# Optimising antibiotic exposure by customising the duration of treatment for respiratory tract infections based on patient needs in primary care

Carl Llor,[a,b,c,*] Niels Frimodt-Møller,[d] Marc Miravitlles,[e] Gunnar Kahlmeter,[f] and Lars Bjerrum[g]

[a]University Institute in Primary Care Research Jordi Gol, Catalan Institute of Health, Barcelona, Spain
[b]CIBER de Enfermedades Infecciosas, Madrid, Spain
[c]Research Unit for General Practice, Department of Public Health, University of Southern Denmark, Odense, Denmark
[d]Department of Clinical Microbiology, Rigshospitalet, Copenhagen, Denmark
[e]Pneumology Department, Hospital Universitari Vall d'Hebron, Vall d'Hebron Institut de Recerca, Vall d'Hebron Hospital Campus, CIBER de Enfermedades Respiratorias, Barcelona, Spain
[f]Department of Clinical Microbiology, Central Hospital, EUCAST Development Laboratory, Växjö, Sweden
[g]Section and Research Unit of General Practice, Department of Public Health, University of Copenhagen, Denmark

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## Summary

**Primary care antimicrobial stewardship programs have limited success in reducing antibiotic use, prompting the search for new strategies. Convincing general practitioners to resist antibiotic prescription amid uncertainty or patient demands usually poses a significant challenge. Despite common practice, standard durations for common infections lack support from clinical studies. Contrary to common belief, extending antibiotic treatment beyond the resolution of symptoms does not seem to prevent or reduce antimicrobial resistance. Shortening the duration of antibiotic therapy has shown to be effective in mitigating the spread of resistance, particularly in cases of pneumonia. Recent hospital randomised trials suggest that ending antibiotic courses by day three for most lower respiratory tract infections is effective and safe. While community studies are scarce, it is likely that these shorter, tailored courses to meet patients' needs would also be effective and safe in primary care. Therefore, primary care studies should investigate the outcomes of advising patients to discontinue antibiotic treatment upon symptom resolution. Implementing patient-centred, customised treatment durations, rather than fixed courses, is crucial for meeting individual patient needs.**



Keywords: Duration of therapy; Anti-bacterial agents; Patient-centered care; Respiratory tract infections; Drug resistance; Microbial; Primary health care

## Introduction

The judicious use of antibiotics preserves millions of lives and safeguards numerous individuals from infectious complications annually. However, their continued viability is threatened by rising rates of antimicrobial resistance (AMR), which was responsible for an estimated 1.27 million deaths worldwide in 2019.[1] Excessive and inappropriate antimicrobial use significantly contributes to this crisis. Research indicates a strong correlation between the consumption of antibiotics and the selection of resistant bacteria, both at societal and individual levels.[2,3]

Primary care is responsible for about 80% of antibiotic prescriptions, and respiratory tract infections (RTIs) account for more than half of all antibiotic prescriptions globally.[4] Given the limited development of new antibiotics, prudent antimicrobial utilisation, particularly in primary care, is crucial to mitigating the spread of AMR.[5] Inappropriate use of antibiotics for uncomplicated RTIs is very common worldwide. In the UK around 50% of all general practice consultations for RTIs result in the prescription of an antibiotic, with a high variability across practices ranging from 20% to 80%.[4] In a study comparing the rate of antibiotic prescribing for acute RTIs in Australian general practice from 2010 to 2015, it was found that antibiotics were prescribed at rates 4–9 times higher than those recommended by Australia's most widely used therapeutic guidelines.[6] Even in the Netherlands, which has the lowest antibiotic use in Europe with slightly under ten defined daily doses per 1000 inhabitants per day, it is estimated that nearly half of RTI prescriptions are not in accordance with local guidelines.[7] In the UK, more than half of the patients with acute rhinosinusitis, acute bronchitis and sore throat seen in primary care are

*Corresponding author. Research Unit of General Practice, Department of Public Health, University of Southern Denmark, Campusvej 55, DK-5230, Odense M, Denmark.
*E-mail address:* cllor@health.sdu.dk (C. Llor).

treated with antibiotics.[8] In addition, in many regions around the world, antibiotics are accessible without prescriptions, as shown in a recent study of 38 studies across 24 countries, revealing 62% of non-prescription antibiotic dispensing, mostly for suspected RTIs.[9] Despite being more prevalent in low-income countries, even in some high- and middle-income countries, non-prescription antibiotic provision is a concern.[10] Most acute uncomplicated RTIs are caused by viruses and, in otherwise healthy adults, these infections are typically self-limiting and antibiotics provide no relevant benefits.[11,12]

