. Based on the complete case analysis, antibiotics were not subsequently dispensed in 28/64 (43·75%) of the visits in which CRP tests were conducted.

**18 – Results of ancillary analysis**

Not applicable
Discussion

Limitations

20 – Main trial limitations (page 15)

This study did not investigate what would happen if patients without prescriptions directly request to be given antibiotics for their RTI rather than merely complaining about their RTI symptoms. This could be addressed in future trials. In addition, although pharmacy staff did not anticipate the visits by the simulated clients, it is not possible to say with certainty that there was no Hawthorne effect. Therefore, this effect may have contributed to some of the effects observed in this study.

Generalisability

21 – Generalisability of findings of the trial (pages 14 & 15)

Antibiotic dispensation for RTI in children was not captured as all the simulated clients were adult, university students who were the only population group readily available to work as simulated clients within the resources available for the study. This may limit the generalizability of the findings of this study to the paediatric population. Additionally, it may be that PCPs that fail to meet the inclusion criteria differ significantly – with respect to blood testing experience – from those that were included in the study, thereby threatening the generalizability of the findings of this study to them. However, this is unlikely to be the case. Malaria and typhoid tests were preferentially used to assess blood testing experience solely because the concerned conditions are not sensitive as to make the individual who assessed eligibility uncomfortable. Most PCPs that fail to meet the inclusion criteria are likely to be equally experienced with blood testing by virtue of offering other blood test services, including blood glucose test which has been shown to be routinely offered by PCPs in Nigeria [8] (Ihekoronye and Osemene, 2020).
Interpretation

22 – Comprehensive interpretation (pages 13 – 15)

This is the first study to assess the impact of access to CRP test kits, and staff training on how to use them in RTI management, on the non-prescription dispensation of antibiotics for RTI in PCPs – a situation that is largely seen in many resource-limited settings [9,23,24] (Akpan et al., 2021; Chen et al., 2020; Zawahir et al., 2022). Previous studies that assessed the impact of access to CRP test kits – and staff training on how to use them in RTI management – in PCPs [25,26] (Sim et al., 2021; Wakeman et al., 2018) focused on how the rate at which patients subsequently visit a general practitioner with the hope of receiving an antibiotic prescription got affected.

This study shows that access to CRP test kits – and staff training on how to use them in RTI management – in PCPs reduces the non-prescription dispensation of antibiotics for RTI; as there was an absolute reduction – in the non-prescription dispensation of antibiotics – of 15·66% and 16%, based on the multiple imputation regarding the adjusted analysis and crude analysis respectively.

Before making treatment decisions, PCPs in the intervention arm conducted CRP tests on simulated clients in 21·40% of visits and 21·67% of visits, based on the complete case analysis and multiple imputation analysis respectively. No such tests were conducted in the control arm. The results of the CRP tests (that is, viral, or bacterial, or uncertain) were not explicitly assessed. However, considering that the simulated clients were healthy adults, they were all expected to have CRP levels of < 30 mg/L (and hence the CRP tests should suggest that they require no antibiotics). Antibiotics were not dispensed in 43·75% of the visits in which CRP tests were conducted, based on the complete case analysis.

Although the percentage of visits in which CRP tests were conducted is not quite high, the observed uptake of CRP testing suggests that CRP testing in PCPs is feasible. At the end of the trial, key pharmacy staff in the intervention arm were interviewed to ascertain any challenges they had regarding CRP testing. This will be reported separately and will, hopefully, provide insight into
strategies that could be used to improve the uptake of CRP testing in future interventions of this kind.

The findings of this trial are similar to that of a trial conducted in Vietnam, a resource-limited setting, to assess the impact of access to CRP test kits – and staff training on how to use them in RTI management – in primary healthcare centres on antibiotic use for RTI. In the trial, Do et al. [11] (2016) reported that access to CRP test kits – and staff training on how to use them in RTI management – reduced antibiotic prescribing for RTI by 20%. This suggests that access to CRP test kits – and staff training on how to use them in RTI management – is as effective in reducing healthcare practitioners’ offer of antibiotics for RTI in PCPs as it is in primary healthcare centres in resource-limited settings.

