A Case for Early Education Toward Sustainable Antibiotic Stewardship

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Abstract
Antimicrobial resistance (AMR) is a global One Health threat jeopardizing healthcare globally, with projections of more than 10 million lives prematurely lost per year by 2050. Several factors underlay this dire predicament, including a poorly educated populace and patients regarding best practices for antibiotic stewardship. Specifically, children and parents have inadequate antibiotic knowledge for basic usage but demanded accessible education. Furthermore, antibiotic stewardship regarding antibiotic disposal and the environmental effect of AMR is highly neglected worldwide but critical to address to prevent harm to human and animal health. Previously, antibiotic stewardship regarding antibiotic disposal was largely ineffective with a typically top-to-bottom approach, which requires a bottom-to-top approach to increase public awareness and support.

California should incorporate antibiotic stewardship into the K-12 education system. Attention to educational initiatives is important because children account for a large proportion of patients prescribed antibiotics, and nearly one in two antibiotics are overprescribed. Childhood educational intervention in Europe was shown to drastically cut antibiotic overuse. Therefore, more education on antibiotic stewardship is necessary to protect the future generation. Overall, to reach the National Action Plan, California must lead to address Objective 2 on conducting public education on antibiotic stewardship. Our research suggests that similar progress could be made in California and America with similar childhood educational interventions.

Keywords
Antibiotic resistance
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Pandemic
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Public Health
K-12 system

Introduction

Antimicrobial resistance (AMR) is a One Health epidemic jeopardizing global health, food security, and development (Jimah, Fenny, & Ogunseitan, 2020; World Health Organization, 2019). By definition, a One Health issue is one that crosses all geographic and national boundaries to affect humans, animals, and the environment (Jimah et al., 2020). It is projected to take 10 million lives and cost 100 trillion dollars by 2050 to both become the leading cause of death and wreak a global financial crisis as catastrophic as the 2008-2009 crisis, respectively (O'Neill, 2016; World Health Organization, 2019). As a result, COVID-19 may not be the only pandemic in the 21st century (Devlin, 2020).

Antimicrobial resistance has multiple causes, including inadequate public knowledge and patient pressure for an antibiotic prescription, which influences physicians to overprescribe antibiotics (Kohut et al., 2020; Ray et al., 2019). As of 2019, 43% of antibiotics are prescribed inappropriately or unnecessarily, which accounts for 30% to 50% of all AMR cases (Ray et al., 2019; Ventola, 2015). As a result, AMR is a major threat to America. Currently, antibiotic stewardship on the correct disposal of antibiotics is highly neglected and important as a highly significant cause of harm for land and aquatic animals and humans alike (Anwar, Iqbal, & Saleem, 2020). Specifically, antibiotic stewardship is defined as "the effort to measure and improve how antibiotics are prescribed by clinicians and used by patients" (Centers for Disease Control and Prevention, 2019). Currently, antibiotic stewardship experts in the medical community are inaccessible (Pulcini & Gyssens, 2013). Most are only available upon request for patients with serious infections (Pulcini & Gyssens, 2013). However, antibiotic stewardship is critical for the simplest infections. For example, common diseases like staphylococcus (staph) are difficult to treat. Staph has over 1,000 strains with over 150 antibiotics available to treat it (Jaramillo & Wuest, 2021; Li & Webster, 2018; e-Bug, n.d.). The World Health Organization estimates that it takes $10 to 30 billion to produce and introduce 10 to 15 new antibiotics (Gunn, 2020; Renwick & Mossialos, 2018). Many large pharmaceutical companies have abandoned this field of work because of the low-profit margin (Outterson & Boucher, 2019; Plackett, 2020World Health Organization " 2020;). Therefore, prudent and responsible use of existing antibiotics is urgent as one of the primary solutions, and we all have to do our part (Federal Task Force on Combating Antibiotic-Resistant Bacteria, 2020).

