Received: 16 March 2023 | Revised: 26 April 2023 | Accepted: 8 May 2023

DOI: 10.1002/hsr2.1276

PERSPECTIVE

Health Science Reports Open Access WILEY

The dawn of repurposing vitamins as potential novel antimicrobial agents: A call for global emergency response amidst AMR crisis

Baraka L. Max[1,2] | Cornel M. Angolile[1,2,3] | Vicky G. Raymond[1,4] | Harold L. Mashauri[1,3,4]

[1]Department of Epidemiology and Biostatistics, Institute of Public Health, Kilimanjaro Christian Medical University College, Moshi, Tanzania

[2]Department of Community Medicine, Institute of Public Health, Kilimanjaro Christian Medical University College, Moshi, Tanzania

[3]Department of Physiology, Kilimanjaro Christian Medical University College, Moshi, Tanzania

[4]Department of Internal Medicine, Kilimanjaro Christian Medical University College, Moshi, Tanzania

Correspondence

Harold L. Mashauri, Kilimanjaro Christian Medical University College (KCMUCo), Moshi, Tanzania.
Email: haroldneweinstein@gmail.com

Abstract

Amidst, the global pandemic of antimicrobial resistance (AMR), the rate at which AMR increases overwhelms the increased efforts to discover new effective antimicrobials. There is a persistent need for alternative treatment modalities so as to keep up with the pace. AMR is the leading cause of death in the world and its health and economic consequences suggest the urgent need for sustainable interventions. Vitamins have consistently proven to have antimicrobial activity as well as slowing down the AMR rate by influencing the AMR genes even towards extensive multidrug resistant strains. Evidences suggest that the use of some vitamins on their own or in combination with existing antimicrobial agents could be a breakthrough towards combating AMR. This will widen the antimicrobial agents' options in the treatment arena, preserve the antimicrobial agents susceptible to develop resistant so that they can be used in severe infections only, reduce the tension and burden of the AMR crisis significantly and give enough room for development of new antimicrobial agents. Moreover, almost all viral, fungal, parasitic and bacterial resistant strains of concern as listed by World Health Organization have been found to be sensitive to several vitamins either synergistically with other antimicrobials or independently. Considering their widened spectrum of immuno-modulatory and antimicrobial effect, some vitamins can further be repositioned as prophylactic antimicrobial agents in clinical situations like in presurgeries prophylaxis so as to avoid unnecessary use of antimicrobials especially antibiotics. Various relevant AMR stakeholders should invest in clinical trials and systematic reviews with available data to enable quick repositioning of some potential vitamins as antimicrobial agents as an emergency rapid response towards AMR Crisis. This includes the preparation of guidelines containing specificity of which vitamin to be used for treatment of which type of infection.

KEYWORDS

antimicrobial agents, antimicrobial resistance crisis, drug repurposing, vitamins

1 | INTRODUCTION

Antibiotics and infectious diseases have a longstanding timeline that comprises preantibiotic era and postantibiotic era. The preantibiotic era was dominated by death that resulted from mild bacterial infections.[1] Thereafter, the postantibiotic era was followed by the golden age, lean years and currently there is a growing threat of postantibiotic era.[2] Antimicrobial resistance (AMR) appears to be a natural phenomenon that has existed for millions of years.[3] However, the burden of resistance is becoming more evident currently due to irrational use of antimicrobials like antibiotics and antibiotic selection pressure on bacteria as it was foreseen by Fleming.[4] AMR is claiming more lives, longer hospital stay and economic burden to patients and governments, and effects are likely to worsen if no immediate measures are taken.[5] Alongside other initiatives taken, the use of drug combination, adjuvants, drug repurposing, sequential treatment and precision medicine are continuously being used to fight resistance at the therapeutic level.[6,7] In light of this, vitamins have been used as adjuvants and showed success in treatment against multiple infectious diseases.[8–11]

This article aims to expound the existing body of evidence for immunoregulatory role and antimicrobial properties of vitamins in fighting AMR. It describes the potentiality of vitamins to increase susceptibility and reduce emergency of resistance.