Given that PCPs play an important role in the unnecessary use of antibiotics for RTI in resource-limited settings as they frequently dispense antibiotics to patients with RTI without prescriptions [9,23,24] (Akpan et al., 2021; Chen et al., 2020; Zawahir et al., 2022), an intervention of this nature has the potential to improve antibiotic use for RTI and therefore reduce the spread of antibiotic resistance when implemented in such settings. If economic analysis shows that the cost of implementing this intervention in resource-limited settings is manageable, then – all things being equal – its implementation by relevant stakeholders in such settings is recommended; as this would be very helpful in the fight against antibiotic resistance.

Access to CRP test kits – and staff training on how to use them in RTI management – in PCPs in Nigeria improved the objective assessment of antibiotic needs in patients with RTI without prescriptions and reduced the dispensation of antibiotics to such patients. All things being equal; if economic analysis shows that the cost of implementing this intervention in resource-limited settings is manageable, its implementation by relevant stakeholders in such settings is recommended – as this would help reduce the burden of antibiotic resistance.
Other information

Registration

23 – Registration number and registry (page 16)

The trial was prospectively registered at the Pan African Clinical Trials Registry. Its registration
number is PACTR202111611256940.

Protocol

24 – Where protocol can be accessed (page 16)

The study protocol will be available to researchers who request it from the corresponding author.

Funding

25 – Funders and their roles (page 16)

This study was funded by the Royal Society of Tropical Medicine and Hygiene, UK, in partnership
with the National Institute for Health and Care Research, UK. The funders did not contribute to the
study design, data collection, data analysis and interpretation, manuscript writing, and submission.

References

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factor for selection of penicillin-resistant \textit{streptococcus pneumoniae} : In vitro kinetic model.


PROTOCOL

Title

Assessing the potential of c-reactive protein testing to reduce antibiotic dispensation for respiratory tract infections by private community pharmacies in Nigeria: protocol for a cluster randomized controlled trial

Summary

In Nigeria, bacteria responsible for different infections frequently resist the antibiotics used to eliminate them, making the treatment of infectious diseases difficult. Antibiotic overuse facilitates the spread of resistant bacteria. Overuse occurs in private community pharmacies where antibiotics are frequently dispensed to respiratory tract infection (RTI) patients without prescriptions. This study fundamentally aims to ascertain if providing private community pharmacies in Nigeria with c-reactive protein test kits and training them on how to use them to assess antibiotic needs in patients with RTI without prescriptions will reduce their use of antibiotics in such patients.

Background

In Nigeria, bacteria responsible for different infections frequently resist the antibiotics used to eliminate them, making the treatment of infectious diseases difficult [1] (Musa et al., 2020). Antibiotic overuse facilitates the spread of resistant bacteria [2] (Riedel et al., 2007). Overuse occurs in private community pharmacies in Nigeria where antibiotics are frequently dispensed to respiratory tract infection (RTI) patients without prescriptions [3] (Akpan et al., 2021), despite the fact that most RTI patients do not require antibiotics [4] (Ieven et al., 2018).
Plasma C-Reactive Protein (CRP) rises above normal when there is a bacterial infection and thus plasma CRP level can be used to diagnose bacterial infections [5] (Hjortdahl et al., 1991). A CRP test can safely be used to assess antibiotic needs in patients with RTI [6] (Do et al., 2016).

This trial aims to evaluate the impact, on the rate of objective assessment of antibiotic needs in patients with RTI without prescriptions and the rate of non-prescription dispensing of antibiotics to patients with RTI, of providing private community pharmacies with CRP test kits and training them on how to use them to inform antibiotic dispensation for RTI. This will be the first study to evaluate this.

**Methodology**

**Study design**

A cluster randomized controlled trial (RCT) will be conducted in Awka, Nigeria. A cluster RCT will be conducted because the intervention is targeted at clusters (private community pharmacies).

**Participants**

Twenty private community pharmacies will participate in the trial.

**Eligibility criteria**

To be included, a private community pharmacy must be registered with the Pharmacists Council of Nigeria and have a registered pharmacist on duty always. Prospective private community pharmacies will be excluded if they do not consent to participate and/or if they already use a diagnostic technique to inform antibiotic dispensation to RTI patients.

**Changes to eligibility criteria**

**Amended/final eligibility criteria**

To be included, a private community pharmacy must be experienced with blood testing. This will be assessed by ascertaining if it provides malaria and/or typhoid blood test services.
Prospective private community pharmacies will be excluded if they do not consent to participate and/or if they already use a diagnostic technique to inform antibiotic dispensation to RTI patients.