Fundamental Knowledge of Antibiotics

Another study (2019) conducted on the American public stated that "nearly half of adults (45%) say they have personally not taken their antibiotics as prescribed by a doctor – one of the leading causes of AMR" (Muñana et al., 2019). According to Pew Research, only 42% of those in high school or less understand that antibiotics are used solely for bacterial, not viral infections (Funk & Goo, 2015). In addition, a survey with 215 respondents discovered that "over 40% of respondents indicated that antibiotics were the best choice to treat a fever or a runny nose and sore throat," despite it being likely the worst option due to it likely being viral (Carter et al., 2016). According to a 2019 study, individuals with "high school education or below were more likely to believe antibiotics kill viruses (43.1% vs. 20.9%, respectively; $p < 0.01$) and that antibiotics work on most coughs and colds (31.4% vs. 16.2%, respectively; $p = 0.01$)" (Seipel et al., 2019). According to a recent study, 47.1% of individuals "stop taking antibiotics when they start feeling better" (Gualano et al., 2014).

Patient Pressure on Healthcare Providers

A major cause is patient pressure for antibiotics that must be addressed through education. There is an increasingly participatory role of patients in an antibiotic prescription,

so patients need to be educated to protect themselves and their dependents (Pulcini & Gyssens, 2013). Specifically, physicians account that it takes "less time to prescribe an antibiotic than to provide a lengthy explanation to a patient as to why an antibiotic is not needed" (Zetts et al., 2018). Overall, studies show a general consensus among physicians feeling "that patients and their families expect tangible actions to address their illnesses or concerns" (Zetts et al., 2018). In fact, there is a "culture of expectation" (Zetts et al., 2018). The public has become increasingly active in communicating with healthcare providers to determine correct antibiotic prescriptions, especially parents of young children (Pulcini & Gyssens, 2013). Perceived patient demand drives physicians to inappropriately or incorrectly prescribe antibiotics (Kohut et al., 2020). Perceived patient expectations and pressure for antibiotics made physicians 31.7% likelier to inappropriately or incorrectly prescribe them (Mangione-Smith et al., 2006). Specifically, a study by Mangione-Smith et al. (2011) found that physicians detected patient pressure for antibiotics in 34% of visits (King, Fleming-Dutra, & Hicks, 2018). When physicians regarded antibiotics as unnecessary, patients were "24.0% [likelier to] question the treatment plan" (Mangione-Smith et al., 2006). Another study found that physicians were 20.2% likelier to prescribe antibiotics with perceived patient pressure for treating the cold (King, Fleming-Dutra, & Hicks, 2018). Some confessed that overprescribing antibiotics could prevent patients from switching health providers (Zetts et al., 2018). Prescribers are tasked with offering optimal antibiotic therapy to patients while preserving their efficacy to prevent AMR. Patient pressures and patient expectations for antibiotics are significant issues that must be addressed through education.

Children are a target of a large proportion of antibiotic overprescribing in the United States (Zetts et al., 2018). Specifically, "patients age ≤19 years accounted for ∼34.8 million antibiotic prescriptions in [outpatient settings] from 2010 to 2011" (Zetts et al., 2018). Furthermore, in 2015, five in six antibiotic prescriptions were prescribed in the outpatient setting, including physician's offices (King, Fleming-Dutra, & Hicks, 2018). Doctors mainly have a need to protect themselves from malpractice, patients switching to other providers, and decreased patient satisfaction scores (Zetts et al., 2018). In addition, "children are especially vulnerable to multidrug-resistant infections because of the lack of pediatric pharmacokinetic and safety data for new antibiotics, which contributes to fewer broad-spectrum antibiotics being approved for pediatric use" (Zetts et al., 2018). Expanding outpatient stewardship efforts can positively impact patient health (Zetts et al., 2018). Namely, the most common cause of adverse drug events–related emergency department (ED) visits in children are antibiotics (Zetts et al., 2018). In the U.S., there are 835 antibiotic prescriptions per 1000 persons in 2014, which is incredibly high compared to other countries like Sweden, with 328 antibiotic prescriptions per 1000 persons in 2014 (Zetts et al., 2018). As a result, children are at risk of antibiotic over-prescription.