## Strategies to reduce unnecessary antibiotic prescribing

Several approaches aimed at reducing unnecessary antibiotic use have been suggested (Table 1). While there have been certain local experiences of success, the reduction in unnecessary antibiotic prescribing ranges from moderate to minimal, and even null. Certain strategies prove more effective than others. The most effective approaches identified include improving communication skills during consultations to better understand patient needs, introducing patient leaflets to help patients understand when and when not to use antibiotics, using delayed antibiotic prescribing, and performing point-of-care tests.[13] The effectiveness of antibiotic stewardship programmes has shown considerable variability, with a less pronounced decrease in unnecessary antibiotic use in primary care compared to other settings. A recent systematic review, including six intervention studies, indicated that antimicrobial stewardship programmes reduce antibiotic use among outpatients by an average of 4%.[14] Interventions that address various stakeholders, including the clinicians, the population, and the healthcare system, are generally more effective in reducing unnecessary antibiotic use compared to those that exclusively target professionals. In addition, the impact of these programmes on antibiotic prescribing wanes with time. As a result, primary care physicians, who are potentially the most influential professionals in tackling the issue of AMR, continue to show a consistently high rate of inappropriate and unnecessary antibiotic prescriptions, contributing not only to AMR but also leading to other harmful consequences (Panel 1). We bear the moral responsibility of protecting patients and society from high prescribers, and therefore, there is a clear need for innovative strategies to curtail unnecessary antibiotic use within the community.

| | |
|---|---|
| Interventions targeting healthcare professionals | • Education for professionals<br>• Communication skills training<br>• Guidelines<br>• Clinical decision support systems<br>• Delayed prescribing<br>• Antibiotic deprescribing<br>• Point-of-care diagnostic tests<br>• Selective susceptibility reporting<br>• Quality indicators<br>• Audit and feedback<br>• Restrictive prescribing measures |
| Interventions targeting the public | • Educational material for the general public, schools<br>• Public commitment<br>• Campaigns on TV, radio, public transport, waiting rooms |
| Interventions aimed at modifying the healthcare system | • Limiting over-the-counter use of antibiotics<br>• Unit dispensing of antibiotics<br>• Reducing the number of available antibiotics<br>• Increasing the price of antibiotics<br>• Prescribers' remuneration system<br>• Patient lists<br>• Pay-for-performance<br>• Sickness leave regulation<br>• Limiting advertising of antibiotics |

*Table 1:* **Summary of the interventions aimed at improving antibiotic use in primary care.**

## Factors contributing to antibiotic overprescribing

One of the primary factors contributing to the high rate of inappropriate antibiotic prescribing for common infections is diagnostic uncertainty. The fear of complications is a significant reason why doctors may hesitate to refrain from prescribing antibiotics when in doubt.[15] In primary care, doctors frequently prescribe antibiotics empirically, relying on clinical judgment derived from patient history and physical examination. Obtaining samples for microbiological analysis is considered cumbersome, impractical, expensive and, in most cases, too slow to make an impact. It can be challenging to discourage doctors from prescribing antibiotics when uncertain. Early control of infection and prompt antibiotic administration are crucial for the outcome of some serious infections, such as pneumonia or septic shock, which occur in very few cases, but the risk of which particularly increases in older and frail individuals.[16] However, a recent paper highlighted the lack of relationship between a patient's level of risk and their likelihood of being prescribed an antibiotic in primary care.[17] Some qualitative studies suggest that doctors, prioritising the preservation of their relationship with

***Panel 1:* Risks that have shown to be associated with unnecessary antibiotic use.**

**Increased AMR**

- Increased severity of diseases
- Increased length of disease
- Increased risk of complications
- Increased mortality rate

Increased risk of adverse effects, some of which might be life-threatening.

Reinforcement of patients' belief in the need for antibiotics.

Higher rates of re-attendance for minor infectious diseases.

Greater medicalisation of self-limiting infectious conditions, contributing to more unnecessary use of antibiotics.