**Reasons for changes to eligibility criteria**

The original inclusion criteria were dropped because they could not be assessed efficiently. The final inclusion criterion was added to ensure that the private community pharmacies included in the study would be able to adapt to the intervention procedure within the timeframe available for the collection of post-intervention data.

**Randomization and masking**

Private community pharmacies will be randomly allocated to the intervention and control arms on a 1:1 basis using the block randomization technique. The random sequence will be generated by an individual who is not part of the trial team. They will share associated codes with the research team after the treatment assignment has been finalized. Accordingly, there will be ten private community pharmacies per study arm. Private community pharmacies will not be masked to assigned treatment. The simulated clients who will collect data will be masked.

**Changes to randomization and masking**

*Amended/final randomization and masking*

Private community pharmacies will be randomly allocated to the intervention and control arms on a 1:1 basis using a stratified block randomization technique. The random sequence will be generated by an individual who is not part of the trial team. They will share associated codes with the research team after the treatment assignment has been finalized. Accordingly, there will be ten private community pharmacies per study arm. Private community pharmacies will not be masked to assigned treatment. The simulated clients who will collect data will be masked.
Reasons for changes to randomization and masking

Stratified block randomization, rather than block randomization, was used. This was to ensure that private community pharmacies in both arms were balanced with respect to the baseline value of the primary outcome.

Procedure

Each private community pharmacy in the intervention group will be provided with CRP test kits and will be trained accordingly on how to use them and how to use test results to make decisions regarding antibiotic dispensation to patients with RTI without prescriptions. Private community pharmacies in the control group will receive no intervention and will manage RTI patients as they usually do.

Outcome

The primary outcome is the rate at which private community pharmacies dispense antibiotics to RTI patients without prescriptions. The secondary outcome is the rate at which private community pharmacies conduct medical tests for identifying bacterial RTI to enable them make informed decisions regarding antibiotic dispensation to RTI patients without prescriptions.

Outcome data will be collected by trained simulated clients who will visit the private community pharmacies without prescriptions, pretending to have RTI. At baseline, 30 simulated clients will collect data over 30 data collection days. On each data collection day, one simulated client will visit and collect data from the 20 PCPs. Post-intervention, 30 simulated clients will collect data over 30 data collection days. On each data collection day, one simulated client will visit and collect data from the 20 PCPs. Data collection will be supervised by a member of the research team who will monitor each visit from a distance. On their visits, the simulated clients will make relevant observations during their transactions. At the end of each visit, they will record their findings on a structured data collection form that will be held by their supervisor.
Statistical considerations

The number of private community pharmacies to be included in the trial and the number of visits to be assessed in each private community pharmacy at baseline and post-intervention is based on the recommendations of the World Health Organization [7] (1993) regarding the number of facilities and visits (encounters) to be assessed when evaluating the impact of interventions on drug use practices in healthcare facilities.

All analyses will be based on the original assignment. Relevant frequencies will be computed using descriptive statistics. The primary outcome in the intervention and control arms will be compared, taking the clustered nature of the data (due to repeated observations per private community pharmacy) into account. P-values (< 5% indicating statistical significance) and 95% confidence intervals will be provided as necessary. If there are missing data, these will be imputed and results will be displayed for analysis done with both the imputed dataset and the incomplete dataset.

Changes to statistical considerations

Amended/final statistical considerations

The number of private community pharmacies to be included in the trial and the number of visits to be assessed in each private community pharmacy at baseline and post-intervention is based on the recommendations of the World Health Organization [7] (1993) regarding the number of facilities and visits (encounters) to be assessed when evaluating the impact of interventions on drug use practices in healthcare facilities.

All analyses will be based on the original assignment. Relevant frequencies will be computed using descriptive statistics. The primary outcome in the intervention and control arms will be compared, taking the clustered nature of the data (due to repeated observations per private community pharmacy), the stratified nature of randomization, and the gender of simulated clients into account. A crude analysis will also be conducted. P-values (< 5% indicating statistical significance) and 95% confidence intervals will be provided as necessary. If there
are missing data, these will be imputed and results will be displayed for analysis done with both the imputed dataset and the incomplete dataset.