Need for Sustainable Antibiotic Disposal Policies and Practices

Antibiotic stewardship regarding the proper waste disposal of antibiotics must be addressed more to the public. Currently, it is a potential driver of AMR as a significantly neglected issue harming humans and animals (Anwar, Iqbal, & Saleem, 2020). Between 2015 and 2030, antibiotic consumption is projected to "increase worldwide by 200%" (Sriram et al., 2021). Specifically, the "inappropriate disposal ends up in landfills, water supplies and drains that lead to contamination of the environment and a wide range of toxicities to humans, animals, and marine life" (Anwar, Iqbal, & Saleem, 2020). When "not degraded or eliminated during wastewater treatment," these antibiotics "reach surface water or are passed into the aquatic environment" (Anwar, Iqbal, & Saleem, 2020). These seemingly negligible concentrations of antibiotics are actually posing extreme health risks through the antibiotic-resistant genes becoming greater and more virulent via horizontal gene transfer (Anwar,

Iqbal, & Saleem, 2020). Recently, antibiotic use and consumption have increased over the past years, causing increased rates of inappropriate antibiotic disposal (Anwar, Iqbal, & Saleem, 2020). In addition, there is a major issue with the increased usage of high-end and last-resort antibiotics globally (Anwar, Iqbal, & Saleem, 2020). Currently, the trend of failed antibiotic therapy being to use more antibiotics has created a high risk of AMR (Anwar, Iqbal, & Saleem, 2020). As a result, the increased usage lends an increased rate of improper antibiotic disposal in the environment that must be urgently addressed in the public health campaigns (Anwar, Iqbal, & Saleem, 2020).

However, the previous public health campaigns have been ineffective. This topic of inappropriate waste disposal is highly neglected, specifically among policymakers and healthcare professionals, which means that the public must be educated on this critical issue (Anwar, Iqbal, & Saleem, 2020). An organization successfully addressing inappropriate waste disposal is the Minnesota Department of Health through offering antibiotic stewardship kits and resources like fact sheets on proper antibiotic disposal and the environmental effects (Minnesota Department of Health, n.d.). Examples include the "Take it to the Box Toolkit" with information on medication drop-off programs within the community (Minnesota Department of Health, n.d.). As a result, California should create a more sustainable environment by promoting correct antibiotic disposal through similar measures, specifically at the k-12 level. In the past, both individual and collective programs with a top-to-bottom approach in informing policymaker and healthcare providers have been ineffective, which requires a grassroots approach targeting public education so that citizens can learn about this behavioral issue to create societal change, as a comprehensive yet customized approach (Anwar, Iqbal, & Saleem, 2020). By 2030, AMR is projected to bring 200 million individuals into extreme poverty (World Health Organization, 2019). AMR is evolving instantaneously, exacerbated by critically neglected environmental dangers from incorrect waste disposal (Anwar, Iqbal, & Saleem, 2020). As a result, individuals with or without access to health are at risk of AMR. With the current time and resource constraints, taking the critical step to address proper antibiotic disposal in the state k-12 curriculum, in addition to correct antibiotic use, is essential to advance antibiotic stewardship efforts worldwide as a necessary catalyst. Through this, society can protect environmental sustainability and support the health of minority individuals that are frequently affected by unsustainable environmental practices.

Implications of COVID-19 Pandemic on Antimicrobial Resistance

The COVID-19 pandemic has set a precedent in revealing the deadly impacts of structural racism and systemic health inequalities on racial and ethnic minorities (Nadimpalli et al., 2021). Specifically, Black and Hispanic/Latinx populations have been disproportionately affected: they comprise less than a third of the national population but accounted for about half of all cases and 37% of all deaths (Nadimpalli et al., 2021). Racial and ethnic minorities have disproportionately high rates of comorbidities and living in crowded areas, which increases the risk of the emergence and transmission of AMR (Nadimpalli et al., 2021). As a result, Americans must contend with the structural racism and systemic health inequalities, especially in minority populations, when addressing the need for education regarding AMR, which is widely regarded as the next global pandemic (Nadimpalli et al., 2021). With higher rates of poverty, it is critical to support the education of minority populations because AMR will disproportionately affect the poor (Nadimpalli et al., 2021).

