

Asian Journal of
Biological
Sciences



Commentary

Mobility of Antibiotic Resistance Through Pharmaceutical Products: A Microbiological Prospective Risk

Mostafa Essam Eissa

Department of Microbiology and Immunology, Cairo University, Cairo, Egypt

Key words: Plasmids, environmental monitoring, transposons, antibiotic resistance, integrons

Citation: Mostafa Essam Eissa, 2018. Mobility of antibiotic resistance through pharmaceutical products: A microbiological prospective risk. Asian J. Biol. Sci., 11: 98-101.

Corresponding Author: Mostafa Essam Eissa, Department of Microbiology and Immunology, Faculty of Pharmacy, Cairo University, Cairo, Egypt
Tel: +201006154853

Copyright: © 2018 Mostafa Essam Eissa. This is an open access article distributed under the terms of the creative commons attribution License, which permits unrestricted use, distribution and reproduction in any medium, provided the original author and source are credited.

Competing Interest: The author has declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

Antibiotic resistance has become a globally known threat that may impact not only human health but even life. Dissemination of multi-antimicrobial resistant microbes has become a popular phenomenon that has impacted the public health¹. Moreover, there is evidence for the ability of the circular DNA plasmid that is responsible for antimicrobial drug resistance to maintain its functionality even after exposure to unfavorable environmental conditions. Researchers of this study have found that *Escherichia coli* could uptake this DNA and acquired drug resistance². Thus, it is surprising to find drug-resistant microbial strains isolated from toilet seats in the International Space Station (ISS) where the environment is confined with limited access and far from the open ecosystem of the planet earth³. Thus, the risk encountered mainly emerges from the resilient nature of antibiotic resistance DNA and the ease of transfer and exchange between micro-organisms. Figure 1 illustrated the exceptional and fast ability of microbial cells to develop drug resistance to the most antimicrobials applied for the cure of infections^{4,5}. An interesting observation showed that the resistance of *Pneumococcus* to Penicillin was found 22 years after its introduction while Levofloxacin resistance was detected in the same year 1996. The earliest evidence of antibiotic resistance was *Staphylococcus* to Penicillin⁵ in 1940. Gram-negative rods were also contributors to the drug resistance such as *Shigella* to Tetracycline and Enterobacteriaceae to Imipenem and Ceftazidime. Based on centers for disease control and prevention (CDC) records, staphylococcal resistance is one of the most observed resistance against antimicrobial drugs⁵.

The diversity of bacteria in human, water and environment is of special concern to the microbiological Quality Control (QC) in the pharmaceutical industry not only to detect objectionable micro-organisms but also to

investigate the kinetics and mobility of the genetic materials that are responsible to the antibiotic resistance. The swapping process of genetic material between contemporary adjacent bacterial cells may be referred to as horizontal gene transfer⁶. Various Antibiotic Resistance Genes (ARGs) are integrated on plasmids, transposons or integrons that works as carriers vectors for the transfer of these genes to the other cells of the same species, different species or even another genus⁷. Three principal mechanisms are responsible for horizontal gene transfer viz transformation, transduction or conjugation. Antibiotic resistance mechanism can occur generally via target modification, efflux, enzyme-catalyzed destruction, immunity and bypass⁸. In an open ecological framework on earth, it is expected that selective pressure from the exposure to the antimicrobials in nature in a closed loop will be transferred to individuals who will be subjected to drug-resistant bacteria even they have not exposed to these antibiotics before⁹.

Despite the rules implemented to establish antibiotic treatment protocol as defense lines against the progression of resistance, there are still other routes through which unintentional selection for the most survivors micro-organisms could prevail. The risk of transfer of antimicrobial resistance from food to the final human consumers has been addressed previously by some researchers^{10,11}. Some drugs promote horizontal gene transfer, for example the antiepileptic drug Carbamazepine¹². Water and air is also another possible source of the transfer of resistance among other environmental sources that should be investigated^{13,14}. Environmental Monitoring (EM) and water samples in a pharmaceutical facility showed the diversity of micro-organisms that could be found from different sources such as personals, water, surfaces and air¹⁵. Even raw ingredients and materials for pharmaceutical product formulation are a possible source for ARGs transfer depending