2 | AMR CRISIS

It took nearly 10 years since the discovery of penicillin by Alexander Fleming for the penicillinase enzyme to be discovered, just before penicillin was officially used for therapeutic purpose.[3] Bacteria cells use efflux pumps, alter their cell membrane permeability, use antibiotic degradation enzymes, develop new metabolic pathways and modify their receptors or antibiotic target sites to counteract the effect of antibiotics.[12] The World Health Organization (WHO) published the list of bacteria that required urgent discovery of new antibiotics. They were classified as critical priority, high priority and medium priority which were resistant to third generation cephalosporins, carbapenem, methicillin among others.[13] The global report on the burden of bacterial AMR reported six pathogen that accounted for high morbidity which are *Escherichia coli*, *Staphylococcus aureus*, *K. pneumoniae*, *S. pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*.[5]

Most recent global data suggest that AMR is the leading cause of death around the world with highest burden in low-resource settings. There were an estimated 4.95 million deaths associated with AMR in 2019, including 1.27 million deaths attributable to bacterial AMR.[5] In 2021, the WHO declared AMR to be among the top 10 global public health threats facing humanity.[14] The cost of AMR to the economy is significant.[15–18] In addition to death and disability, prolonged illness results in longer hospital stays, the need for more expensive medicines and financial challenges for those impacted.[14] There is persistent need to come up with interventions to combat AMR.

3 | VITAMINS AND ANTIMICROBIAL ACTIVITY

Vitamins are known for their outstanding immunoregulatory effect of both humoral and cellular immunity.[19] Generally, vitamins enhance stability of physical barriers, proliferation, differentiation, and proper functionality of various immune components.[20] Apart from immunoregulatory roles, vitamins have a long-standing history of anti-infective properties.[21] In the era of AMR, discovery of novel antimicrobial agents is being promoted. Alongside this, adjuvant molecules that can enhance the action of antibiotics is important to halt the growing burden of AMR.[22] Different studies have documented vitamins to possess anti-microbial properties, improving host immune responses and enhancement of antibiotic activity against bacterial infections.[8,23]

The water-soluble vitamins comprise of vitamins B and C, both have potential in fighting infections and modulating the immune system even towards multidrug-resistant strains and they have shown synergism antibiotic effect when combined with other antibiotics.[24,25] Moreover, majority of bacteria have a well-established and developed vitamin B transport system to help them acquire it from the host and environment. This makes vitamin B a potential molecule for conjugation with antibiotic molecules to enhance influx into the bacterial cell.[11] Vitamin C has been suggested to be safe and effective antibiotic agent independently against both gram negative and positive bacterial strains including resistant strains while being stable at different temperatures.[26,27] One study showed that vitamin C exhibited independent antibiotic effect significantly in both in vitro and in vivo settings in a mouse model against carbapenem-resistant hypervirulent Klebsiella pneumonia.[28]

The other group of vitamins is the fat-soluble vitamins comprising of vitamins A, D, E, and K. The use of vitamin A as an anti-infective agent dates far before the second world war when it was thought to reduce morbidity caused by respiratory tract infections, puerperal sepsis and measles among other infectious diseases.[21] Subsequent studies found contradicting results that did not support the hypothesized anti-infective property of vitamin A.[29] Despite presence of contradicting evidence for anti-infective properties for vitamin A, it has immunoregulatory potential.[19] Vitamin D is an immunoregulatory molecule mediated by the vitamin D receptor, improves bacterial cell permeability and expresser of cathelicidin and β-defensin both of which are potent antimicrobial peptides.[30] Not only that, vitamin D possess bacteriostatic effect.[9,31] Another important bacteriostatic vitamin is vitamin E.[32] Vitamin E owes a potent ability of reducing biofilm formation in medical devices[33] and increasing susceptibility of bacteria.[34]

Vitamin K plays a great role in improving cell membrane permeability and fighting AMR, specifically by preventing efflux of antimicrobial agents.[35,36] For example, in *staphylococcus aureus*, vitamin K diminishes the expression of NorA gene to act as efflux pump inhibitor.[35] Unlike vitamin B, vitamin K interrupts the cell membrane stability, as a result increases its permeability to antibiotic molecules,[36] and also interacts efflux pumps to inhibit efflux of antibiotic molecules from bacterial cells.[35]

The WHO reported the prevalence of resistance of 10% among human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDs) population initiated on first line ART regimen by 2021 and reported the rising of resistance among antimalarial drugs too.[37,38] There are limited studies on the potential antimicrobial role of vitamins in treatment of viral and parasitic infection especially of resistant strains. Nevertheless, several studies have supported the fact that vitamins A, B, C, D, and E might act synergistically or independently with both immunomodulatory and antimicrobial effect in treatment of both viral and parasitic infections like HIV/AIDs and Malaria.[39–51] One study specifically shown that vitamin C can inhibit blood stage plasmodium significantly via oxidative stress and suggested that this vitamin is effective enough in inhibiting even chloroquine or artemisinin-resistant parasites.[45] Vitamin B3 also was found to have specific antimicrobial effect towards HIV[52] and *Plasmodium falciparum*,[53] *African Trypanosomes*[54] and showed antileishmanial activity in vitro.[55]