**Reasons for changes to statistical considerations**

The stratified nature of randomization was added to what would be accounted for while comparing the primary outcome in the intervention and control arms. This was done in response to the randomization technique changing from block randomization to stratified block randomization. A decision was made to conduct a crude analysis in order for the impact of adjustments to be seen. The gender of the simulated clients was included in the statistical models in order to account for any effects it may have on the outcomes.

**Ethics**

**Ethical approval**

Ethics approval will be obtained, as necessary, from the Research Ethics Committee of Chukwuemeka Odumegwu Ojukwu University Teaching Hospital (COOUTH), Awka, Nigeria.

**Consent**

All prospective private community pharmacies, through their managers, will be given a thorough explanation of what the study entails, their rights, and how their data will be handled – that is, with strict confidentiality – by the principal investigator. Prospective private community pharmacies will only be included in the study after their managers have signed relevant consent forms.

“Confidentiality” here means that measures, notably proper de-identification, will be taken to ensure that participants cannot be identified by anyone outside the research team.
Data sharing

All the data from this study will be made available, where appropriate, after they have been carefully de-identified. They will be available for 5 years from the publication date. The study protocol, statistical analysis plan, statistical codes, and informed consent form will equally be available. To access these, researchers have to send a request to the corresponding author who will review and grant access, where appropriate, after relevant data access agreements have been signed.

Declaration of interests

No competing interests are declared.

Funding

This trial is funded by the Royal Society of Tropical Medicine and Hygiene, UK, and the National Institute for Health and Care Research, UK

References


64 PC pharmacies were assessed for eligibility

44 PC pharmacies were excluded
- 41 did not meet the inclusion criteria
- 3 declined to participate

20 PC pharmacies were included in the trial and 600 visits were made at baseline
- 5 baseline visits had no data – relevant primary and secondary outcome analysis respectively leveraged multiple imputation and complete case analysis

20 PC pharmacies were randomized

10 PC pharmacies were allocated to the intervention arm
- 10 PC pharmacies received the allocated treatment

10 PC pharmacies were allocated to the control arm
- 10 PC pharmacies received the allocated treatment

No PC pharmacy withdrew from the trial
- 300 visits were made post-intervention
  - 1 visit had no data

No PC pharmacy withdrew from the trial
- 300 visits were made post-intervention
  - 7 visits had no data

Data from 10 PC pharmacies was analysed post-intervention
- Data from 300 visits were included in the multiple imputation analysis
- Data from 299 visits were included in the complete case analysis

Data from 10 PC pharmacies was analysed post-intervention
- Data from 300 visits were included in the multiple imputation analysis
- Data from 293 visits were included in the complete case analysis

Figure 1: Trial profile
Evidence before this study

We searched the title, abstract, and keywords in Scopus using the following terms: (respiratory AND tract AND infection*) OR (upper AND respiratory AND tract AND infection*) OR rti OR urti AND (antibiotic*) AND ((c-reactive AND protein) OR (c AND reactive AND protein) OR crp) AND (pharmacy OR pharmacies). No restrictions were placed on the search. Two studies, that assessed the impact of access to CRP test kits – and staff training on how to use them in RTI management – in PCPs on the rate at which patients with RTI subsequently visit general practitioners with the hope of getting antibiotic prescriptions, were found. They were conducted in the United Kingdom and Australia.

The added value of this study

The studies found through our search did not assess the impact of access to CRP test kits – and staff training on how to use them in RTI management – on the rate of non-prescription dispensing of antibiotics for RTI. Instead, they assessed the impact of access to CRP test kits – and staff training on how to use them in RTI management – on the rate at which patients with RTI subsequently visit general practitioners with the hope of getting antibiotic prescriptions. This means that no study has assessed the impact of access to CRP test kits, and staff training on how to use them in RTI management, on the rate of non-prescription dispensing of antibiotics for RTI in PCPs – a situation that is frequently seen in resource-limited settings. This study addresses this gap by assessing how access to CRP test kits – and staff training on how to use them in RTI management – impacts the rate at which PCPs objectively assess antibiotic needs in patients with RTI without prescriptions and the rate at which they dispense antibiotics to such patients.

Implications of all the available evidence

Access to CRP test kits – and staff training on how to use them in RTI management – in PCPs in Nigeria improved the objective assessment of antibiotic needs in patients with RTI without prescriptions and reduced the dispensation of antibiotics to such patients. All things being equal; if economic analysis shows that the cost of implementing this intervention in resource-limited settings is manageable, its implementation by relevant stakeholders in such settings is recommended – as this would help reduce the burden of antibiotic resistance.