There is a further concern with racial and ethnic minorities being disproportionately impacted by low-income, which stimulates the allure of easy antibiotic access with inadequate regulations in lower and middle-income countries creates a reliance on cheaper nonprescription (Haque, 2017). However, the cost of AMR is deadly. Currently, the annual toll of AMR in the U.S. includes 2.8 million illnesses, 35,000 deaths, and economic costs in

the range of $6000–$30,000 per person, totaling $20 billion to cripple low-income individuals (Center for Disease Control and Prevention, 2020a; Carter, 2016). Specifically, while African American, Latino, and Asian individuals "may receive fewer antibiotic prescriptions over their lifetimes than do" Caucasian individuals, they may be likelier to consume non-prescription antibiotics (Nadimpalli et al., 2021). A cross-study on 35 community surveys across five continents showed that nonprescription use occurred globally, which likely impacts the culture regarding antibiotics of immigrants in which America is created by immigration (Morgan et al., 2011). Nonprescription accounted for "19–100% of antimicrobial use outside of northern Europe and North America," which should be considered with California's population comprising of 64% racial and ethnic minorities and 27% immigrants (more than double any other state) (Haque, 2017; Public Policy Institute of California, 2021). Regarding this, race or ethnicity is just one factor that might cause disparities in AMR, in which other factors include low income, undocumented status, lack of insured, or residing in crowded urban areas, regardless of race or ethnicity, that may hinder access to healthcare and increase nonprescription (Nadimpalli et al., 2021). Society has an obligation to prevent "racial and ethnic minorities and economically disadvantaged people" from being disproportionately burdened by AMR (Nadimpalli et al., 2021). As a result, it is necessary to promote a holistic education outside of healthcare alone to prioritize public health among minority individuals, immigrants, and economically disadvantaged people, among others, because of nonprescription.

The Importance of Targeting the K-12 Education System

There is a high need to strengthen the education system regarding health education and infection prevention with the pervasive use of antibiotics with the high over-prescription rates, paired with the COVID-19 pandemic that creates a scenario of potential antibiotic misuse for it or its secondary infections (Clancy et al., 2020). As a result, there must be interventions to target the k-12 system because it is critical to ensuring adequate antibiotic stewardship outside of the healthcare setting to protect low-income and racial minorities, among other people, from getting AMR through nonprescription. Specifically, O'Neil's "Tackling Drug-Resistant Infections Globally: Final Report and Recommendations" (2016), a cornerstone AMR report, has identified children and teenagers as the main focus demographic of public awareness campaigns of drug resistance to prevent them from being the brunt of AMR as the age group most susceptibility to infections (Casadevall & Pirofski, 2018). Currently, the federal government's "National Action Plan for Combating Antibiotic-Resistant Bacteria, 2020 – 2025" emphasizes Objective 2 to "engage the public and other stakeholders to develop, expand, and increase national and State education . . . focused on using antibiotics responsibly, stopping the spread of AMR, and preventing infections and life-threatening conditions like sepsis" (Federal Task Force on Combating Antibiotic-Resistant Bacteria, 2020). Therefore, California must emphasize antibiotic stewardship education to align with the national standards to support efforts to protect vulnerable populations like minorities, the uninsured, and the economically disadvantaged to prevent AMR from being the next pandemic of inequality (Devlin, 2020).

According to Pulcini & Gyssens (2013), antibiotic stewardship habits must develop as young as possible to foster positive habits into adulthood. In addition, children get prescribed antibiotics more than any other drug (Lovegrove et al., 2018). However, one in two antibiotics is inappropriately or unnecessarily prescribed (Spivak et al., 2018). As a result, the community-level educational focus must include the k-12 education to educate students and their parents, in which children account for a large proportion of antibiotic prescribing (Zetts et al., 2018). Furthermore, parents wanted health education regarding AMR for health

promotion (Bosley et al., 2018). Overall, there is a high need and demand for education to the k-12 demographic to effectively protect children from antibiotic resistance.

California must learn from states like Michigan, Oregon, and Minnesota in creating antibiotic stewardship material for the k-12 system (Michigan Antibiotic Resistance Reduction Coalition, n.d.; Minnesota Department of Health, n.d.). Specifically, Michigan has the Michigan Antibiotic Resistance Reduction Coalition (MARR) successfully targets the k-12 system through its wide reach across over 30 additional states and many countries (Centers for Disease Control and Prevention, n.d.; Michigan Antibiotic Resistance Reduction Coalition, n.d.). In addition, the Minnesota Department of Health has created comprehensive sources to promote antibiotic stewardship resources at the k-12 system regarding the One Health aspect (Minnesota Department of Health, n.d.). Lastly, the Oregon Alliance Working for Antibiotic Resistance Education (AWARE) offers specific modules on incorporating antibiotic stewardship at the high school, middle, and elementary school levels (Oregon.gov., n.d.). Currently, the AWARE programs are also at various states like California, Texas, and Arizona, but these states are not incorporating education on antibiotic stewardship at the k-12 level (Center for Disease Control and Prevention, 2020b). As a result, California must follow these states in addressing antibiotic resistance at the k-12 level.

Europe: Example of Successful Public Education on Antibiotics

Currently, Europe is leading public education on antibiotic stewardship. Many European nations have integrated antibiotic stewardship into the elementary, middle, and high school levels via the e-Bug game (e-Bug, n.d.b). Specifically, the e-Bug curriculum is led by Gloucester's Health Protection Agency Primary Care Unit with ten associate partner countries "(Belgium, Czech Republic, Denmark, France, England, Greece, Italy, Poland, Portugal, and Spain) and eight collaborating partner countries (Croatia, Finland, Hungary, Ireland, Latvia, Lithuania, Slovakia, and Slovenia) as a project covering 62% (334 million) of the European population (Lecky et al., 2010). Other major initiatives include Do Bugs Need Drugs? and Microbes in question mobile children's health education campaign (Pulcini & Gyssens, 2013). Specifically, the "'Do Bugs Need Drugs?' is a community and professional education program designed to address AMR by decreasing the inappropriate use of antibiotics" (Carson & Patrick, 2015). They developed resources "for physicians, pharmacists, nurses and the public, including children, their parents and caregivers, teachers, employers and workers, and long-term care facilities" (Carson & Patrick, 2015). It began "as a small six-month pilot in 1997 in Grande Prairie, Alberta, the program expanded to Edmonton in 2000 and to all of Alberta and to British Columbia in 2005" (Carson & Patrick, 2015). Results show that, in 1998, "27% of respondents to a public survey were able to correctly define AMR," which spiked to 77% in British Columbia by 2014 (Carson & Patrick, 2015). In essence, the United Kingdom reveals the effectiveness of educational interventions at the k-12 level.

Conclusion

Antimicrobial Resistance is expected to be the leading cause of death by 2050. Childhood educational intervention in Europe has been shown to drastically reduce antibiotic overuse (Carson & Patrick, 2015). We make the case here that similar strategies could be effective in California and other states in the United States.

References

American Lunch Association. (2021). *Tobacco Control Milestones.* https://www.lung.org/research/sotc/tobacco-timeline.

Anwar, M., Iqbal, Q., & Saleem, F. (2020) Improper disposal of unused antibiotics: an often overlooked driver of antimicrobial resistance, *Expert Review of Anti-infective Therapy,* 18:8, 697-699, DOI: 10.1080/14787210.2020.1754797.

Barlam, T. F., Neuhauser, M. M., Tamma, P. D., & Trivedi, K. K. (Eds.). (2018). *Practical Implementation of an Antibiotic Stewardship Program*. Cambridge University Press.

Bosley, H., Henshall, C., Appleton, J. V., & Jackson, D. (2018). A systematic review to explore influences on parental attitudes towards antibiotic prescribing in children. *Journal of Clinical Nursing*, *27*(5-6), 892-905.

Brownlee, S., & Garber, J. (2019). *Overprescribed: High cost isn't America's only drug problem.* STAT. https://www.statnews.com/2019/04/02/overprescribed-americas-other-drug-problem/.

Bunce, J. T., & Hellyer, P. (2018). Antibiotic resistance and antibiotic prescribing by dentists in England 2007–2016. *British Dental Journal*, *225*(1), 81-84.