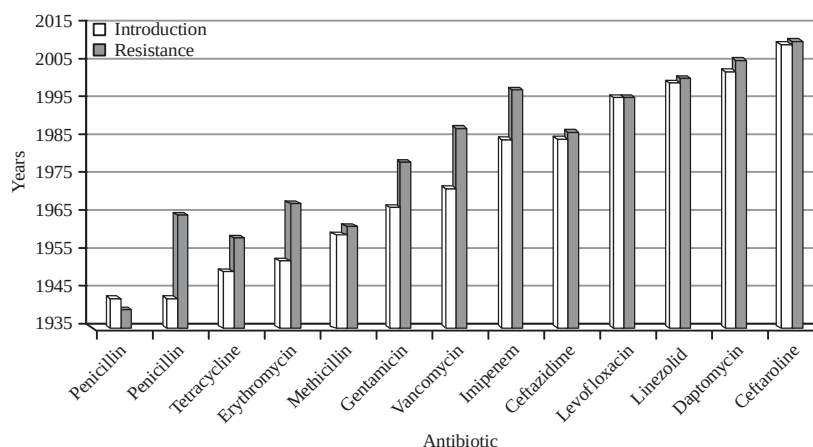


Fig. 1: Recorded years of observed microbial resistance for some antimicrobial drugs since their introduction

Source: Marty *et al.*⁴ and CDC⁵

Table 1: Natural and man-caused selective dynamic spreading of ARGs in nature through main interchangeable sources

Effect on antibiotic resistance	Origin	Causes
Selecting	Nature	Protection against heavy metals, endogenous and naturally occurring antibiotics in addition to alternative cellular rules of the resistance proteins
	Medicine	Pharmaceutical production of antibiotics and its consumption
	Agriculture	Application of antibiotics and its consumption
Spreading	Physical forces	Wind and water
	Biological factors	Animal, insects, birds and human activities

Source: Allen *et al.*,¹⁷

on their microbiological quality and purity¹⁶. Table 1 demonstrated the possible pools of ARGs which are dynamic and mobile between them¹⁷.

Although conventional or culture-based techniques are considerably cheap and reproducible, they are known to underestimate the total number of bacteria by up to several orders of magnitude, even with prolonged incubation times and temperature variations. It has long been documented that artificial culture media lead to only a very small fraction 1 in 10000 to 1 in 100 of the total viable bacterial count present in any given sample¹⁸. Viable but non-culturable (VBNC) cells have also been shown to be antibiotic tolerant, as well as exhibiting tolerance to heavy metals, environmental stress conditions and ethanol¹⁹. Therefore, although significant financial/legal costs linked to culture media-based results, application of selective agents in any culture-based method, including those for pathogens, is likely to lead to a considerable skipping bioburden fraction from the actual number of potentially infective bacteria present. The distinction between “persisters” and VBNC cells appear artificial and while there has been much of work published in recent years on the former, the literature on the latter is voluminous and to date there are no convincing studies indicating they are not the same or at least variants of the same phenomenon²⁰. Interestingly, drug-resistance genes can withstand harsh environmental conditions and reach microbiome of the patient to be absorbed by bacteria as indicated earlier in a previous study². Thus, current QC tests in pharmaceutical microbiology laboratories under any circumstances are not indicative for the risk associated with antibiotic resistance transfer through pharmaceutical dosage forms, especially if classical official methods were used instead of the new Rapid Microbiological Methods (RMMs) and technologies which are not common in the developing countries particularly.

No reported work relating the role of pharmaceutical manufacturing water, personnel and environment to the mobility of ARG to the final consumers is available till now in our hands. It is encouraged that extensive researches focusing in this dilemma in healthcare industry generally and pharmaceutical sector specifically being performed to access

the degree of hazard that could ensue from the kinetics of ARGs from the product to the final consumer who is normally is expected to be in ill-health status and more prone than the normal individuals to the devastating consequences of resistant microbes. Extensive researches are being made to discover new anti-microbial molecules. Nevertheless, there is a great concern over the possibility of balance shifting towards the emergence of the aggressive resistance against antimicrobials in a higher rate rather than susceptibility due to the high adaptability of the microbial cells.

REFERENCES

1. Van Hoek, A.H.A.M., D. Mevius, B. Guerra, P. Mullany, A.P. Roberts and H.J.M. Aarts, 2011. Acquired antibiotic resistance genes: An overview. *Front. Microbiol.*, Vol. 2. 10.3389/fmicb.2011.00203.
2. Thiel, C.S., S. Tauber, A. Schütte, B. Schmitz, H. Nuesse, R. Moeller and O. Ullrich, 2014. Functional activity of plasmid DNA after entry into the atmosphere of earth investigated by a new biomarker stability assay for ballistic spaceflight experiments. *PLoS One*, Vol. 9. 10.1371/journal.pone.0112979.
3. Universe Today, 2018. Antibiotic resistant bacteria has been found on the space station's toilet. Universe Today. <https://www.universetoday.com/140723/antibiotic-resistant-bacteria-has-been-found-on-the-space-stations-toilet/>
4. Marty, F.M., W.W. Yeh, C.B. Wennersten, L. Venkataraman and E. Albano *et al.*, 2006. Emergence of a clinical daptomycin-resistant *Staphylococcus aureus* isolate during treatment of methicillin-resistant *Staphylococcus aureus* bacteremia and osteomyelitis. *J. Clin. Microbiol.*, 44: 595-597.
5. CDC., 2018. What exactly is antibiotic resistance? Centers for Disease Control and Prevention (CDC). <https://www.cdc.gov/drugresistance/about.html>
6. Zhaxybayeva, O. and W.F. Doolittle, 2011. Lateral gene transfer. *Curr. Biol.*, 21: R242-R246.
7. Miller, R.V., 1998. Bacterial gene swapping in nature. *Sci. Am.*, 278: 66-71.
8. Smith, R.D. and J. Coast, 2002. Antimicrobial resistance: A global response. *Bull. World Health Organiz.*, 80: 126-133.

9. Da Costa, P.M., L. Loureiro and A.J.F. Matos, 2013. Transfer of multidrug-resistant bacteria between intermingled ecological niches: The interface between humans, animals and the environment. *Int. J. Environ. Res. Public Health*, 10: 278-294.
10. Wang, H., J.C. McEntire, L. Zhang, X. Li and M. Doyle, 2012. The transfer of antibiotic resistance from food to humans: Facts, implications and future directions. *Rev. Sci. Tech.*, 31: 249-260.
11. Marshall, B.M. and S.B. Levy, 2011. Food animals and antimicrobials: Impacts on human health. *Clin. Microbiol. Rev.*, 24: 718-733.
12. Wang, Y., J. Lu, L. Mao, J. Li, Z. Yuan, P.L. Bond and J. Guo, 2018. Antiepileptic drug carbamazepine promotes horizontal transfer of plasmid-borne multi-antibiotic resistance genes within and across bacterial genera. *ISME J.* 10.1038/s41396-018-0275-x.
13. Vaz-Moreira, I., O.C. Nunes and C.M. Manaia, 2014. Bacterial diversity and antibiotic resistance in water habitats: Searching the links with the human microbiome. *FEMS Microbiol. Rev.*, 38: 761-778.
14. Li, J., J. Cao, Y.G. Zhu, Q.L. Chen and F. Shen *et al.*, 2018. Global survey of antibiotic resistance genes in air. *Environ. Sci. Technol.*, 52: 10975-10984.
15. Ashour, M.S., M.S. Mansy and M.E. Eissa, 2011. Microbiological environmental monitoring in pharmaceutical facility. *Egypt. Acad. J. Biol. Sci.*, 3: 63-74.
16. Eissa, M.E., 2016. Distribution of Bacterial Contamination in Non-Sterile Pharmaceutical Materials and Assessment of Its Risk to the Health of the Final Consumers Quantitatively. *Beni-Suef Univ. J. Basic Applied Sci.*, 5: 217-230.
17. Allen, H.K., J. Donato, H.H. Wang, K.A. Cloud-Hansen, J. Davies and J. Handelsman, 2010. Call of the wild: Antibiotic resistance genes in natural environments. *Nat. Rev. Microbiol.*, 8: 251-259.
18. Watkins, J. and X. Jian, 1997. Cultural Methods of Detection for Microorganisms: Recent Advances and Successes. In: *The Microbiological Quality of Water*, Sutcliffe, D.W. (Ed.), Freshwater Biological Association, Ambleside, UK., ISBN: 0-900386-57-6, pp: 19-27.
19. Nowakowska, J. and J.D. Oliver, 2013. Resistance to environmental stresses by *Vibrio vulnificus* in the viable but nonculturable state. *FEMS Microbiol. Ecol.*, 84: 213-222.
20. Wood, T.K., S.J. Knabel and B.W. Kwan, 2013. Bacterial persister cell formation and dormancy. *Applied Environ. Microbiol.*, 79: 7116-7121.