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## Antibiotics and acne: an emerging iceberg of antibiotic resistance?

### Authors:

Sarah- Jo Sinnott<sup>1</sup>, Ketaki Bhate<sup>1</sup>, David J. Margolis<sup>2</sup>, Sinéad M. Langan<sup>1</sup>

1. Department of Non-Communicable Disease Epidemiology, London School of Hygiene & Tropical Medicine, Keppel St, London. WC1E7HT
2. Department of Dermatology and Centre for Clinical Epidemiology and Biostatistics, University of Pennsylvania, Philadelphia, PA 19104-4283

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In the entire history of medicine, few therapeutic options have been as successful in curing disease as antibiotics. However, the future effectiveness of antibiotics is now in jeopardy, with the World Health Organisation declaring the threat of antibiotic resistance (AR) a most urgent crisis.<sup>1</sup> Similarly, in the UK, the Chief Medical Officer (CMO) has warned of the apocalyptic nature of AR and more recently has suggested that gains achieved in mortality reductions during the last century could be offset by increases in AR related mortality.<sup>2</sup>

Acne vulgaris is an important disease to focus on in relation to AR as more than 80% of adolescents and young adults have acne, and prolonged broad-spectrum oral antibiotic treatment is standard-of-care for moderate-to-severe acne.<sup>3,4</sup> While clinical experience strongly favours the use of oral antibiotics to treat acne, there is a dearth of data exploring the association between AR in and long-term antibiotic use in acne.<sup>5</sup>

Layton *et al.* highlight the issue of inappropriate antibiotic prescribing for acne in the UK, demonstrating that amongst recent referrals to secondary care, the mean duration of antibiotic use was 305 days.<sup>6</sup> In primary care, antibiotic usage extends to 6 months on average, with a third of acne patients continuing to use antibiotics for longer than this duration.<sup>3</sup> The consequences of unrestrained antibiotic use to treat acne are twofold. First, *P. acnes* is increasingly resistant to standard antibiotics for acne. In approximately 1000 patients attending specialist clinics in Harrogate, 80% had resistance to erythromycin or clindamycin or both, while 25% were resistant to tetracyclines.<sup>7</sup> These results are in concordance with a wider European pattern.<sup>8</sup> The second consequence extends beyond acne treatment. Adverse consequences including higher rates of upper respiratory tract infections have been reported in people treated with oral antibiotics for acne.<sup>9</sup> Such outcomes may result from changing the microbial milieu leading to selective pressure for resistant bacteria, such as *Streptococcus pyogenes*.<sup>10</sup> The emergence of erythromycin resistant *Staphylococcus aureus* strains after the use of topical erythromycin in acne is equally concerning.<sup>11</sup>

The UK CMO has launched a multi-pronged approach to tackling AR, concentrating on improving antibiotic stewardship and enhancing global leadership on maintaining the effectiveness of currently used antibiotics.<sup>2</sup> What can those who treat acne, namely dermatologists and GPs, do to play their part in this battle?

First, the most important step is antibiotic stewardship; ensuring judicious use of both oral and topical antibiotics. There are now several guidelines for the management of acne that are in unison in their recommendations for the prudent use of antibiotics. All recommendations advise against using an oral and topical antibiotic together, and all recommend using a topical retinoid or benzoyl peroxide in combination with oral antibiotics to reduce the potential for resistance.<sup>12-14</sup>

However, there are slight disparities on the advised timelines for use of oral antibiotics. For example, the NICE Clinical Knowledge Summaries advise that a review of antibiotic therapy is conducted at 6-8 weeks, and if there is evidence of some response, treatment can be continued for up to 6 months.<sup>12</sup> In contrast, the American Academy of Dermatology suggests review of antibiotic treatment at 3-4 months.<sup>13</sup> Meanwhile, the most recent European guidelines state that oral antibiotic treatment be limited to 3 months.<sup>14</sup> To mount an effective group response to this potential global health crisis, those treating acne with antibiotics must agree on unified guidelines and then enforce those guidelines. At that point, stewardship will be a powerful tool, as previously demonstrated in the UK in relation to methicillin resistant *Staphylococcus aureus* infections.<sup>15</sup>

Secondly, the role of diagnostics and drug development may be an area for exploration to inform the safe use of antibiotics or to find alternatives to antibiotic treatment in acne. Given that one in four acne patients is colonised by a tetracycline-resistant *P. acnes* strain<sup>7</sup>, swabbing, culturing and testing for resistant strains may be one way to help avoid chronic use of ineffective antibiotics. Admittedly, these investigations would introduce a financial and time cost to prescribers and patients, although future point of care testing may reduce the burden. While we cannot be certain that tetracyclines mediate their whole effect via anti-bacterial action, at the very least this approach would create cohorts of patients who are most likely to benefit, assuming tetracyclines have some antibiotic effect on *P.acnes*. Many dermatologists use antibiotics for their anti-inflammatory effect in acne. Much work on the molecular processes underpinning acne has revealed that Toll like receptors and protease-activated receptors are key mediators in the inflammatory process.<sup>16,17</sup> These molecular substrates hold promise for drug development in this clinical area, offering potential advantages in limiting the extent to which antibiotics are used. Other innovative therapeutic approaches with potential utility include: retinoic acid metabolism blocking agents; ectopeptidase inhibitors; new formulations of benzyl and hydrogen peroxide topical preparations; dapsone gel; metformin; and 5-lipoxygenase inhibitors.<sup>18</sup>

Third, prescribers of antibiotics have questioned the link between their personal prescribing and the emergence of antimicrobial resistance.<sup>19</sup> Ultimately, as clinicians, we aim to achieve the best outcomes for patients by balancing the benefits and risks of a chosen treatment. In the case of AR however, the risk will ultimately be at the population level rather than at the individual level. Thus, generating evidence to identify whether there are negative consequences from the overuse of antibiotics in acne is imperative. Aside from the work of Margolis *et al.* there is little evidence to support the global ramifications resulting from antibiotic use in acne.<sup>9</sup> Academic dermatologists and GPs in the UK are uniquely positioned to investigate this problem further using rich datasets such as the Clinical Practice Research Datalink (CPRD) in collaboration with international colleagues.

The use of antibiotics in acne to achieve the best outcomes with the least risk has been declared a key treatment uncertainty by both health professionals working in dermatology and patients with acne.<sup>20</sup> Given the global health emergency of AR, the dominant role of antibiotics in the treatment of acne and the current perceived need for greater evidence surrounding antibiotics in acne, there is a requirement to fulfil the many knowledge gaps that exist. Crucial questions concerning the role of antibiotics in acne (and alternative treatment modalities), their ideal duration of use and the impact of their use on AR should now be urgently addressed.

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