Vaccines in the fight against antimicrobial resistance – perspectives from South Africa

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Antimicrobial resistance (AMR), in which microbes adapt to and resist current therapies, is a well-recognised global problem that threatens to reverse gains made by modern medicine in the last decades. AMR is a complex issue; however, at its core, it is driven by the overuse and inappropriate use of antimicrobials. Socioeconomic factors have been identified as significant contributors to the emergence and exacerbation of AMR, especially in populations facing inadequate access to healthcare, poor sanitation services and high morbidity and mortality rates. Weak healthcare systems and water, sanitation and hygiene have been highlighted as fundamental risk factors for AMR emergence and transmission. Behavioural factors, such as purchasing antibiotics without a prescription from a registered healthcare professional, not completing the prescribed course or overly prolonged courses of antibiotics, using antibiotics to treat viral infections, lack of access to quality antibiotics, and the proliferation of substandard or falsified (SF) drugs, have also been identified as significant contributors to AMR. Low- and middle-income countries have a higher incidence of antibiotics being dispensed without a prescription than higher-income countries.

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Preventing infections precludes the need for antimicrobials and reduces the selection pressure for the development and escalation of antimicrobial resistance (AMR). In this context, vaccines, alongside hygiene and access to clean water, can play a major role in fighting AMR.[1-5] By preventing infections, vaccines limit the emergence and transmission of susceptible and drug-resistant strains, lowering the risk of secondary infections and reducing the need for antimicrobial use (AMU) (Fig. 1).[6] However, despite a growing body of evidence on the impact of vaccines in decreasing the emergence of AMR, the link is inadequately leveraged, with little to no integration between AMR and vaccination strategies. The Global Antibiotic Resistance Partnership – South Africa (GARP-SA) group met in Cape Town on 11 October 2023 to review the available evidence on the impact of vaccines on AMR in South Africa (SA) and discuss barriers, enablers and solutions in integrating vaccination as a pivotal strategy in efforts to combat AMR.

Evidence on the impact of vaccines on AMR in South Africa

Recent modelling studies have highlighted the potential impact of vaccines on AMR in SA. The following examples illustrate how existing vaccines and vaccines in development can reduce not only morbidity and mortality of the target disease but also antibiotic use,

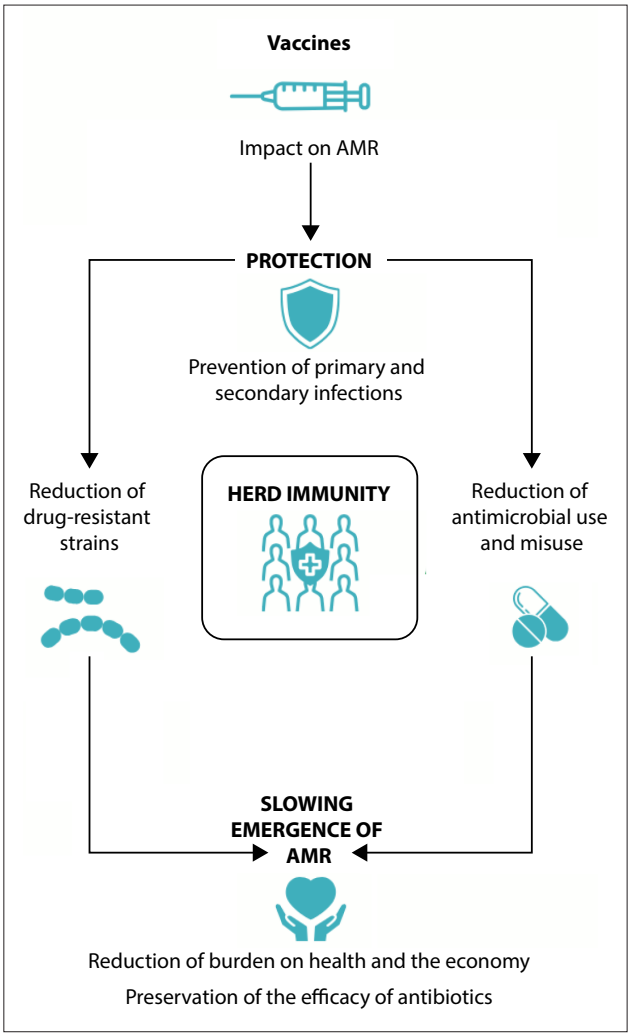

Fig. 1. The role of vaccines in addressing antimicrobial resistance (AMR).[6]