Increased healthcare costs.

patients, are reluctant to forgo antibiotic prescriptions, considering it a minor matter. Interestingly, these studies reveal that doctors express more concern about potential consequences for their future relationships with patients than about the threat of AMR.[18] When doctors perceive a demand for antibiotics from patients, they are more inclined to prescribe them. The presence of comorbidities and the inability to effectively negotiate or explain the appropriate use of antibiotics also play crucial roles in explaining the overuse of antibiotics.[19]

## Reducing the duration of antibiotic treatment for respiratory tract infections to combat antimicrobial resistance

Most bacterial RTIs show equal efficacy with fewer adverse events in shorter compared to standard antibiotic courses in clinical trials. This is based on the principle of 'shorter is better,' initially conceived one decade ago.[20] However, there are two notable exceptions: otitis media among children under the age of two and streptococcal pharyngitis, in which shorter first-line antibiotic courses are less effective than standard antibiotic courses.[21,22]

Over the last few decades, most guidelines have recommended standard antimicrobial therapy durations of seven to ten days for lower RTIs. However, few randomised clinical trials have been conducted to determine the minimal effective treatment durations. Despite the low number of patients included in some of these studies, shorter treatment durations, such as two to three days, have been demonstrated not to be inferior to longer durations in terms of clinical efficacy.[23–26] Initially advocated for uncomplicated urinary tract infections in the early 2000s, an increasing body of evidence suggests that shorter durations of antibiotics are also effective in treating most RTIs (Table 2). Some recent clinical guidelines, like the WHO AWaRe antibiotic book, advocate for five-day courses of antibiotics for acute rhinosinusitis, COPD exacerbations, and community-acquired pneumonia.[33] Despite this evidence, most clinicians still use standard or longer courses.[34–36]

## The importance of pharmacokinetic/pharmacodynamic properties for correct dosing of antibiotics

Craig et al. refined the concept of the importance of the time above the minimal inhibitory concentration (MIC) for beta-lactam antibiotics, which refers to the duration of time that serum levels of the antibiotic remain above the MIC at the site of infection. They suggested that for penicillins, this parameter or index should reach at least 50% of the dosing interval to ensure treatment effectiveness.[37,38] For antibiotics like fluoroquinolones, the optimal pharmacokinetic/pharmacodynamic (PK/PD) index is the area under the curve above the MIC (AUC/MIC ratio).[39]

In a recent randomised clinical trial concerning phenoxymethylpenicillin treatment of streptococcal pharyngotonsillitis it was shown that a short course of higher doses of penicillin V, taken four times daily for five days, was non-inferior in clinical outcome to the standard dose taken thrice daily for 10 days.[40] This fits with the above concept that penicillin V due to its relatively short serum elimination half-life should be dosed at least every 6 h to secure a time > MIC of at least 50%. Optimising the bacterial kill also shortens the duration of treatment needed for effect. The optimised dosing regimen concurrently reduces selection of resistance.[41]

| RTI | Studies and population 9 | Evidence |
|---|---|---|
| Streptococcal pharyngitis[22] | 50 RCTs; n = 19,004. 43 studies included outpatients, 1 inpatients, 3 both, 3 unknown. 30 studies included only children. | No differences in clinical cure between shorter (3–5 days) and longer courses (7–14 days), but clinical cure and bacteriological eradication for the first-line antibiotic (penicillin V) favoured longer therapy. |
| Acute bacterial sinusitis[27] | 12 RCTs; n = 4430. All the studies included outpatients with radiologically-confirmed sinusitis. | No differences in clinical improvement in clinical improvement between shorter (3–7 days) and longer courses (6–10 days). |
| Acute otitis media[28] | 49 RCTs; n = 12,045. Randomisation was unclear in one study. All the studies included outpatient children. | The risk of treatment failure was higher with shorter courses (<7 days) compared to longer courses (≥7 days). A subsequent RCT confirmed that a shorter five-day treatment was less effective than a ten-day treatment (66% and 84% clinical cure rate, respectively) in children under two years of age.[21] |
| Acute exacerbations of COPD and chronic bronchitis[29] | 21 RCTs, n = 10,698. 12 studies included outpatients, 1 inpatients, 2 both, 5 unknown. | No differences in clinical improvement between shorter (5 days) and longer courses (7–10 days). The same results were observed in a subsequent systematic review with only spirometrically diagnosed COPD patients.[30] |
| Community-acquired pneumonia (adults)[31] | 15 RCTs; n = 2796. 2 studies included outpatients, 4 inpatients, 6 studies both. | No differences in clinical failure between shorter (3–7 days) and longer courses (8–14 days). Subsequent RCTs confirmed the same results. |
| Community-acquired pneumonia (children)[32] | 9 RCTs; n = 11,143. All studies included outpatients. | No differences in clinical failure between shorter (3–5 days) and longer courses (5–10 days). |

COPD, chronic obstructive pulmonary disease; RCT, randomised clinical trial.

*Table 2:* **Comparison of the effectiveness of short and long courses of antibiotics in systematic reviews in non-severe patients.**

### 'Complete the antibiotic course', a dogma to be debunked

In medical schools we have been taught to advise our patients to always complete an antibiotic course once initiated. This was deemed suitable to minimise the development of AMR.[42] However, this often-heard statement that to prevent AMR it is necessary for patients to complete the entire course, even after the resolution of symptoms, by eradicating every bacterium that could result in a future relapse, remains unproved. To the contrary, the longer patients and the environment are exposed to antibiotics, the greater the selective pressure driving AMR.

Even short courses of antibiotics can have long-term effects causing persistence of resistant organisms lasting years and altering the normal gut microbiome and might be detrimental.[43] By shortening antibiotic duration, overall antibiotic exposure is lessened, reducing the selection pressure for multidrug-resistant organisms.[44] This is particularly evident in patients with pneumonia as some randomised clinical trials have demonstrated that shorter treatments yield similar clinical outcomes to longer courses but are associated with lower rates of infection recurrence and AMR.[23,45] This observation is consistent with what we know about natural selection.[46] AMR emerges at the site of infection in only a few types of infections; moreover, resistance typically emerges off target, among colonising flora away from the site of infection. A recent study showed that for eight of nine potential pathogens of interest, over 80% of their exposures to commonly used antibiotic classes in the outpatient setting occur when the organisms are asymptomatically colonising the microbiome, not causing disease.[47]

Over the last years there has been an increasing number of independent bodies, scientific academies and institutions abandoning this principle on completing antibiotic courses. In addition, in 2017, the World Health Organization abandoned this dogma.[48] The best way to contravene this historical belief is by providing new evidence from randomised clinical trials setting a revised standard for antimicrobial therapy durations. Conventional stewardship strategies aimed at patients not requiring antibiotics do not help those who truly need them but receive excessively long treatment. However, encouraging a minimum duration of therapy might be more attainable than completely refraining from antibiotic therapy, as shown in qualitative studies.[49] In such instances, the potential harm posed by unnecessary therapy to patients without bacterial infections is considerably lower compared to adhering to standard durations, and it can prove beneficial to those with genuine bacterial infections.[50]

### Antibiotic duration for respiratory tract infections should be tailored to the patient's needs

It is evident that there is substantial interindividual variability in how drugs are handled, and it seems unlikely that the optimal duration of therapy is precisely the same for all patients.[51] Factors such as age, comorbidities, underlying health conditions, frailty, and immune status vary among individuals, making it unlikely that a one-size-fits-all approach would be effective. This highlights the importance of individualised and patient-centred medical care, considering the unique characteristics and needs of each patient when determining the duration of therapy for RTIs. Llewelyn et al. emphasized that the traditional idea of completing a fixed antibiotic course overlooks the reality that patients can react differently to the same antibiotic.[52] In hospital settings, several studies indicate that biomarkers like procalcitonin can help determine when to discontinue antibiotic treatment.[53] However, outside of hospitals, where frequent testing is not feasible, patients might be advised to stop treatment once they start feeling better. A clinical trial found that using fever resolution as a guide for stopping antibiotics in cases of community-acquired pneumonia reduced the average duration of antibiotic treatment by half without compromising clinical success.[54] In a landmark study, a three-day antibiotic course with intravenous amoxicillin was as efficacious as 8 days of treatment in adults admitted to hospital with mild to moderate-severe community-acquired pneumonia who substantially improved after an initial three days of therapy, which accounted for 78.5% of the participants.[24] It would not be unreasonable to think that the percentage of patients with pneumonia who feel better after three days would be even higher in primary care. However, studies evaluating the efficacy and safety of discontinuing antibiotic therapy upon the resolution of symptoms have not yet been conducted in the primary care setting.

### Research on customising antibiotic treatment duration to meet individual patient needs is required in primary care

When evaluating a patient with an RTI, our primary objective is to determine whether antibiotic therapy is necessary. There is substantial evidence indicating that antibiotics have little to no impact on self-limiting infections or when a non-bacterial infection is suspected. If patients are taking antibiotics prescribed by another doctor, or if they started taking antibiotics on their own from leftover medications or pharmacy purchases, and the current doctor determines that the antibiotics are no longer needed, they should be stopped (Panel 2). For patients with RTIs in which antibiotic therapy is warranted, more evidence is needed to determine the optimal treatment durations. Traditional two-arm randomised clinical trials comparing fixed antibiotic durations have limitations, as they provide little insight into the minimal necessary duration for various infections[55] and fail to account for the differing needs of individual patients. Based on clinical judgement made from patient history, examination, and precise diagnostic

*Panel 2*: Definitions.

**Antibiotic deprescription**

The act of persuading patients to discontinue a course of antibiotics prescribed by other doctors or self-administered (from leftovers at home or obtained illegally) if deemed unnecessary by clinicians. This approach has been proven to be safe compared to completing the full antibiotic course, with no significant difference in the duration of severe and moderate symptoms. Doctors are more inclined to deprescribe when patients have made the decision to start taking the medication, as opposed to when the antibiotic was prescribed by another doctor (prescriber etiquette). It has been shown to decrease patients' antibiotic use by 80% in uncomplicated respiratory tract infections.[58]

**Delayed antibiotic prescription**

Also known as a back-up prescription, it is given with the advice not to be issued on the same day. It should be issued after a period of time if the symptoms worsen or do not improve. This approach has been proven to be safe in uncomplicated respiratory tract infections, such as acute pharyngotonsillitis or acute otitis media, unless severe symptoms are present. It has been shown to decrease patients' antibiotic use by 60% in uncomplicated respiratory tract infections, with no significant difference in complication rates.[59]

tests, doctors should be encouraged to prescribe first-line treatments at appropriate doses to optimise PK/PD properties, except when contraindicated. Unless the infection is deemed potentially serious, when managing patients with a prescribed fixed antibiotic duration, new studies should ascertain whether treatment cessation upon symptom resolution, prior to completing the antibiotic course, is feasible. In fact, one third of the patients already do that by themselves. Studies using medication event monitoring systems reveal that in real-life scenarios, only one-third of patients adhere to the prescribed antibiotic course.[56] If the results of these studies align with expectations, patients could then be advised to discontinue medication once they feel better and are afebrile.

In potentially serious RTIs, studies should determine the feasibility of nurse-led reassessment for clinical examination and/or point-of-care testing before discontinuing antibiotic therapy. Research conducted in hospital settings, where patients are continuously monitored by electronic devices and healthcare providers, suggests that vital signs are reliable indicators of clinical deterioration.[57] The emergence of artificial intelligence (AI), which is transforming biomedical and healthcare research, particularly in home environments, can help tailor antibiotic therapy courses based on the vital signs and health data of individual patients with the use of AI-powered monitoring systems. However, further research is required to determine if a follow-up visit to a healthcare professional is necessary before discontinuing antibiotics even in suspected serious RTIs.

Although the potential to tailor the duration of therapy for patients with RTIs based on such a strategy has scarcely been evaluated, it is highly likely that antibiotic exposure could be reduced in the near future with the emergence of new evidence. Advocating for a randomised clinical trial that assigns patients with acute RTIs to either a fixed standard duration course or stopping treatment when feeling better in primary care would better evaluate the efficacy and safety of such a strategy. Ultimately, we should replace the old dogma of continuing therapy past the resolution of symptoms with a new dogma advocating for 'shorter therapy tailored to patient needs'.

## Outstanding questions

It is hard to convince doctors not to prescribe antibiotics at all when they are in doubt or in the face of patient expectations. The limited to moderate impact in reducing unnecessary antibiotic use in primary care observed in antimicrobial stewardship programmes necessitates the exploration of new strategies. We need to change the message to healthcare professionals, policymakers, and educators regarding the idea of always completing a full course of antibiotics. Several systematic reviews show that shorter antibiotic courses are as effective as standard durations for most RTIs. Studies focused on reducing unnecessary antibiotic prescribing and on tailoring antibiotic therapy, dose, and length of therapy to patients' needs, present a promising strategy in primary care. This can be encouraged based on randomised clinical trials indicating that patients most often recover within three days. In the end, we are not treating RTIs, we are treating patients with RTIs.

**Contributors**

CL conceived the idea. NFM, MM, GK and LB were involved in the conceptualisation of the analysis. CL wrote the first draft of the manuscript. All co-authors reviewed and provided insightful comments to the analysis and manuscript drafts. All authors reviewed and contributed to subsequent drafts to improve the manuscript and approved the final version.

**Declaration of interests**

Dr Miravitlles has received consulting fees from AstraZeneca, Atriva Therapeutics, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, CSL Behring, Inhibrx, Ferrer, Menarini, Mereo Biopharma, Spin Therapeutics, Specialty Therapeutics, ONO Pharma, Palobiofarma SL, Takeda, Novartis, Novo Nordisk, Sanofi, Zambon and Grifols, speaker

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