In 2022, the WHO again declared a list of fungal priority infections that are of public health threatening concern because of resistance reasons towards antifungals.[56] There are limited studies also on the role of vitamins towards combating fungal infections. Since fungal infections are more likely in immunocompromised individuals[57] and Vitamins possess immunomodulatory effect, it is more likely too for vitamins to be of pharmacological help in such infections. It was found that vitamin B complex was effective as an adjuvant therapy for the treatment of complicated vulvovaginal candidiasis in mice when used with fluconazole.[58] Vitamin B3 have exhibited independent antimicrobial effect in both candida species and non-candida species including *Cryptococcus neoformans*.[59] Another study suggested that vitamin C is of potential antimicrobial agent towards *Candida albicans* infections through inhibition of Hsp90-Mediated Morphogenesis.[60]

4 | VITAMINS AND GENOMIC INFLUENCE ON RESISTANT MICROBIAL AGENTS

Exposure of microbial organism to sub-optimal dosages of antimicrobial agents triggers mutations.[61] As a result, bacterial cells undergo mutations and evolution which is made possible by genetic instability and horizontal gene transfer. Therefore, bacteria use their DNA replication, recombination and repair systems to acquire more virulent features and protective mechanism that are genetically encoded.[62] The existing body of knowledge appreciates the significant role of vitamins on DNA/RNA replication and ensuring genetic stability.[63,64] However, with advancement of microbial genomics, it may be possible to utilize vitamins to target DNA/RNA so as to prevent growth and cause death.[65,66] Example, vitamins B and C can interfere with the normal DNA methylation causing reduced thermodynamic stability and expression of the restriction modification system of *Mycobacterium bovis* (BCG).[67] Vitamin B_{12} serve as a nonpeptidic carrier for peptide nucleic acid to target the messenger RNA so as to inhibit gene expression in *E. coli*.[68] Not only that, vitamin E has a potential of binding to BcnA protein of *Burkholderia cenocepacia*, hence increasing its susceptibility to antibiotics.[34] Last, vitamin K targets the NorA gene by interrupting with the signaling pathways of the gene expression, ultimately inhibiting the efflux pump of *Staphylococcus aureus*.[35]

An experimental study to demonstrate the effect of ascorbic acid (vitamin C) on bacterial gene expression of AMR genes showed that the expression levels of all tested AMR genes and biofilm associated genes were downregulated under ascorbic acid-treated condition compared to untreated culture. This experiment was specific to resistant strains of *Pseudomonas aeruginosa* but confirms the potentiality of vitamin C to be used as alternative therapy to combat the AMR pandemic.[69]

5 | DISCUSSION

Amidst a global AMR, efforts have been set to increase public awareness on effects of irrational use of antimicrobial agents, improve surveillance, infection prevention strategies and increase research for new antimicrobial agents.[70] However, the discovery of new antimicrobial agents has been less successful, whilst infectious diseases claim millions of lives each year.[71] It is time that nutritive vitamins to be repositioned and be utilized as antimicrobial agents due to presence of promising epigenetic findings in combating infectious diseases, ability to improve the host immune response and attacking the pathogens. The use of nutritive vitamins as antimicrobial agents is coherently with use of antimicrobial peptides which are part of the innate immunity.[72,73] Vitamins may be also instrumental to avert AMR due to their interaction with microbial genome and also usefulness in precision medicine.[74,75] This is a win–win initiative that will improve host immunity, delineate bactericidal or bacteriostatic effect, reduce virulence and increase susceptibility.

Some studies have reported significant synergistic effect of some vitamins like vitamins A, B1, B2, B12, C, K, E, and D when used as adjunct treatment along other antibiotics even to resistant strains[24,76,77] while others have reported that some vitamins including vitamins C and E can act independently on their own as effective antibiotic agents.[69,78] Moreover, in 2017, the WHO listed bacterial strains like *Acinetobacter*, *Pseudomonas* and various Enterobacteriaceae (including *Klebsiella*, *E. coli*, *Serratia*, and *Proteus*), *Salmonella* and *Mycobacterium Tuberculosis* as resistant bacteria which poses public health threat and needs urgent new antibiotics discovery.[79] Almost all of these strains have been found to be sensitive to several vitamins either synergistically with other antibiotics or independently.[8,24,27,52,67,80,81] This makes vitamins ideal agents to be repositioned towards the fight against AMR Crisis.