thereby slowing the emergence of AMR and reducing its burden on public health, the health system and the economy.

Tuberculosis

A hypothetical post-exposure tuberculosis (TB) vaccine for adolescents and adults was projected to avert 10 000 cases of rifampicin-resistant TB (RR-TB), or 8.3% (95% confidence interval (CI) 7.5 - 9.2) of all TB cases over 15 years in SA,[7] and to prevent 2 900 RR-TB deaths, or 6.7% (95% CI 5.5 - 7.8) of all TB deaths. These findings suggest an important role of a post-exposure vaccine in preventing drug-resistant TB for the similar M72/AS01 E vaccine in phase 3 clinical trials.[8]

Pneumococcal disease

A study modelling the impact of the pneumococcal conjugate vaccine (PCV), which has a coverage rate in children in SA of ~83%, estimated that it prevents 6.9 (95% CI 1.1 - 16) annual cases of antibiotic-treated *Streptococcus pneumoniae*-attributable acute respiratory illness (ARI) per 100 children aged 24 - 59 months.[9] The same study estimated the incidence of ARI, given PCV protection, as either invasive pneumococcal disease or acute otitis media, at 8.6 (95% CI 1.4 - 20.5) and 12.4 (95% CI 2 - 29.5) cases per 100 children aged 24 - 59 months, respectively, each year. These results indicate that the vaccine has been very effective at preventing antibiotic-treated ARI incidence in the country.

Klebsiella pneumoniae

A mathematical modelling study showed the potential impact of a hypothetical maternal *Klebsiella pneumoniae* vaccine. In SA, assuming a 70% vaccine efficacy and coverage equivalent to the maternal tetanus vaccine, the hypothetical vaccine could avert an estimated 1 717 neonatal sepsis cases and 344 neonatal sepsis deaths annually, accounting for ~4% of all such deaths.[10]

Rotavirus

In addition to vaccines that target bacterial infections, those for viral pathogens can also mitigate AMR by reducing disease incidence, including secondary infections that may be inappropriately treated with antibiotics. For example, evidence shows that the live-attenuated rotavirus vaccine, which was introduced into the national childhood immunisation programme in 2009,[11] could directly prevent an estimated 5.4 (95% CI 0.9 - 11.1) cases of antibiotic-treated, rotavirus-attributable diarrhoea per 100 children <2 years of age annually, assuming a coverage rate of 80%.[9] The incidence of this illness (given the vaccine protection) in SA was estimated at 8.1 (95% CI 1.1 - 17) cases per 100 children,[9] suggesting that the vaccine has been highly effective at preventing inappropriate antibiotic use.

Respiratory syncytial virus

A randomised placebo-controlled trial with >2 400 SA participants estimated that the maternal respiratory syncytial virus vaccine reduced the incidence of antibiotic prescriptions in the first 3 months of life from 43.1 to 37.3 per 100 children, representing a vaccine efficacy against antimicrobial prescribing of 13.4% (95% CI 1.7 - 26.3).[12]

Influenza virus

Another study suggested that vaccinating just 30% of the population aged >65 years against seasonal influenza could avert >11 000 inappropriate antibiotic prescriptions each year in SA (assuming a vaccine effectiveness of 50%).[13]

