

## **Commentary: Overuse of antibiotics: Can viral vaccinations help stem the tide?**

Antibiotics have been the cornerstone of modern medicine for the past 80 years and are one of the most common drugs prescribed in healthcare systems worldwide. However, overuse of antibiotics is driving the development and spread of antimicrobial resistance (AMR), compromising the utility of antibiotics to treat and prevent infections [1]. Antibiotic exposure can alter a host's microbiome, thereby increasing the risk of adverse drug events and infections from opportunistic pathogens [2]. If strategies are not implemented to control antibiotic overuse, adverse health and economic impacts are likely, with the burden of AMR disproportionately affecting low and middle-income countries [1].

Within the UK, there has been a reported 32% rise in the total number of bloodstream infections (BSI) caused by bacteria resistant to one or more key antibiotics from 2014-2018 [3]. Over 2000 deaths annually are attributable to resistant infections in the UK [3].

Therefore, to maintain the efficacy of available antibiotics and ensure the continuity of safe and effective healthcare, the UK government has continued to push for the optimisation of antibiotic use.

Since 2014 progress in the UK has been promising, with an estimated 9% reduction in total healthcare antibiotic prescriptions [3]. The majority of this reduction is a result of a drop in primary care antibiotic prescribing, where approximately three-quarters of total UK prescribing takes place [3,4]. Implementation of several antibiotic stewardship interventions, including educational tools, campaigns and financial incentives have contributed to the reduction in antibiotic prescribing in primary care [3].

While, for example, lower levels of amoxicillin prescribing in primary care are associated with lower levels of resistance against amoxicillin and trimethoprim among urinary specimens [5], this does not necessarily result in a reduction in resistance against antibiotics that are almost exclusively used in the hospital setting [3]. Moreover, within England, the reported number of macrolide-resistant BSI for gram-positive bacteria increased between 2014 and 2018, even though prescribing for macrolides decreased in both hospitals and primary care [3]. Sustained or increased resistance in the absence of antibiotic exposure could be a result of multiple factors, including resistance genes imposing a negligible fitness cost, continued use of other antibiotics that are co-selecting for resistance, or lagged effects of antibiotic reductions [5].

In secondary care, antibiotic prescribing is on the rise in England, with a 3% increase in prescriptions since 2014 [3]. Antibiotic stewardship programmes such as the Combined Sepsis and AMR Commissioning for Quality and Innovation (CQUIN) have improved prescribing practice within secondary care, with more prescriptions reviewed within 72 hours and reduced use of last-resort antibiotics [3]. However, only around 25% of the trusts met their target reduction in total antibiotic use from 2017-2019 [3]. A recent study suggests that antibiotic prescribing in NHS hospitals in England could be safely reduced by up to one third [6]. Greater understanding of behaviours hindering progress are needed to optimise antibiotic prescribing [7].

With the threat of AMR being overlooked within the current Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) pandemic, ensuring sustainability and efficacy of antibiotic stewardship programmes will be essential to secure the appropriate use of antibiotics within healthcare.

In England, the number of antibiotic prescriptions in primary care has dropped dramatically after implementation of the lockdown end of March. While there were more antibiotic prescriptions in March 2020 than in March 2019 (2%), during April-July 2020 there were 1.4 million prescriptions less than in the same period the year before, a reduction of 14% (<https://openprescribing.net/bnf/050101/>). This decline was especially marked for penicillin with a reduction of 25% (1.1 million prescriptions).

Reductions are likely a result of strict social isolation measures that have decreased transmission of other communicable diseases in addition to altered health-seeking behaviour in response to the pandemic. Therefore, SARS-CoV-2 may have positive repercussions for both optimal antibiotic prescribing and AMR in primary care. However, in secondary care, antibiotic treatment is reportedly very high within suspected SARS-CoV-2 patients [8]. Moreover, disruption to immunisation programs nationally and globally within this pandemic may have substantial repercussions for future infectious disease burden and associated prescribing.

Detailed analysis of primary and secondary care prescribing rates throughout this pandemic will help to understand the impact of SARS-CoV-2. Development of an effective SARS-CoV-2 vaccine that is safe amongst various patient groups will be crucial in alleviating both current and future burden to healthcare and the economy. In the meantime, national catch up immunisation programmes, reducing SARS-CoV-2 test turnaround time, and supporting antibiotic stewardship will be needed to help mitigate the risk of AMR as England goes into the second wave of the pandemic.

Vaccines offer distinctive benefits as an intervention to help optimise antibiotic prescribing and prevent selection for AMR. Bacterial vaccines can directly reduce the incidence of resistant infections and indirectly reduce antibiotic use and selection for AMR [9]. For instance, it is estimated that universal coverage within 75 countries of an existing pneumococcal conjugate vaccine could avert up to 11.4 million days of antibiotics annually for paediatric pneumonia caused by *Streptococcus pneumoniae* [1]. Viral vaccinations can indirectly impact AMR by reducing infectious disease healthcare presentation, thereby reducing antibiotic prescribing [9]. An analysis of the live attenuated influenza vaccine in children, suggested a 13% to 15% associated reduction in amoxicillin prescribing over 2013/14 and 2014/15, respectively [10]. However, the impact of viral vaccinations on AMR is uncertain [9].

A reduction in antibiotic treatment as a result of viral vaccinations will reduce antibiotic exposure, and the risk of selection of resistance for all bacterial host strains not just the therapeutic target (bystander selection) [2,5]. Moreover, antibiotic treatment could increase or maintain resistance to other antibiotics different to those prescribed (co-selection) [5]. A reduction in antibiotic use from viral vaccinations may have a cascading

impact on both the selection of AMR, and subsequently, the adverted need for additional antibiotic treatment. Vaccine models that incorporate the dynamics of antibiotic use and resistance will help to establish the impact of viral vaccinations on AMR.

Influenza, Respiratory Syncytial Virus (RSV) and most recently SARS-CoV-2 vaccines, of which RSV and SARS-CoV-2 candidate vaccines are still in evaluation within phase III trials, hold particular promise as they target leading causes of respiratory tract infections in the UK. Paediatric RSV burden is estimated to contribute to 416,133 antibiotic prescriptions within an average RSV season in the UK [11]. Interestingly, one recent cost-effective analysis predicted that no national influenza immunisation programme is likely to have a substantial effect on reducing antibiotic consumption and AMR [12]. The above results are not conclusive as the underlying estimates of viral-attributable antibiotic prescribing were dependent on poorly coded RTI's in English primary care [4].

Viral vaccines hold promise as a sustainable alternative for the treatment of infectious disease as viral resistance to vaccines is infrequent [9]. The success of vaccines as an intervention for antibiotic optimisation faces several challenges. Development of vaccines is a difficult process that requires considerable time and financial support [9]. Potential cost-effectiveness of vaccines is likely to be enhanced by accounting for effects on AMR, as most cost-effectiveness models have not yet included impact on antibiotic use and resistance [9]. This is a critical gap as evidence-based cost-effectiveness models will be vital to inform policy decision making and ensuring support for development.

Success of vaccine programmes also rely heavily on the public's acceptance of immunisation. The current uptake of vaccine programmes within the UK is sub-optimal. For instance, from 2018-2019 coverage of all routine child vaccinations have shown a decline of 0.2 to 1% ([http://bit.ly/child\\_vacc\\_stats\\_annual](http://bit.ly/child_vacc_stats_annual)). Additionally, the uptake of the Measles, mumps, and rubella vaccine 1 (live) for 5-year olds is consistently below the national 95% coverage target since the first reports in 2013. A recent survey by the Royal Society of Public Health suggests that the most important barriers to getting vaccinated – among those not explicitly anti-vaccination – were timing and availability of appointments and childcare duties [13]. However, with both SARS-CoV-2 and RSV vaccines on the horizon, it will be crucial to better understand the barriers and facilitators of vaccine uptake and how behavioural responses to the pandemic may have changed these.

Viral vaccines can alleviate substantial infectious disease burden, support further optimisation of antibiotic prescribing, and potentially help reduce the selection of AMR. The evidence base informing vaccine policy decisions needs to reflect this for true benefits to be realised and support to be maintained. Improvements in the quality of clinical coding throughout healthcare and up to date analysis of prescribing rates within this SARS-CoV-2 pandemic will help to inform more reliable estimates of viral infectious disease burden and associated prescribing within the UK. These will be vital to inform new viral vaccine cost-effectiveness models that include impact on antibiotic use and AMR. Further research to understand the barriers and facilitators of vaccine uptake will be crucial to achieve the optimal benefits of immunisation programmes. In a time of rising resistant infections, viral vaccinations have the potential to support antibiotic stewardship practice by safely reducing

the need for prescribing. However, further studies that also incorporate specific cost-effectiveness models are required to confirm this proposition.

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There are no competing interests to declare.

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