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# Inhaled antibiotics for acute lower respiratory tract infections in primary care: an hypothesis

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Acute respiratory tract infections are the greatest single contributor to global disease burden as measured by disability-adjusted life years.<sup>1</sup> Acute lower respiratory infections (aLRTI) are the most common condition managed by primary care internationally,<sup>2</sup> but around 50% antibiotics given for aLRTI are considered inappropriate,<sup>3</sup> unnecessarily contributing to antimicrobial resistance (AMR) in both target and 'bystander' bacteria.<sup>4</sup> Antibiotic resistant aLRTIs are the leading cause of AMR deaths worldwide.<sup>5</sup>

Around 95% of aLRTIs managed in primary care affect the conducting airways ('acute bronchitis') and do not affect the lung parenchyma (pneumonia). Strong evidence suggests that for people with airways infection and without chronic lung diseases (such as asthma, chronic obstructive pulmonary disease (COPD) and bronchiectasis), the benefits of oral antibiotics (a one-day reduction in a 21 day illness)<sup>6</sup> do not outweigh the harms. Despite this, they are prescribed to around 80% of patients with aLRTI, often 'just in case'. We consider that reducing antibiotic use in these groups should be an antimicrobial stewardship priority.

However, patients with chronic lung disease and acute bronchitis are considered 'at risk' and are usually treated with antibiotics (and often corticosteroids). We hypothesise that inhaled World Health Organisation (WHO) 'access' antibiotics, such as doxycycline, amoxicillin and clarithromycin, could be at least as clinically effective as oral antibiotics for the treatment of aLRTI in primary care in these groups, and could reduce bystander AMR effects.

We conducted a systematic review (November 2021) and found no studies in any language reporting the effectiveness of antibiotics administered using a portable inhaler, for patients presenting to primary care with aLRTI.

A recent pan-European study investigating aLRTI aetiology isolated a viral pathogen in 38%, a bacterial pathogen in 11% and both viral and bacterial pathogens in 10% of cases.<sup>7</sup> The most prevalent bacterial species were *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Mycoplasma pneumoniae*.<sup>7</sup> *Moraxella catarrhalis* is also an important pathogen in patients with COPD.

NICE recommends doxycycline as the first-choice antibiotic for aLRTI. Doxycycline is suitable in penicillin allergy, requires smaller oral doses (100-200mg vs. 500mg for the alternatives, which is advantageous for inhaled formulations), and is non-cytotoxic. It also exhibits concentration-dependent antimicrobial activity – it being usual to select such antibiotics for delivery by inhalation where high airway concentrations can be obtained. We therefore propose doxycycline as the most appropriate drug for the treatment of aLRTIs by inhalation.

Lung tissue concentrations after inhaled administration are greater than following intravenous antibiotic administration. Consequently, the doses of antibiotics currently administered by inhalation (e.g. tobramycin, gentamicin, aztreonam, colistimethate, ciprofloxacin, levofloxacin and ceftazidime) are never greater than the dose of the same drug administered systemically, and typically 0.25-0.75 times smaller.<sup>8</sup> One study found the maximum concentration in lung fluid after administration of doxycycline by inhalation to rats was 9-10 times higher than when given intravenously.<sup>9</sup> Therefore, a suitable dose of inhaled doxycycline is likely to be 25 to 75mg (compared with a maintenance daily oral dose of 100mg for respiratory infections). A dose of 50mg doxycycline dissolved in a typical LLF volume of 30ml<sup>10</sup> gives a concentration of 1666 mg/L, which is 2-3 orders of magnitude greater than the reported MIC90 values for the relevant pathogens.

Delivery of a dose of 25-75mg of doxycycline by inhalation will require use of either a nebuliser or a dry powder inhaler, as other systems (such as pressurised metered dose inhalers) cannot deliver

such large a dose. Nebulisers are expensive, bulky, less portable than other devices, require cleaning and maintenance, and are time consuming to use. We therefore consider a dry powder inhaler formulation of doxycycline to be optimal, with ideal characteristics including: (i) consistent and high bronchial drug delivery across the full range of inspiratory profiles in the target population; (ii) quick and intuitive to use for the target population with few steps required to prepare the inhaler for use; (iii) easy to teach, learn and remember how to use correctly; (iv) portability; (v) contains the entire treatment course in one multidose device with a dose counter; (vi) provision of confirmation that a dose has been correctly inhaled; (vii) low cost; (viii) environmentally sustainable; and (ix) stability over 2-3 years minimum. The two dry powder inhaler devices currently in use meeting most of these criteria are the Podhaler® (delivering tobramycin) and the Turbospin® (delivering colistimethate), though other devices under development (such as the Oribital® inhaler) may prove more suitable.

Reducing all inappropriate antibiotic prescribing is key to reducing AMR,<sup>3</sup> but if our hypothesis were true and inhaled antibiotics were used only where appropriate, the key benefit would be a reduction in the use of systemic antibiotics. This would result in reduced AMR bystander effects, particularly among susceptible gut bacteria which are indiscriminately destroyed by oral antibiotics, allowing resistant bacteria to proliferate<sup>4</sup> and cause disease. Given the antibiotic dose delivered to the infected airways could even be higher with inhaled than oral antibiotics, it is also possible that they could be more effective.

Key to testing the hypothesis is the provision of an antibiotic inhaler device. We estimate the cost of developing a dry powder doxycycline formulation to be circa £8-10million with circa £50million required for clinical trials – expensive but considerably less than the circa £1billion needed to develop a new agent. Governments around the world have pledged to make funds available to encourage the development of new antibiotics (<https://www.gov.uk/government/news/development-of-new-antibiotics-encouraged-with-new-pharmaceutical-payment-system>), and we call on these funds to be made available for companies to develop new drug delivery systems.

In summary, we hypothesise that inhaled antibiotics could be a useful therapeutic alternative to oral antibiotics for the treatment of aLRTI in primary care, and we propose doxycycline as a suitable candidate for delivery development via a dry powder inhaler device.

## Author contributions

ADH conceived the idea for the paper, wrote the first draft including the overview summary of previous literature, contributed to the systematic review, and approved the final version. AB wrote the elements relating to the microbiology, and approved the final version. ALH conducted and wrote the first draft of the systematic review, and approved the final version. MJ wrote the elements related to inhaler development, and approved the final version.

## Declaration of interests

The authors state they have no conflicts of interest to declare.

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