Table 1: Research in context
Table 2: Demographic characteristics of simulated clients who collected post-intervention and baseline data

<table>
<thead>
<tr>
<th></th>
<th>Post-intervention (n = 30)</th>
<th>Baseline (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>15 (50%)</td>
<td>14 (46.7%)</td>
</tr>
<tr>
<td>Male</td>
<td>15 (50%)</td>
<td>16 (53.3%)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 – 21</td>
<td>11 (36.7%)</td>
<td>17 (56.7%)</td>
</tr>
<tr>
<td>22 – 25</td>
<td>19 (63.3%)</td>
<td>13 (43.3%)</td>
</tr>
</tbody>
</table>

Data in the post-intervention and baseline columns are number of simulated clients (%).

Table 3: Characteristics of PCPs regarding the percentage of visits in which antibiotics were dispensed, and the percentage of visits in which relevant tests were conducted, at baseline

<table>
<thead>
<tr>
<th></th>
<th>Analysis</th>
<th>Percentage</th>
<th>Relative interpretation</th>
<th>Intervention (n = 10)</th>
<th>Control (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visits in which antibiotics were dispensed</td>
<td>Multiple imputation</td>
<td>&lt; 70%</td>
<td>Low</td>
<td>2 (20%)</td>
<td>2 (20%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>70% – 89%</td>
<td>Moderate</td>
<td>5 (50%)</td>
<td>5 (50%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 90%</td>
<td>High</td>
<td>3 (30%)</td>
<td>3 (30%)</td>
</tr>
<tr>
<td>Visits in which relevant tests were conducted</td>
<td>Complete case</td>
<td>0%</td>
<td></td>
<td>10 (100%)</td>
<td>10 (100%)</td>
</tr>
</tbody>
</table>

Data in the intervention and control columns are number of PCPs (%).
**Table 4:** Post-intervention visits in which antibiotics were dispensed

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Intervention</th>
<th>Control</th>
<th>OR (95% CI)</th>
<th>P-value</th>
<th>AE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adjusted analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple imputation</td>
<td>209/300 (69·67%)</td>
<td>256/300 (85·33%)</td>
<td>0·279 (0·107 – 0·726)</td>
<td>0·0090</td>
<td>15·66%</td>
</tr>
<tr>
<td>Complete case</td>
<td>208/299 (69·57%)</td>
<td>250/293 (85·32%)</td>
<td>0·273 (0·104 – 0·716)</td>
<td>0·0083</td>
<td>15·75%</td>
</tr>
<tr>
<td><strong>Crude analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple imputation</td>
<td>208/300 (69·33%)</td>
<td>256/300 (85·33%)</td>
<td>0·299 (0·098 – 0·911)</td>
<td>0·034</td>
<td>16%</td>
</tr>
<tr>
<td>Complete case</td>
<td>208/299 (69·57%)</td>
<td>250/293 (85·32%)</td>
<td>0·297 (0·097 – 0·907)</td>
<td>0·033</td>
<td>15·75%</td>
</tr>
</tbody>
</table>

- Data in the intervention and control columns are events/n (%).
- AE means absolute effect. Data in AE are the absolute difference between the percentages in the intervention and control columns.
- OR means odds ratio.
- CI means confidence interval.

**Table 5:** Post-intervention visits in which relevant tests (CRP tests) were conducted, with clarification regarding those without subsequent antibiotic dispensation

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Intervention</th>
<th>Control</th>
<th>AE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visits in which relevant tests were conducted</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple imputation</td>
<td>65/300 (21·67%)</td>
<td>0/300 (0%)</td>
<td>21·67%</td>
</tr>
<tr>
<td>Complete case</td>
<td>64/299 (21·40%)</td>
<td>0/293 (0%)</td>
<td>21·40%</td>
</tr>
<tr>
<td>Visits without antibiotic dispensation following relevant tests</td>
<td>Complete case</td>
<td>28/64 (43·75%)</td>
<td>..</td>
</tr>
</tbody>
</table>

- Data in the intervention and control columns are events/n (%).
- AE means absolute effect. Data in AE are the absolute difference between the percentages in the intervention and control columns.
- The multiple imputation model is that of the adjusted analysis.
Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: