On Arsenic and Plague

To the Editor—There is evidence that plague is not an ancient fear of the past centuries [1]. Different strains of *Yersinia pestis* actually give rise to sporadic outbreaks of zoonotic origin worldwide, with high incidence in African countries. Due to the attribution of reservoir to wild as well as domestic animals, including pigs and dogs [2], and the risk of person-to-person transmissibility [3], the acquisition of multidrug resistance in *Y. pestis* is a potentially serious threat to human health [4]. Several articles, and a more recent study [5], identified a self-transmissible genetic element conferring arsenic resistance in the Java 9 strain of *Y. pestis* mobilome, the transposon Tn2503. The acquisition of arsenic resistance in *Yersinia enterocolitica* through the homologous transposon Tn2502 was previously described in 1997 by Neyt and coworkers [6]. Of importance, arsenic resistance has been linked to multidrug-resistant phenotypes [7]. Eppinger et al [5] cite Neyt et al [6] as the only support to the hypothetical origin of arsenic resistance in *Yersinia* species, advancing that arsenic resistance might have been raised upon the traditional use of formulations containing arsenic derivatives to cure farm animals, in particular swine dysentery. However, Neyt et al were “unable to produce written documentation of this practice” [6]. Therefore, no reference relative to arsenic-based veterinary drugs was actually available in these
publications. We wish to advise historical scientific literature documenting the use of arsenical compounds in veterinary (and human) medicine that adds to the suggestions on the origin of arsenic resistance previously proposed. In 1935, E. Roberts and W. M. Dawson of the University of Illinois [8] tested experimentally the detrimental effects of arsenical Fowler solution. (The English physician Thomas Fowler invented the solution containing 1% potassium arsenite in 1786; it was prescribed to cure periodic fever and syphilis, and later as a tonic. Also called Kali arsenicosum, Kali arseniatum, Liquor potassii arseniti, or Liquor potassae arsenitis, it was in use until the late 1950s. Of note, considering the role of rodents as immune reservoirs of *Y. pestis*, the actual wide use of potassium arsenite as a pesticide and rodenticide raises concern.) The preparation reported in their article, containing 1% arsenic trioxide, was popular as a farm-animal feeding to accelerate fat accumulation and to obtain lustrous hair [8]. From their critical point of view, Roberts and Dawson observed an increased susceptibility to infections in experimental rabbits fed Fowler solution, in line with the empirical experience of farmers. Thirty years earlier, in 1904, Quitman of the Veterinary College of the United States after colonization, and was born Royal Society), was diffused in the United States for almost 150 years. Actually, arsenical and antimonial compounds, as part of the Pharmacopoeia and Materia Medica (Medical Materials), including plants, minerals, and animal derivatives, were in use in Europe upon the influence of the Middle Ages physicians Avicenna (Ibn Sina, 980–1037) and Averroes (Ibn Rushd, 1126–1198) and of Paracelsus (Theophrastus Philippus Aureolus Bombastus von Hohenheim [1493–1541], German-Swiss physician and scholar) teachings in Renaissance medical schools. In the “Book of the Plague” (published posthumously in 1576), Paracelsus suggested amulets containing arsenic or quicksilver (xenicon), based on his experience to prevent and cure the plague that was raging in Switzerland in 1534. Paracelsus’s treatises on medicine were written in accessible vernacular German, in opposition to the official Latin Galenic texts. The medical approach of Paracelsus spread and persisted for centuries (the first edition of the Latin translation of Paracelsus’s collected writings appeared in 1658 in England, under the auspices of the newborn Royal Society), was diffused in the United States after colonization, and was still in use until the middle 19th century. In Eastern countries, traditional Chinese medicine prescribes ointments for topical use or beverages containing arsenic sulfide (realgar) to treat human and animal diseases, including swine hyperpyrexia syndrome. The discontinuous exposure to low, nontoxic doses of arsenical preparations present in almost all coded pharmacopoeias in Western and Eastern countries might have favored the development and exchange of plasmids carrying arsenic resistance in host microorganisms. It cannot be excluded that farm animals arriving from England and Germany during the colonization of America could have already been exposed to low-dose arsenic and become carriers of arsenic-resistant bacteria in their gut.

**Note**

**Potential conflict of interest.** Author certifies no potential conflicts of interest.

The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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