California Department of Education. (2020). *Health Education Framework.* https://www.cde.ca.gov/ci/he/cf/.

Carson, M., & Patrick, D. M. (2015). Antimicrobial stewardship: "Do Bugs Need Drugs?" A community education program for the wise use of antibiotics. *Canada Communicable Disease Report, 41*(4), 5.

Carter, R. R., Sun, J., & Jump, R. L. (2016, May). A survey and analysis of the American public's perceptions and knowledge about antibiotic resistance. *Open Forum Infectious Diseases, 3*, 1-7. doi:10.1093/ofid/ofw112.

Casadevall, A., & Pirofski, L. A. (2018). What is a host? Attributes of individual susceptibility. *Infection and Immunity, 8*6(2).

Centers for Disease Control and Prevention. (2019). *Antibiotic Prescribing and Use in Hospitals and Long-Term Care.* https://www.cdc.gov/antibiotic-use/core-elements/index.html.

Center for Disease Control and Prevention. (2020a). *Biggest Threats and Data.* https://www.cdc.gov/drugresistance/biggest-threats.html.

Center for Disease Control and Prevention. (2016). *CDC: 1 in 3 antibiotic prescriptions unnecessary.* https://www.cdc.gov/media/releases/2016/p0503-unnecessary-prescriptions.html.

Centers for Disease Control and Prevention. (2020b). *Current Report.* https://www.cdc.gov/antibiotic-use/stewardship-report/current.html.

Centers for Disease Control and Prevention. (n.d.). *Michigan Provides Education and Tools on Appropriate Antibiotic Use.* https://www.cdc.gov/antibiotic-use/community/pdfs/16_272181-A_StateHealthDept_MI_508.pdf.

Clancy, C. J., Buehrle, D. J., & Nguyen, M. H. (2020). PRO: the COVID-19 pandemic will result in increased antimicrobial resistance rates. *JAC-Antimicrobial Resistance*, *2*(3), dlaa049.

Devlin, M. (2020). Antimicrobial Resistance: The Next Pandemic? *Microbiology Society.* https://microbiologysociety.org/blog/antimicrobial-resistance-the-next-pandemic.html.

e-Bug. (n.d.a). *e-Bug Junior*. https://e-bug.eu/homepage.html?level=junior.

e-Bug. (n.d.b). *Welcome to e-Bug.* https://e-bug.eu/ind_home.aspx?cc=ind&ss=1&t=Welcome%20to%20e-Bug.

Essilini, A., Kivits, J., Caron, F., Boivin, J. M., Thilly, N., & Pulcini, C. (2020). 'I don't know if we can really, really change that': a qualitative exploration of public perception towards antibiotic resistance in France. *JAC-Antimicrobial Resistance, 2*(3), dlaa073.

Federal Task Force on Combating Antibiotic-Resistant Bacteria. (2020). *National Action Plan For Combating Antibiotic-resistant Bacteria 2020-2025.* https://aspe.hhs.gov/system/files/pdf/264126/CARB-National-Action-Plan-2020-2025.pdf.

Funk, C., & Goo, S.K. (2015). *A look at what the public knows and does not know about science.* Pew Research. http://assets.pewresearch.org/wp-content/uploads/sites/14/2015/ 09/2015- 09-10_science-knowledge_FINAL.pdf.

Garcia, E., Ly, N., Diep, J. K., & Rao, G. G. (2021). Moving from Point-based Analysis to Systems-based modeling: Integration of Knowledge to Address Antimicrobial Resistance against MDR Bacteria. *Clinical Pharmacology & Therapeutics*.

Gualano, M. R., Gili, R., Scaioli, G., Bert, F., & Siliquini, R. (2015). General population's knowledge and attitudes about antibiotics: a systematic review and meta-analysis. *Pharmacoepidemiology and Drug Safety, 24*(1), 2-10. Chicago.

Gunn, S. (2020). *Pharma abandons antibiotics.* Front Line Genomics. https://d4-pharma.com/pharma-abandons-antibiotics/.

Haque, M. A. (2017). Antimicrobial use, prescribing, and resistance in selected ten selected developing countries: A brief overview. *Asian Journal of Pharmaceutical and Clinical Research, 10*(8), 37-45.

Hospitals: antimicrobial stewardship, Cal. S.B. 1311. (2013-2014), (Cal. Stat. 2014). https://leginfo.legislature.ca.gov/faces/billTextClient.xhtml?bill_id=201320140SB1311.

Jaramillo, A. V. C., & Wuest, W. M. (2021). *Antibacterials. American Chemical Society.* Chicago.

Jimah, T., Fenny, A.P. & Ogunseitan, O.A. (2020). Antibiotics stewardship in Ghana: a cross-sectional study of public knowledge, attitudes, and practices among communities. *One Health Outlook, 2,* 12. https://doi.org/10.1186/s42522-020-00021-8.

King, L. M., Fleming-Dutra, K. E., & Hicks, L. A. (2018). Advances in optimizing the prescription of antibiotics in outpatient settings. *BMJ (Clinical research ed.)*, 363, k3047. https://doi.org/10.1136/bmj.k3047

Kohut, M. R., Keller, S. C., Linder, J. A., Tamma, P. D., Cosgrove, S. E., Speck, K., ... & Szymczak, J. E. (2020). The inconvincible patient: how clinicians perceive demand for antibiotics in the outpatient setting. *Family Practice, 37*(2), 276-282.

Kourkouta, L., Koukourikos, K., Iliadis, C., Plati, P., & Dimitriadou, A. (2018). History of antibiotics. *Sumerianz Journal of Medical and Healthcare, 1*, 51-5.

Lecky, D. M., McNulty, C. A., Touboul, P., Herotova, T. K., Beneš, J., Dellamonica, P., ... & Campos, J. (2010). Evaluation of e-Bug, an educational pack, teaching about prudent antibiotic use and hygiene, in the Czech Republic, France and England. *Journal of Antimicrobial Chemotherapy, 65*(12), 2674-2684.

Lee, C. R., Lee, J. H., Kang, L. W., Jeong, B. C., & Lee, S. H. (2015). Educational effectiveness, target, and content for prudent antibiotic use. *BioMed research International, 2015*.

Li, B., & Webster, T. J. (2018). Bacteria antibiotic resistance: New challenges and opportunities for implant-associated orthopedic infections. *Journal of Orthopaedic Research, 36*(1), 22-32.