Vitamins exhibit both immunomodulatory and antimicrobial effects also towards both viral, parasitic and fungal infections despite the fact that evidences in these areas are still few compared to those in bacterial infections. This might be attributed to the fact that bacterial infections are more common to the extent of being studied more compared to viral and parasitic infections. However, the

available evidences are supportive enough to consider repositioning of some vitamins as potential antimicrobial agents towards viral and parasitic infection.

6 | CONCLUSION AND RECOMMENDATION

The battle between microbes with AMR patterns and antimicrobials is getting worse and antimicrobials are undeniably losing the battle. AMR has grown into major global health threat claiming millions of lives yearly. Despite the efforts in discovering new antimicrobials, this problem accelerates at a pace which requires a look on alternative treatment modalities to control this pandemic. Several studies have proved that vitamins have a number of properties than can help in slowing down the rate of AMR crisis. They have shown antimicrobial activity as well as genomic influence on different microbial resistant strains even to the extensive multidrug resistant strains. Therefore, to a great extent they can improve the treatment outcomes of patients infected with resistant strains of both viral, parasitic, fungal and bacterial type.

Despite the fact that most studies have suggested the use of vitamins as adjuvants to antimicrobial agents in clinical settings, evidences support the fact that vitamins can be repositioned as antimicrobial agents on their own. This will widen up the antimicrobial agents' options in the treatment arena, preserve the antimicrobial agents susceptible to develop resistance so that they can be used in severe infections only, reduce the tension and burden of the AMR crisis significantly and give enough room for development of new antimicrobial agents. Considering their widened spectrum of immunomodulatory and antimicrobial effect, some vitamins can be further repositioned as prophylactic antimicrobial agents in clinical situations like in presurgeries prophylaxis so as to avoid unnecessary use of antimicrobials especially antibiotics.

Most reported studies on antimicrobial effect of different vitamins have been done in bacterial infections. Such effect should be explored more also in different viral, fungal and parasitic infections. More studies on mechanism of action of vitamins with antimicrobial effect should be conducted extensively at a molecular level so as to understand when and to what kind of infections exactly such vitamins can be useful and why. Moreover, various relevant international and local AMR stakeholders should invest in clinical trials and systematic reviews with available data to enable quick repositioning of some potential vitamins as antimicrobial agents as an emergency rapid response towards AMR Crisis. This includes the preparation of guidelines containing specificity of which vitamin to be used for treatment of which type of infection.

AUTHOR CONTRIBUTIONS

Baraka L. Max: Data curation; writing—original draft. **Cornel M. Angolile**: Data curation; writing—original draft; writing—review & editing. **Vicky G. Raymond**: Data curation; writing—original draft. **Harold L. Mashauri**: Conceptualization; data curation; project administration; supervision; validation; writing—review & editing.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Not applicable.

TRANSPARENCY STATEMENT

The lead author Harold L. Mashauri affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

ORCID

Baraka L. Max https://orcid.org/0009-0004-6999-651X
Cornel M. Angolile https://orcid.org/0000-0002-8895-4639
Vicky G. Raymond https://orcid.org/0009-0008-2046-7560
Harold L. Mashauri http://orcid.org/0000-0001-6012-234X

REFERENCES

1. Besirbellioglu BA, Coskun O, Eyigun CANP. War and infection in the pre-antibiotic era: the Third Ottoman Army in 1915. *Scand J Infect Dis*. 2011;43:690-695. doi:10.3109/00365548.2011.577801
2. Davies J, Davies D. Origins and evolution of antibiotic resistance. *Microbiol Mol Biol Rev*. 2010;74:417-433. doi:10.1128/MMBR.00016-10
3. Perry J, Waglechner N, Wright G. The prehistory of antibiotic resistance. *Cold Spring Harb Perspect Med*. 2016;6(6):a025197.
4. Aminov RI, Otto M, Sommer A. A brief history of the antibiotic era: lessons learned and challenges for the future. *Front Microbiol*. 2010;1:134. doi:10.3389/fmicb.2010.00134
5. Antimicrobial Resistance Collaborators. Articles global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *The Lancet*. 2022;399:P629-655. doi:10.1016/S0140-6736(21)02724-0
6. Nabavi-rad A, Azizi M, Jamshidizadeh S, et al. The Effects of vitamins and micronutrients on *Helicobacter pylori* pathogenicity, survival, and eradication: a crosstalk between micronutrients and immune system. *J Immunol Res*. 2022;2022.
7. Boyd NK, Teng C, Frei CR. Brief overview of approaches and challenges in new antibiotic development: a focus on drug repurposing. *Front Cell Infect Microbiol*. 2021;11:684515. doi:10.3389/fcimb.2021.684515
8. Patti G, Pellegrino C, Ricciardi A, et al. Potential role of vitamins A, B, C, D and E in TB treatment and prevention: a narrative review. *Antibiotics (Basel)*. 2021;10(11):1354.
9. Kim EW, Teles RMB, Haile S, Liu PT, Modlin RL. Vitamin D status contributes to the antimicrobial activity of macrophages against Mycobacterium leprae. *PLoS Negl Trop Dis*. 2018;12(7):e0006608.
10. Coussens AK, Martineau AR, Wilkinson RJ. Anti-Inflammatory and Antimicrobial Actions of Vitamin D in Combating TB/HIV. *Scientifica (Cairo)*. 2014;2014:903680.
11. Zhao S, Wang Z, Wen X, et al. Synthesis of vitamin B 12-antibiotic conjugates with greatly improved activity against gram-negative bacteria. *Org Lett*. 2020;16:6632-6636. doi:10.1021/acs.orglett.0c02403
12. Ferri M, Ranucci E, Romagnoli P, Giaccone V. Antimicrobial resistance: a global emerging threat to public health systems. *Crit Rev Food Sci Nutr*. 2017;57(13):2857-2876. doi:10.1080/10408398.2015.1077192

13. Asokan GV, Ramadhan T, Ahmed E, Sanad H. WHO global priority pathogens list: a bibliometric analysis of Medline-PubMed for knowledge mobilization to infection prevention and control practices in Bahrain. *Oman Med J*. 2019;34:184-193. doi:10.5001/omj.2019.37
14. World Health Organization. Antimicrobial resistance 2021. Accessed March 13, 2023. https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance
15. Dadgostar P. Antimicrobial resistance: implications and costs. *Infect Drug Resist*. 2019;12:3903-3910. doi:10.2147/IDR.S234610
16. Shrestha P, Cooper BS, Coast J, et al. Enumerating the economic cost of antimicrobial resistance per antibiotic consumed to inform the evaluation of interventions affecting their use. *Antimicrob Resist Infect Control*. 2018;7:98. doi:10.1186/S13756-018-0384-3/TABLES/8
17. Palmer GH, Buckley GJ, eds. *Combating Antimicrobial Resistance and Protecting the Miracle of Modern Medicine*. National Academies Press; 2022. doi:10.17226/26350
18. World Bank. By 2050, drug-resistant infections could cause global economic damage on par with 2008 financial crisis 2016. April 26, 2023. https://www.worldbank.org/en/news/press-release/2016/09/18/by-2050-drug-resistant-infections-could-cause-global-economic-damage-on-par-with-2008-financial-crisis
19. Elmadfa I, Meyer AL. The role of the status of selected micronutrients in shaping the immune function. *Endocr Metab Immune Disord Drug Targets*. 2019;19:1100-1115. doi:10.2174/1871530319666190529101816
20. Noor S, Piscopo S, Gasmi A. Nutrients Interaction with the Immune System. *Arch Razi Inst*. 2021;76(6):1579-1588. doi:10.22092/ari.2021.356098.1775
21. Semba RD. Vitamin A as "anti-infective" therapy, 1920-1940. *J Nutr*. 1999;129(4):783-791.
22. Wright GD. Antibiotic adjuvants: rescuing antibiotics from resistance. *TIM*. 2016;24:862-871. doi:10.1016/j.tim.2016.06.009
23. Shakoor H, Feehan J, Mikkelsen K, et al. Be well: a potential role for vitamin B in COVID-19. *Maturitas*. 2021;144:108-111. doi:10.1016/j.maturitas.2020.08.007
24. Shahzad S, Ashraf MA, Sajid M, Shahzad A, Rafique A, Mahmood MS. Evaluation of synergistic antimicrobial effect of vitamins (A, B1, B2, B6, B12, C, D, E and K) with antibiotics against resistant bacterial strains. *J Glob Antimicrob Resist*. 2018;13:231-236. doi:10.1016/J.JGAR.2018.01.005
25. Mousavi S, Bereswill S, Heimesaat MM. Immunomodulatory and antimicrobial effects of vitamin C. *Eur J Microbiol Immunol*. 2019;9:73-79. doi:10.1556/1886.2019.00016
26. Mumtaz S, Mumtaz S, Ali S, et al. Evaluation of antibacterial activity of vitamin C against human bacterial pathogens. *Braz J Biol*. 2021;83:247165. doi:10.1590/1519-6984.247165
27. Abdelraheem WM, Refaie MMM, Yousef RKM, Abd El Fatah AS, Mousa YM, Rashwan R. Assessment of antibacterial and anti-biofilm effects of vitamin C against pseudomonas aeruginosa clinical isolates. *Front Microbiol*. 2022;13:1594. doi:10.3389/FMICB.2022.847449/BIBTEX
28. Xu C, Dong N, Chen K, et al. Bactericidal, anti-biofilm, and anti-virulence activity of vitamin C against carbapenem-resistant hypervirulent *Klebsiella pneumoniae*. *iScience*. 2022;25:103894. doi:10.1016/J.ISCI.2022.103894
29. Kjolhede CL, Chew FJ, Gadomski AM, Marroquin DP. Clinical trial of vitamin A as adjuvant treatment for lower respiratory tract infections. *J Pediatr*. 1995;126:807-812.
30. Golpour A, Bereswill S, Heimesaat MM. Antimicrobial and immune-modulatory effects of vitamin D provide promising antibiotics-independent approaches to tackle bacterial infections - lessons learnt from a literature survey. *Eur J Microbiol Immunol*. 2019;9:80-87. doi:10.1556/1886.2019.00014
31. Youssef DA, Miller CW, El-abbassi AM, et al. Antimicrobial implications of vitamin D. *Dermato-endocrinology*. 2011;3:220-229.
32. Shahzad S, Ashraf MA, Sajid M, Shahzad A, Rafique A, Mahmood MS. Evaluation of synergistic antimicrobial effect of vitamins (A, B1, B2, B6, B12, C, D, E and K) with antibiotics against resistant bacterial strains. *J Glob Antimicrob Resist*. 2018;13:231-236. doi:10.1016/j.jgar.2018.01.005
33. Vergalito F, Pietrangelo L, Petronio GP, et al. Vitamin E for prevention of biofilm-caused Healthcare-associated infections. *Open Med (Wars)*. 2020;15:14-21.
34. Naguib MM. crossm Vitamin E Increases Antimicrobial Sensitivity by Inhibiting Bacterial Lipocalin Antibiotic Binding n.d.
35. Tintino SR, de Souza VCA, da Silva JMA, et al. Effect of vitamin K_3 inhibiting the function of NorA efflux pump and its gene expression on *Staphylococcus aureus*. *Membranes (Basel)*. 2020;10(6):130.
36. Andrade JC, Flaviana M, Braga BM, Guedes M, Tintino SR, Freitas MA. Menadione (vitamin K) enhances the antibiotic activity of drugs by cell membrane permeabilization mechanism. *Saudi J Biol Sci*. 2017;24(1):59-64. doi:10.1016/j.sjbs.2015.09.004
37. World Health Organization. Fact Sheet: HIV Drug Resistance. 2022. Accessed March 15, 2023. https://www.who.int/news-room/fact-sheets/detail/hiv-drug-resistance
38. World Health Organization. Tackling emerging antimalarial drug resistance in Africa. 2022. Accessed March 15, 2023. https://www.who.int/news/item/18-11-2022-tackling-emerging-antimalarial-drug-resistance-in-africa
39. Lương KVQ, Nguyễn LTH. The role of thiamine in HIV infection. *Int J Infect Dis*. 2013;17:e221-e227. doi:10.1016/J.IJID.2012.11.019
40. Jiménez-Sousa MÁA, Martínez I, Medrano LM, Fernández-Rodríguez A, Resino S. Vitamin D in human immunodeficiency virus infection: influence on immunity and disease. *Front Immunol*. 2018;9:458. doi:10.3389/FIMMU.2018.00458
41. Alvarez N, Aguilar-Jimenez W, Rugeles MT. The potential protective role of vitamin D supplementation on HIV-1 infection. *Front Immunol*. 2019;10:2291. doi:10.3389/FIMMU.2019.02291/BIBTEX
42. Layden AJ, Finkelstein JL. B-vitamins and HIV/AIDS. In: Mehta S, Finkelstein JL, eds. *Nutrition and HIV: Epidemiological Evidence to Public Health*. CRC Press; 2018. doi:10.1201/9781351058193-2
43. Mehta S, Fawzi W. Effects of vitamins, including vitamin A, on HIV/AIDS patients. *Vitam Horm*. 2007;75:355-383. doi:10.1016/S0083-6729(06)75013-0
44. Nwachukwu NF, Mishra M, Marcelle T, Owolabi JB. Effects of vitamins in augmentation of malaria treatment: a review. *Asian Pacific Journal of Health Sciences*. 2016;3:34-43. doi:10.21276/APJHS.2016.3.4.6
45. Shi X, Wei M, Xu Z, et al. Vitamin C inhibits blood-stage plasmodium parasites via oxidative stress. *Front Cell Dev Biol*. 2021;9:639944. doi:10.3389/FCELL.2021.639944/FULL
46. Zeba AN, Sorgho H, Rouamba N, et al. Major reduction of malaria morbidity with combined vitamin A and zinc supplementation in young children in Burkina Faso: a randomized double blind trial. *Nutr J*. 2008;7:7. doi:10.1186/1475-2891-7-7/FIGURES/2
47. Wrenger C, Knöckel J, Walter RD, Müller IB. Vitamin B1 and B6 in the malaria parasite: requisite or dispensable? *Braz J Med Biol Res*. 2008;41:82-88. doi:10.1590/S0100-879X2008005000006
48. Yakoob MY, Qadir M, Hany O. Vitamin A supplementation for prevention and treatment of malaria during pregnancy and childhood: a systematic review and meta-analysis. *J Epidemiol Glob Health*. 2018;8:20-28. doi:10.2991/J.JEGH.2018.04.104
49. Achan J, Mpimbaza A. Editorial: vitamin A as adjunct therapy for cerebral malaria: what is the evidence? *Afr Health Sci*. 2012;12:87. doi:10.4314/AHS.V12I2.1
50. Sudfeld CR, Buchanan A, Ulenga N, et al. Effectiveness of a multivitamin supplementation program among HIV-infected adults in Tanzania. *AIDS*. 2019;33:93-100. doi:10.1097/QAD.0000000000002033

51. Huey SL, Mehta S. Human immunodeficiency virus and vitamin A. In: Mehta S, Finkelstein JL, eds. *Nutrition and HIV: Epidemiological Evidence to Public Health*. CRC Press; 2018 doi:10.1201/9781351058193-1
52. Murray MF. Nicotinamide: an oral antimicrobial agent with activity against both mycobacterium tuberculosis and human immunodeficiency virus. *Clin Infect Dis*. 2003;36:453-460. doi:10.1086/367544
53. Prusty D, Mehra P, Srivastava S, et al. Nicotinamide inhibits Plasmodium falciparum Sir2 activity in vitro and parasite growth. *FEMS Microbiol Lett*. 2008;282:266-272. doi:10.1111/J.1574-6968.2008.01135.X
54. Unciti-Broceta JD, Maceira J, Morales S, García-Pérez A, Muñóz-Torres ME, Garcia-Salcedo JA. Nicotinamide inhibits the lysosomal cathepsin b-like protease and kills African trypanosomes. *J Biol Chem*. 2013;288:10548-10557. doi:10.1074/JBC.M112.449207
55. Sereno D, Alegre AM, Silvestre R, Vergnes B, Ouaissi A. In vitro antileishmanial activity of nicotinamide. *Antimicrob Agents Chemother*. 2005;49:808-812. doi:10.1128/AAC.49.2.808-812.2005
56. World Health Organization. WHO releases first-ever list of health-threatening fungi. 2022. Accessed March 15, 2023. https://www.who.int/news/item/25-10-2022-who-releases-first-ever-list-of-health-threatening-fungi
57. Low CY, Rotstein C. Emerging fungal infections in immunocompromised patients. *F1000 Med Rep*. 2011;3:14. doi:10.3410/M3-14
58. Sun MG, Huang Y, Xu YH, Cao YX. Efficacy of vitamin B complex as an adjuvant therapy for the treatment of complicated vulvovaginal candidiasis: an in vivo and in vitro study. *Biomed Pharmacother*. 2017;88:770-777. doi:10.1016/J.BIOPHA.2017.01.001
59. Xing X, Liao Z, Tan F, Zhu Z, Jiang Y, Cao Y. Effect of nicotinamide against *Candida albicans*. *Front Microbiol*. 2019;10:595. doi:10.3389/FMICB.2019.00595
60. Van Hauwenhuyse F, Fiori A, Van Dijck P. Ascorbic acid inhibition of *Candida albicans* Hsp90-Mediated morphogenesis occurs via the transcriptional regulator Upc2. *Eukaryotic Cell*. 2014;13:1278-1289. doi:10.1128/EC.00096-14
61. Shapiro RS. Antimicrobial-Induced DNA Damage and Genomic Instability in Microbial Pathogens. 2015:1-8. doi:10.1371/journal.ppat.1004678
62. Darmon E, Leach DR. Bacterial genome instability. *Microbiol Mol Biol Rev*. 2014;78:1-39. doi:10.1128/MMBR.00035-13
63. Sc E. Bacterial growth. 1921:441-445.
64. Lúcia A, Arigony V, Oliveira IMDe, et al. The influence of micronutrients in cell culture: a reflection on viability and genomic stability. *Biomed Res Int*. 2013;2013:597282.
65. Manuscript A, Genomics M, Diseases I. NIH Public Access. 2012;365:347-357. doi:10.1056/NEJMra1003071.Microbial
66. Joshi H, Verma A, Soni DK. Impact of microbial genomics approaches for novel antibiotic target. In: *Microbial Genomics in Sustainable Agroecosystems*. Springer Nature. 2019:75-88. doi:10.1007/978-981-32-9860-6_5
67. Song N, Zhu Y, Cui Y, et al. Vitamin B and vitamin C affect DNA methylation and amino acid metabolism in *Mycobacterium bovis* BCG. *Front Microbiol*. 2020;11:1-12. doi:10.3389/fmicb.2020.00812
68. Wojciechowska M, Wierzba AJ, Maximova K, et al. Inhibition of *Escherichia coli* growth by vitamin B_{12}–peptide nucleic acid conjugates. *ACS Omega*. 2019;4:819-824. doi:10.1021/acsomega.8b03139
69. Abdelraheem WM, Refaie MMM, Kamal R, Yousef M, Lazar V. Assessment of antibacterial and anti-biofilm effects of vitamin C against *Pseudomonas aeruginosa* clinical isolates. *Front Microbiol*. 2022;13:1-9. doi:10.3389/fmicb.2022.847449
70. Gulumbe BH, Haruna UA, Almazan J, Ibrahim IH. Combating the menace of antimicrobial resistance in Africa: a review on stewardship, surveillance and diagnostic strategies. *Biol Proced Online*. 2022;24:19. doi:10.1186/s12575-022-00182-y
71. Infectious A, Notes D. Where are all the new antibiotics? The new antibiotic paradox. *Can J Infect Dis Med Microbiol*. 2005;16:159-160.
72. Nur SM, Rath S, Ahmad V, Ahmad A, Ateeq B, Khan MI. Nutritive vitamins as epidrugs. *Crit Rev Food Sci Nutr*. 2021;61:1-13. doi:10.1080/10408398.2020.1712674
73. Rončević T, Puizina J, Tossi A. Antimicrobial peptides as anti-infective agents in pre-post-antibiotic era? 2019;20(22):5713.
74. Ortiz JPM, Read MN, Mcclure DD, et al. High throughput genome scale modeling predicts microbial vitamin requirements contribute to gut microbiome community structure. *Gut Microbes*. 2022;14:2118831. doi:10.1080/19490976.2022.2118831
75. Merker M, Tueffers L, Vallier M, et al. Evolutionary approaches to combat antibiotic resistance: opportunities and challenges for precision medicine. *Front Immunol*. 2020;11:1938. doi:10.3389/fimmu.2020.01938
76. Cursino L, Chartone-Souza E, Nascimento AMA. Synergic interaction between ascorbic acid and antibiotics against Pseudomonaspseudomonas aeruginosa. *Braz Arch Biol Technol*. 2005;48:379-384. doi:10.1590/S1516-89132005000300007
77. Hartmann MS, Mousavi S, Bereswill S, Heimesaat MM. Vitamin E as promising adjunct treatment option in the combat of infectious diseases caused by bacterial including multi-drug resistant pathogens – results from a comprehensive literature survey. *Eur J Microbiolo Immunol*. 2020;10:193-201. doi:10.1556/1886.2020.00020
78. Golpour A, Bereswill S, Heimesaat MM. Antimicrobial and immune-modulatory effects of vitamin D provide promising antibiotics-independent approaches to tackle bacterial infections – lessons learnt from a literature survey. *Eur J Microbiolo Immunol*. 2019;9:80-87. doi:10.1556/1886.2019.00014
79. World Health Organization. WHO publishes list of bacteria for which new antibiotics are urgently needed 2017. Accessed March 14, 2023. https://www.who.int/news/item/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed
80. Nandi M, Sikri K, Chaudhary N, Mande SC, Sharma RD, Tyagi JS. Multiple transcription factors co-regulate the mycobacterium tuberculosis adaptation response to vitamin C. *BMC Genomics*. 2019;20:887. doi:10.1186/S12864-019-6190-3/TABLES/1
81. Vilchèze C, Kim J, Jacobs WR. Vitamin C potentiates the killing of mycobacterium tuberculosis by the first-line tuberculosis drugs isoniazid and Rifampin in mice. *Antimicrob Agents Chemother*. 2018;62(3):e02165-17. doi:10.1128/AAC.02165-17

How to cite this article: Max BL, Angolile CM, Raymond VG, Mashauri HL. The dawn of repurposing vitamins as potential novel antimicrobial agents: a call for global emergency response amidst AMR crisis. *Health Sci Rep*. 2023;6:e1276. doi:10.1002/hsr2.1276