

**Title:** “Complete the antibiotic course to avoid resistance”; non-evidence-based dogma which has run its course?

**Standfirst.** Policy makers, educators and doctors should drop the message that completing the course prevents antibiotic resistance.

## **Introduction**

Antibiotics are vital to modern medicine and antibiotic resistance is a global, urgent threat to human health. There is an unambiguous relationship between antibiotic exposure and antibiotic resistance at the population level<sup>1</sup> and in individual patients.<sup>2</sup> Therefore reducing unnecessary antibiotic use is a key measure to mitigate antibiotic resistance.

Avoiding antibiotic overuse requires healthcare professionals and the public to be well informed about antibiotic treatment. The first objective of the World Health Organisation (WHO) Global Action Plan is to *‘Improve awareness and understanding of antimicrobial resistance through effective communication, education and training.’*<sup>3</sup>

A major theme of public communication about antibiotics is that patients who fail to complete prescribed antibiotic courses put themselves and others at risk of antibiotic resistance. For example, in materials supporting this year’s Antibiotic Awareness Week the WHO advises patients *‘always complete the full prescription, even if you feel better, because stopping treatment early promotes the growth of drug-resistant bacteria’*.<sup>4</sup> Similar advice appears in national campaigns in Australia,<sup>5</sup> Canada,<sup>6</sup> the USA,<sup>7</sup> and for European Antibiotic Awareness week<sup>8</sup>. Without explicitly contradicting this advice, current public information materials from the U.S. Centers for Diseases Control and Public Health England and have replaced ‘complete the course’ with messages advocating taking antibiotics ‘exactly as prescribed’.<sup>9,10</sup> However, ‘complete the course to avoid resistance’ persists in local guidance (e.g. from NHS choices in the U.K,<sup>11</sup> and the Mayo Clinic in the U.S.<sup>12</sup> and in education (in the U.K it is included as fact in the curriculum for secondary school children<sup>13</sup>). The WHO recommends increasing public

awareness of the importance of completing antibiotic courses as a strategy to reduce antibiotic resistance.<sup>14</sup>

The idea that stopping antibiotic treatment early encourages antibiotic resistance is false in most situations. Furthermore, it is a significant barrier to optimising antibiotic treatment of individual patients. Policy makers, educators and doctors should stop using this message when communicating with the public. Further, they should publicly and actively state that this was not evidence-based and is incorrect.

### **Origins of the idea**

Concern that giving too little antibiotic treatment could select for antibiotic resistance can be traced back to the dawn of the antibiotic era.

When Howard Florey's team treated Albert Alexander's staphylococcal sepsis with penicillin in 1941 they eked out all the penicillin they had (around 4g, less than one day's worth with modern dosing) over a period of four days by repeatedly recovering the drug from the patient's urine. When the drug ran out, the clinical improvement they had noted reversed and he subsequently succumbed to his infection.<sup>15</sup> There was no evidence that this was due to resistance but the experience may have planted the idea that prolonged therapy was needed to avoid treatment failure.

Fleming's early work demonstrated that sensitive bacteria could be 'acclimatised' to penicillin in the laboratory.<sup>16</sup> In his 1945 Nobel prize acceptance speech, Fleming painted a vivid clinical vignette in which an imagined patient with a streptococcal throat infection who takes insufficient penicillin, transmits the infection -- now in resistant form -- to his wife, and is thus responsible for her subsequent death from antibiotic-resistant disease.<sup>17</sup> Fleming advised 'If you use penicillin, use enough!' Ironically, *Streptococcus pyogenes* has never developed resistance to penicillin, and we now know that for most forms of antibiotic resistance which currently threaten patients, selection of resistance in the infection being treated is of very limited importance in routine clinical practice.