Barriers

Despite being a critical tool in AMR mitigation, vaccination as a strategy is unrecognised in this context. Similarly, AMR is not included as a metric in vaccine evaluation strategies. Several factors undermine the relationship between AMR and vaccines, such as inadequate health literacy, inequities in access to healthcare, infrastructure and data gaps, and overall lack of co-ordination between health programmes (Fig. 2). Quantitative estimations of how vaccines can mitigate AMR have traditionally been hampered by the lack of electronic patient-level data and local data on the health and economic burden associated with AMR. Mathematical modelling has been able to overcome some of these challenges, and country-specific evidence on the impact of vaccines on AMR has recently been accumulating. These data must now be used to raise awareness and inform immunisation and AMR policies in ways that can impact policy at the national level.

Another barrier to integrating AMR and immunisation strategies is the lack of co-ordination between different programmes. Although immunisation is mentioned as a tool within infection prevention control in the national AMR strategy in SA, no specific objectives or indicators exist for how it can contribute to reducing AMR.[14] This has been largely due to an inadequate understanding of the AMR burden and the relationship between AMR and vaccines. However, an opportunity has arisen to fill this gap and introduce measurable targets for AMR mitigation through vaccines. In addition to the lack of evidence on the impact of specific vaccines against pathogens relevant to public health, the structural cause for the inadequate integration of these programmes

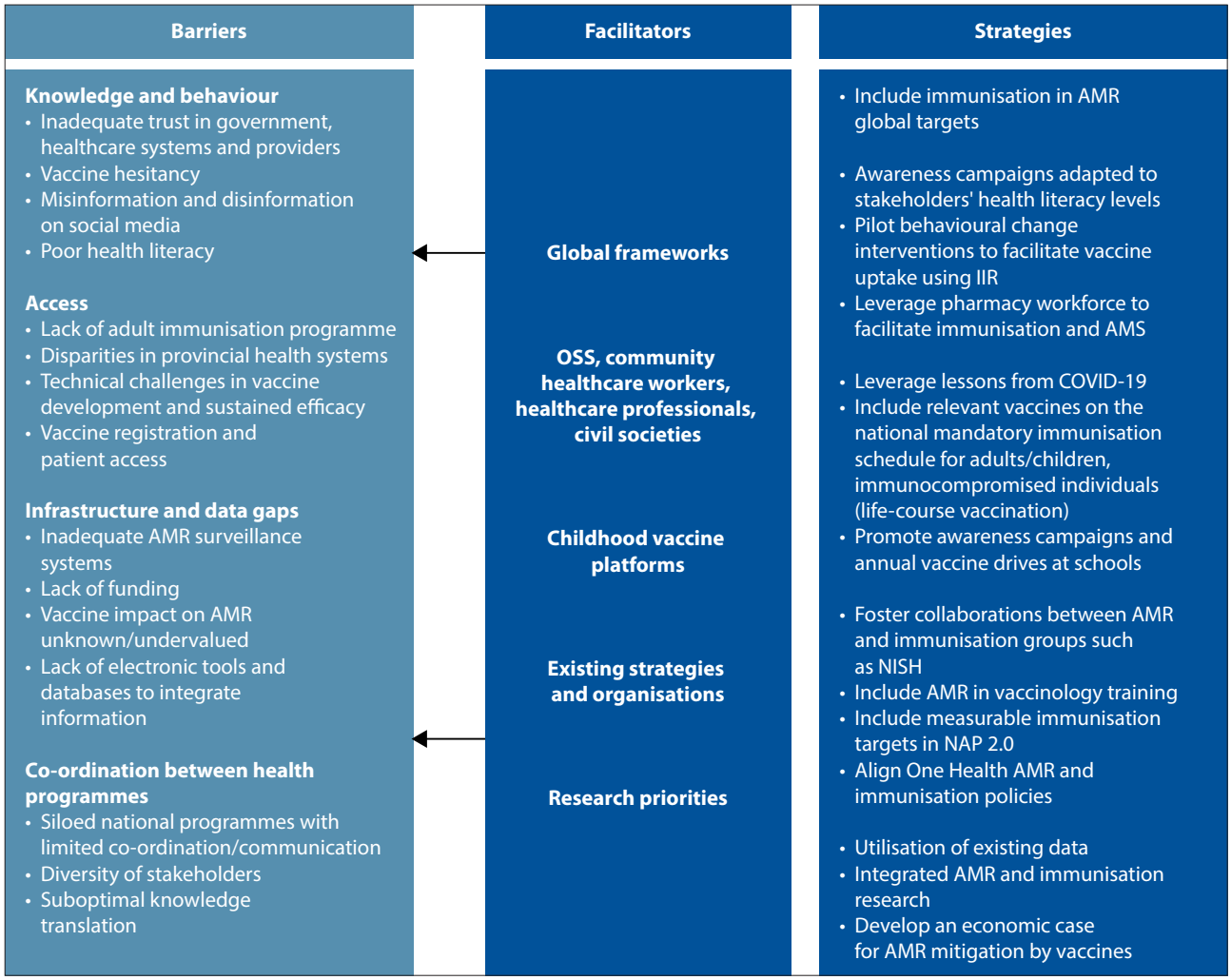

Fig. 2. Identified barriers, facilitators and strategies. (AMR = antimicrobial resistance; OSS = Operation Sukuma Sakhe; IIR = intervention and implementation research; AMS = antimicrobial stewardship; NISH = National Immunization Technical Advisory Group Support Hub; NAP 2.0 = National Action Plan version 2.0.)

lies in the lack of co-ordination and communication between them, further complicated by the diversity of stakeholders involved.[15]

At the other end of the spectrum, these additional benefits of vaccine uptake must be communicated to the public. However, vaccine hesitancy, often attributable to misinformation and disinformation on social media and other communication platforms, represents an ongoing challenge. An official life-course vaccination strategy has been suggested as an effective way to increase immunisation and decrease AMR. However, despite SA's well-supported and structured childhood vaccination programme, adult vaccinations are not similarly provided within a routine immunisation programme. The lack of an official adult immunisation schedule and accessible adult immunisation programme may also contribute to AMR. Influenza vaccinations have been shown to reduce AMR by preventing infections and reducing AMU by up to 64% among adults, likely reducing the selection pressure that drives AMR.[16] The pneumococcal vaccine has been shown to directly reduce the need for antibiotics and decrease the carriage, transmission and prevalence of drug-resistant invasive pneumococcal disease by up to 30%.[17] However, vaccination alone is not enough to overcome habitual antimicrobial prescribing practices, and this emphasises the need for concurrent, judicious antibiotic-use interventions as part of antimicrobial stewardship (AMS) practices.[17]

Policy-related barriers to implementing a life-course vaccination strategy include high programme costs and difficulty determining and verifying eligibility and prioritisation when supplies are low. Considerable challenges also exist with complacency and compliance, as adults are less likely to accept vaccinations even when they are available.

Facilitators

Increasing the collaboration between AMR and immunisation initiatives requires a concerted effort among diverse stakeholders, including scientists, clinicians, policy-makers, industry leaders and communities, to enact practical and meaningful change to the working structure. Fortunately, this work can build from a growing body of knowledge on the health and economic case for increased collaboration. Although much of this knowledge is confined to academic journals, such published evidence can influence policy if adapted to the country's health system context and resources. Additionally, SA benefits from a strong and well-funded childhood immunisation programme, which can be leveraged, in addition to the Operation Sukuma Sakhe infrastructure that aims to integrate the services of government in order to ensure that it enriches the lives of SA citizens, for a 'whole of government approach' that encourages ongoing government-community interaction to support meaningful change at the community level.

A comprehensive strategy to increase collaboration between AMR and immunisation initiatives requires recognising mutually beneficial interests, thoroughly understanding barriers and facilitators, and considering all stakeholders, including the pharmaceutical industry and medical insurance companies. The proposed National Health Insurance, which is SA's strategy to reach universal health coverage, could strengthen primary healthcare, including vaccination programmes, improve AMR surveillance and improve adherence to antibiotic regimens.

Investments in vaccines that will reduce the infectious disease burden and address AMR do not solely depend on understanding their value and cost-effectiveness. For many countries, the costs associated with the introduction of and sustainable access to vaccines are prohibitive. SA is a middle-income country (MIC) and, therefore, not eligible for support from GAVI, the Vaccine Alliance. Recent reports from GAVI and partners have acknowledged the challenges MICs face with new vaccine introductions and coverage, prompting GAVI to assess how these countries could be supported. Recently, SA transitioned from PCV 13 (the vaccine that protects against 13 serotypes) to PCV 10 (the vaccine that protects against 10 serotypes) within the childhood immunisation programme. This shift allowed the inclusion of new vaccines into the childhood immunisation schedule. These additions included the introduction of a rubella-containing vaccine and additional booster doses of acellular pertussis vaccines administered to adolescents and during pregnancy. With GAVI's support for MICs, SA could consider introducing PCV 15 or PCV 20, once these vaccines are registered, without incurring additional costs. Additionally, a compelling economic case must be made to the government that sustainable access to affordable vaccines and AMR mitigation will decrease healthcare costs over the long term by reducing resource use and the length of hospital stays. Therefore, including immunisation in the next iteration of SA's National Action Plan on AMR would be beneficial and should highlight clear outcome indicators, such as increased vaccination rates based on specific targets and decreased incidence rates for vaccine-preventable diseases. The power of an effective communication team should not be underestimated. The success of many health-related policies, including vaccinations (childhood, life-course, epidemic-related, etc.), is often in the hands of the public will. The COVID-19 pandemic is an ideal example of this. The speed at which misinformation spread through social media, television and radio far outstripped how fast healthcare professionals could counteract it, resulting in an increase in vaccine hesitancy and a growing antivaccination mindset. Messages to the public must include all literacy levels by using layman's terms, breaking down complex concepts and using visual aids where possible. A top-down approach to improving public health literacy and awareness is to engage pharmacists to promote both immunisation and antimicrobial prescription stewardship. Including health-related topics, such as immunisation and AMR, in high school and tertiary education would also benefit public awareness.

The challenge of presenting the results of mathematical modelling to improve immunisation programmes and reduce AMR could be bypassed by involving policy-makers early in the process, thereby facilitating a better understanding and improved applicability of models to actionable policy. Surveillance used to collect data in these models could benefit from transitioning to web application-based methods for tracking AMR and immunisation.

Conclusion

Faced with evidence on the burden of AMR and mitigating power of vaccines within an AMS programme, it is critical for AMR and immunisation initiatives to harness the full potential of their collaboration. Data must be used to inform policies at the national level and support integrated research projects that can quantify vaccine impact on infectious diseases and AMR. The AMR mitigation potential of vaccines is an important metric that must be considered in their investment case. It will not only form the foundations of a One Health approach, but also provide a platform for more complex stewardship interventions.