Livestock: use of antimicrobial drugs, Cal. S.B. 27. (2015-2016), (Cal. Stat. 2015). https://leginfo.legislature.ca.gov/faces/billNavClient.xhtml?bill_id=201520160SB27.
Lovegrove, M. C., Geller, A. I., Fleming-Dutra, K. E., Shehab, N., Sapiano, M. R., & Budnitz, D. S. (2019). US emergency department visits for adverse drug events from antibiotics in children, 2011–2015. *Journal of the Pediatric Infectious Diseases Society*, *8*(5), 384-391.
Mangione-Smith, R., Elliott, M. N., Stivers, T., McDonald, L. L., & Heritage, J. (2006). Ruling out the need for antibiotics: are we sending the right message?. *Archives of Pediatrics & Adolescent Medicine*, *160*(9), 945-952.
Michigan Antibiotic Resistance Reduction Coalition. (n.d.). *Educational Programs.* https://mi-marr.org/educational-programs/index.php.
Minnesota Department of Health. (n.d.). *Antibiotic Resistance and Stewardship Resources for Educators.* https://www.health.state.mn.us/diseases/antibioticresistance/educators/ index.html.
Morgan, D. J., Okeke, I. N., Laxminarayan, R., Perencevich, E. N., & Weisenberg, S. (2011). Non-prescription antimicrobial use worldwide: a systematic review. *The Lancet Infectious Diseases*, *11*(9), 692-701.
Muñana, C., Kirzinger, A, Lopes, L., Hamel, L., & Brodie, M. (2019). *Antibiotic Resistance.* KFF. https://www.kff.org/other/issue-brief/data-note-public-awareness-antibiotic-resistance/.
Nadimpalli, M. L., Chan, C. W., & Doron, S. (2021). Antibiotic resistance: a call to action to prevent the next epidemic of inequality. *Nature medicine*, *27*(2), 187-188.
O'Neill, J. (2016). *Tackling drug-resistant infections globally: final report and recommendations.* Analysis & Policy Observatory. https://apo.org.au/node/63983.
Oregon.gov. (n.d.). *Oregon Alliance Working for Antibiotic Resistance Education.* https://www.oregon.gov/oha/ph/DiseasesConditions/CommunicableDisease/AntibioticResistance/Pages/index.aspx.
Outterson, K., & Boucher, H.Wang. (2019). *Medicare payment rules hinder the fight against superbugs*. STAT. https://www.statnews.com/2019/04/17/medicare-payment-antibiotics-hinder-superbug-fight/.
Placket, B. (2020). *Why big pharma has abandoned antibiotics.* Nature. https://www.nature.com/articles/d41586-020-02884-3.
Public Policy Institute of California. (2021). *California's Population.* https://www.ppic.org/publication/californias-population/.
Pulcini, C., & Gyssens, I. C. (2013). How to educate prescribers in antimicrobial stewardship practices. *Virulence*, *4*(2), 192-202.
Ravina, K. (2019). *The Antibiotic Apocalypse: Superbugs vs. Humans.* TED. https://www.ted.com/talks/ravina_kullar_the_antibiotic_apocalypse_superbugs_vs_human.
Ray, M. J., Tallman, G. B., Bearden, D. T., Elman, M. R., & McGregor, J. C. (2019). Antibiotic prescribing without documented indication in ambulatory care clinics: national cross sectional study. *BMJ*, *367*.
Redfern, J., Bowater, L., Coulthwaite, L., & Verran, J. (2020). Raising awareness of antimicrobial resistance among the general public in the UK: the role of public engagement activities. *JAC-Antimicrobial Resistance*, *2*(1). dlaa012.
Renwick, M., & Mossialos, E. (2018). What are the economic barriers of antibiotic R&D and how can we overcome them?. *Expert opinion on drug discovery*, *13*(10), 889-892.

Seipel, M. B. A., Prohaska, E. S., Ruisinger, J. F., & Melton, B. L. (2019). Patient knowledge and experiences with antibiotic use and delayed antibiotic prescribing in the outpatient setting. *Journal of Pharmacy Practice*, 0897190019889427.

Spivak, E. S., Hicks, L. A., & Srinivasan, A. (2018). Stewardship Need for Programs. *Practical Implementation of an Antibiotic Stewardship Program*, 1.

Sriram, A., Kalanxhi, E., Kapoor, G., Craig, J., Balasubramanian, R., Brar, S., Criscuolo, N., Hamilton, A., Klein, E., Tseng, K., Van Boeckel, T., & Laxminarayan, R. (2021). *The State of the World's Antibiotics Report in 2021.* The Center for Disease Dynamics, Economics & Policy. https://cddep.org/blog/posts/the-state-of-the-worlds-antibiotics-report-in-2021/.

Van Belkum, A., & Melles, D. C. (2009). Not all Staphylococcus aureus strains are equally pathogenic. *Discovery Medicine*, *5*(26), 148-152.

Ventola, C.L. (2015). The antibiotic resistance crisis: part 1: causes and threats. *Pharmacy and Therapeutics*, *40*(4), 277–283.

World Health Organization. (2020). *Lack of new antibiotics threatens global efforts to contain drug-resistant infections.* https://www.who.int/news/item/17-01-2020-lack-of-new-antibiotics-threatens-global-efforts-to-contain-drug-resistant-infections.

World Health Organization. (2019). *Ten threats to global health in 2019.* https://www.who.int/news-room/spotlight/ten-threats-to-global-health-in-2019.

World Health Organization. (2015). *WHO multi-country survey reveals widespread public misunderstanding about antibiotic resistance.* https://www.who.int/news/item/16-11-2015-who-multi-country-survey-reveals-widespread-public-misunderstanding-about-antibiotic-resistance.

Zetts, R. M., Stoesz, A., Smith, B. A., & Hyun, D. Y. (2018). Outpatient antibiotic use and the need for increased antibiotic stewardship efforts. *Pediatrics*, *141*(6).