### **Antibiotic treatment as a driver of antibiotic resistance**

The scenario envisaged by Fleming was of **target-selected resistance** (see box). Infections typically begin when a small population of micro-organisms gain access to the host and replicate. Genetic mutations conferring antibiotic resistance may arise spontaneously during replication and be selected for during treatment. Target-selected resistance may occur with inadequate antimicrobial dosing or with monotherapy for infections where spontaneous resistant mutations arise on treatment such as tuberculosis and HIV. Early tuberculosis treatment trials demonstrated emergence of resistance during monotherapy<sup>18</sup> and underpin the need for combination therapy for this disease. Transmission of such professional pathogens during or following inadequate treatment may allow resistant strains to spread from person to person. Target-selected antibiotic resistance is however of very limited relevance to the bacterial species now posing the greatest problems due to antibiotic resistance.

The main bacterial species in which antibiotic resistance is a clinical threat today (e.g. *Escherichia coli* and the so-called ESKAPE organisms (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter spp*, *Pseudomonas spp*, *Enterobacter spp*)) are all found harmlessly in us, on us or in our environment. They can also act as 'opportunistic' pathogens. They are the commonest causes of urinary, abdominal and most forms of nosocomial infection. When a patient takes antibiotics for any reason, antibiotic sensitive species and strains present among commensal flora on their skin or gut or in the environment are replaced by resistant species and strains ready to cause infection in the future.<sup>19</sup> It is now clear that this **collateral-selection** (see box) is the predominant driver of the important forms of antibiotic resistance which affect patients today. The longer the antibiotic exposure these 'opportunist' bacteria are subjected to, the greater the pressure to select for antibiotic resistance.<sup>2,20</sup> Importantly for these opportunistic pathogens, resistant strains are transmitted between asymptomatic carriers, rather than people with disease. Furthermore, many resistance-conferring genes can pass easily between bacterial strains or species. Thus antibiotic selection may drive outbreaks of resistant infections independently of transmission of a specific strain or species.<sup>21</sup>

## **Antibiotic courses; from fear of under-treatment to demonstrable harm from over-treatment**

Traditionally, antibiotics are prescribed in courses of recommended durations. Fundamental to the very concept of an antibiotic course is the notion that treatment for shorter than the course will be inferior. There is, however, a striking lack of evidence that currently recommended durations are minimums, below which patients will be at increased risk of treatment failure leading to a poor outcome.

Historically, antibiotic course durations were set by precedent, driven by fear of under-treatment, with little concern for antibiotic overuse. For many indications, recommended durations have got shorter as evidence for similar clinical outcomes with shorter courses has been generated (Table 1). However, the picture is patchy and complicated by comparisons of new against established agents which may have different pharmacological properties (e.g. long-acting macrolides vs. short-acting penicillins). For most indications, studies to identify the minimum effective treatment duration with commonly used agents simply have not been performed.<sup>22</sup> For example, pyelonephritis has historically been treated for two-weeks. Trials have demonstrated the efficacy of shorter duration treatment using quinolones (7-days ciprofloxacin<sup>23</sup> and 5-days levofloxacin<sup>24</sup>) but no such data exist for beta-lactams which are the main antibiotic class used. Current international guidelines continue to recommend 10-14 days' treatment with beta-lactams, based purely on absence of data for shorter courses.<sup>25</sup> In contrast, there are very few situations where shorter-duration treatment has been shown to have reduced clinical efficacy. A notable example is otitis media where 5 days' treatment is associated with a lower clinical cure rate (66%) than 10 days (84%) in the under 2 year old age group.<sup>26</sup> Even in this situation though differences relate to prolongation of symptoms not treatment failure, disease recurrence or selection for resistant pathogens.

**For the opportunist pathogens which pose the greatest AMR threat, no clinical trial has demonstrated increased risk of antibiotic resistance among patients taking shorter duration treatment.**

The key argument for changing how we discuss antibiotic course durations with patients is that shorter treatment is clearly better for individual patients. Not only does an individual patient's risk of resistant infection depend on their personal previous antibiotic exposure<sup>2,20</sup> but reducing that exposure by using shorter duration treatment is associated with reduced risk of resistant infection and better clinical outcome. In hospital-acquired pneumonia, for example, randomised-controlled trial data indicate that short-duration treatment strategies are not only equivalent for clinical outcome but also associated with lower rates of infection recurrence and antibiotic resistance.<sup>27,28</sup>

It seems highly inappropriate to suggest patients contribute to antibiotic resistance by not following advice to complete a 'course' of treatment which is lacking in evidence, which itself contributes to antibiotic use and hence resistance selection both at a population level and in the patient themselves.

### **Is the concept of an antibiotic 'course' still valid at all?**

The concept of an antibiotic course ignores the fact that patients may respond very differently to the same antibiotic treatment depending on diverse patient and disease factors. Currently we largely ignore this fact and instead make non-evidence-based indication-specific recommendations for antibiotic duration at the time of diagnosis. This situation is changing in hospital practice where biomarkers of treatment response, such as procalcitonin, can guide stopping antibiotic treatment.<sup>29</sup> Outside hospital, where repeated testing may not be feasible, patients may be best advised to stop treatment when they feel better, in direct contradiction of WHO advice.<sup>4</sup> Of note, a recent clinical trial found that using fever resolution to guide stopping antibiotics in community-acquired pneumonia halved the average duration of antibiotic treatment with no reduction in clinical success.<sup>30</sup>

### **'Complete the course': a barrier to antibiotic conservation**

The fallacious belief that antibiotic courses should always be completed to minimise resistance is likely to be a significant barrier to reducing unnecessary antibiotic use both in clinical practice and in developing a research evidence-base to guide optimal antibiotic use. This idea is deeply embedded and both

doctors and patients currently regard failure to complete a course of antibiotics as irresponsible behaviour.<sup>31,32</sup>

In primary care, strategies have been effective in avoiding unnecessary antibiotic courses being started, for example, through enhanced communication training, point-of-care tests, and use of delayed prescriptions.<sup>33-5</sup> However in secondary care, strategies to reduce antibiotic overuse aim to change or ideally stop antibiotics 48-72 hours after they have started but are challenging to implement<sup>36</sup>. Reasons for this include diagnostic uncertainty and team behaviour but patient and healthcare professional concerns about the risks of incomplete treatment are likely to contribute. Designing trials of antibiotic-sparing treatment is notoriously difficult<sup>37</sup>, particularly if participants are invited to consent to receiving shortened antibiotic treatment on the basis that this could reduce their risk of antibiotic resistance, when they have been taught from school level that this increases the risk of resistance.

### **What should we advise patients about duration of antibiotic treatment?**

The 'complete the course' message has persisted despite good evidence to the contrary and previous arguments that it should be replaced.<sup>21,38</sup> One reason it may be so resilient is that – given the overwhelming threat of antimicrobial resistance - it is simple and unambiguous, and the behaviour it advocates is clearly defined and easy to carry out. Nevertheless, there is overwhelming evidence that, in many situations, stopping antibiotics sooner is a safe and effective way to reduce antibiotic overuse. While in hospital practice, daily review of the continued need for antibiotics is a cornerstone of antibiotic stewardship,<sup>39</sup> in primary care, where 85% of antibiotic prescriptions are written, no such ongoing assessment of need is attempted.

There are reasons to be optimistic that the public will accept that 'complete the course to prevent resistance' is wrong if the medical profession openly acknowledges that this is so rather than simply substituting subtle alternatives such as 'exactly as prescribed'. It goes against one of the most fundamental and widespread medication beliefs people have which is that one should take as little medication as necessary.<sup>40</sup> Concerted and consistent efforts have been successful in educating the public that antibiotics do not treat viral infections, for example.

Research should be undertaken to determine which simple alternative messages such as 'stop when you feel better' are most appropriate. Until then, public education about antibiotics should highlight the fact that antibiotic resistance is primarily the result of antibiotic overuse and not prevented by completion of a course. The public should be encouraged to recognise that **antibiotics are a precious and finite natural resource, which should be conserved**. This will allow patient-centred decision making about antibiotic treatment, where patients and doctors can balance confidence that a complete and lasting cure will be achieved against a desire to minimise antibiotic exposure unimpeded by the spurious concern that shorter treatment will cause antibiotic resistance.

### **Key messages**

- 1) Patients are put at unnecessary risk from antibiotic resistance when antibiotic treatment is given for longer than necessary, not when treatment is stopped early.
- 2) There is no evidence for any common bacterial infection that stopping antibiotic treatment early increases a patient's risk of resistant infection.
- 3) Antibiotics are a precious and finite natural resource which should be conserved by tailoring treatment duration for individual patients.
- 4) Clinical trials are required to determine the most effective strategies for optimizing antibiotic treatment durations and which simple alternative messages such as 'stop when you feel better' are most appropriate.

## **Contributors and Sources**

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## **Competing Interests**

The authors declare they have read and understood BMJ policy on declaration of interests and have no competing interests.

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### **Box 1: Antibiotic resistance selection**

**Target-selection.** For certain 'professional' pathogens, such as *Mycobacterium tuberculosis*, spontaneous resistance-conferring mutants may be selected during treatment, can be transmitted before cure is achieved or can re-emerge following treatment failure. Other professional pathogens where this may apply include HIV, malaria, gonorrhoea and *Salmonella typhi*.

**Collateral-selection.** Many of the bacterial species which live harmlessly in the gut, on our skin and mucus membranes, or in the environment can also cause disease as 'opportunistic' pathogens. For such organisms, resistance selection occurs predominantly during antibiotic treatment of other infections. Resistance in opportunists may be passed easily to other strains of the same species of bacteria or to different bacterial species. Key examples include methicillin resistance in *Staphylococcus aureus*, Extended-spectrum beta-lactamase producing *Enterobacteriaceae* and carbapenem resistance in *Klebsiella pneumoniae*.

**Table 1****Key indications for which duration of antibiotic treatment has been evaluated by randomised controlled trial**

| Indication                                 | Treatment, days   |                    | Key evidence   | Evidence on resistance  |
|--|-------------------|--------------------|--|---|
|  | Standard duration | Evaluated duration |  |   |
| Otitis Media <sup>26</sup>                 | 10                | 5                  | <b>Inferiority</b> of 5 days vs 10 days for clinical failure demonstrated in RCT   | Similar short term selection of resistance in nasopharyngeal organisms.   |
| Streptococcal pharyngitis <sup>41</sup>    | 10                | 3-6                | <b>Comparable</b> effect of 3-6 days oral antibiotics to 10 days penicillin in children with streptococcal throat infection in Cochrane review of 20 studies                                     | Not assessed  |
| Community acquired pneumonia <sup>30</sup> | 7-10              | 5                  | <b>Non-inferiority</b> of 5 day course once afebrile and clinical stability improving compared with physician guided therapy (median 10 days) for clinical success in RCT                        | Not assessed within RCT. Beta-lactam treatment >5 days associated with greater carriage of resistant <i>S. pneumoniae</i> . |
| Cellulitis <sup>42</sup>                   | 7-14              | 5                  | <b>Non-inferiority</b> of 5 day course of levofloxacin compared with 10 days for clinical resolution in RCT  | Not assessed  |
| Pyelonephritis <sup>23,24</sup>            | 14                | 5-7                | <b>Non-inferiority</b> of 7 v 14 days ciprofloxacin for cure <sup>15</sup> and 5 days levofloxacin vs 10 days ciprofloxacin for eradication of infection and clinical cure in RCTs <sup>16</sup> | Not assessed  |
| Nosocomial pneumonia <sup>27,28</sup>      | 10-15             | 7-8                | <b>Non inferiority</b> of short course treatment of suspected pneumonia among critical care patients for ICU mortality and infection recurrence in RCTs  | Lower risk of further or resistant infection in patients receiving shorter duration therapy                                 |
| Intra-abdominal sepsis <sup>43</sup>       | 7-14              | 4                  | <b>Non-inferiority</b> of fixed 4 day course compared with physician-guided therapy (median 8 days) for surgical-site infection, recurrent intraabdominal infection, or death in RCT             | Statistically non-significant lower rates of extra-abdominal resistant infection in short course group                      |

**Note: RCT= randomised controlled trial**

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