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1. Cavany S, Nanyonga S, Hauk C, et al. The uncertain role of substandard and falsified medicines in the emergence and spread of antimicrobial resistance. Nature Commun 2023;14(1):6153. https://doi.org/10.1038/s41467-023-41542-w
2. Walsh TR, Gales AC, Laxminarayan R, Dodd PC. Antimicrobial resistance: Addressing a global threat to humanity. PLoS Med 2023;20(7):e1004264. https://doi.org/10.1371/journal.pmed.1004264
3. Li J, Zhou P, Wang J, et al. Worldwide dispensing of non-prescription antibiotics in community pharmacies and associated factors: A mixed-methods systematic review. Lancet Infect Dis 2023;23(9):e361-e370. https://doi.org/10.1016/S1473-3099(23)00130-5
4. Godman B, Egwuenu A, Wesangula E, et al. Tackling antimicrobial resistance across sub-Saharan Africa: Current challenges and implications for the future. Expert Opin Drug Safety 2022;21(8):1089-10111. https://doi.org/10.1080/14740338.2022.2106368
5. Do NT, Vu HT, Nguyen CT, et al. Community-based antibiotic access and use in six low-income and middle-income countries: A mixed-method approach. Lancet Glob Health 2021;9(5):e610-e619. https://doi.org/10.1016/S2214-109X(21)00024-3
6. One Health Trust. ARVac Consortium Overview. Washington, DC: One Health Trust, n.d. https://onehealthtrust.org/projects/arvac-consortium/ (accessed 8 January 2024).
7. Fu H, Lewnard JA, Frost I, Laxminarayan R, Arinaminpathy N. Modelling the global burden of drug-resistant tuberculosis avertable by a postexposure vaccine. Nature Commun 2021;12(1):424. https://doi.org/10.1038/s41467-020-20731-x
8. Gates Foundation. Wellcome and the Gates Foundation to fund late-stage development of a tuberculosis vaccine candidate that could be the first in 100 years if proven effective. Seattle: Gates Foundation, 2023. https://www.gatesfoundation.org/ideas/media-center/press-releases/2023/06/funding-commitment-m72-tb-vaccine-candidate (accessed 8 January 2024).
9. Lewnard JA, Lo NC, Arinaminpathy N, Frost I, Laxminarayan R. Childhood vaccines and antibiotic use in low- and middle-income countries. Nature 2020;581(7806):94-99. https://doi.org/10.1038/s41586-020-2238-4
10. Kumar CK, Sands K, Walsh TR, et al. Global, regional, and national estimates of the impact of a maternal *Klebsiella pneumoniae* vaccine: A Bayesian modeling analysis. PLoS Med 2023;20(5):e1004239. https://doi.org/10.1371/journal.pmed.1004239
11. Page N, Seheri L, Groome M, et al. Temporal association of rotavirus vaccination and genotype circulation in South Africa: Observations from 2002 to 2014. Vaccine 2018;36(47):7231-7237. https://doi.org/10.1016/j.vaccine.2017.10.062
12. Lewnard JA, Fries LF, Cho I, Chen J, Laxminarayan R. Prevention of antimicrobial prescribing among infants following maternal vaccination against respiratory syncytial virus. Proc Nat Acad Sci 2022;119(12):e2112410119.
13. Knight GM, Clarkson M, de Silva TI. Potential impact of influenza vaccine roll-out on antibiotic use in Africa. J Antimicrob Chemother 2018;73(8):2197-2200. https://doi.org/10.1093/jac/dky172
14. National Department of Health, South Africa. South African Antimicrobial Resistance National Strategy Framework: A One Health Approach 2018 - 2024. Pretoria: NDoH, 2018. https://www.who.int/publications/m/item/south-africa-south-african-antimicrobial-resistance-national-strategy-framework-a-one-health-approach (accessed 8 January 2024).
15. Van Heuvel L, Paget J, Dückers M, Caini S. The impact of influenza and pneumococcal vaccination on antibiotic use: An updated systematic review and meta-analysis. Antimicrob Resistance Infect Control 2023;12(1):70. https://doi.org/10.1186/s13756-023-01272-6
16. Williams CT, Zaidi STR, Saini B, Castelino R. The role of adult vaccines as part of antimicrobial stewardship: A scoping review. Antibiotics 2023;12(9):1429. https://doi.org/10.3390/antibiotics12091429
17. Van Werkhoven CH, Bolkenbaas M, Huijts SM, Verheij TJ, Bonten MJ. Effects of 13-valent pneumococcal conjugate vaccination of adults on lower respiratory tract infections and antibiotic use in primary care: Secondary analysis of a double-blind randomized placebo-controlled study. Clin Microbiol Infect 2021;27(7):995-999. https://doi.org/10.1016/j.cmi.2020.09.011

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