

LETTER

Open Access



A brief comment on vaccinations for opportunistic microorganisms

Ferhat Arslan* and Haluk Vahaboğlu

See related research by Rello et al., <https://ccforum.biomedcentral.com/articles/10.1186/s13054-017-1601-9>

We read with interest the manuscript by Rello et al. published in *Critical Care* [1]. The authors conducted a randomized, placebo-controlled vaccine study against *Pseudomonas aeruginosa* among intensive care unit (ICU) patients and concluded that vaccination against *P. aeruginosa* failed to protect the patients from infection with this microorganism. Interestingly, invasive *P. aeruginosa* infections were more common among the vaccinated population (vaccinated, 39/263; placebo, 6/92; risk ratio (RR) 1.169; 95% confidence interval (CI) 1.027–1.332; one-sided Fischer's exact test, $p = 0.042$; Stata 13.1).

Vaccines have been used with great success against pathogenic microorganisms such as Measles virus, Variola virus, and *Corynebacterium diphtheriae*. In the past decade, vaccine development against opportunistic and environmental microorganisms has gained attention. *Streptococcus pneumoniae*, a member of the human microbiome, has been a target for vaccine developers. From this study, we now understand that *P. aeruginosa*, a ubiquitous environmental microorganism, is another potential vaccine target.

A common feature of opportunistic microorganisms is that, under normal conditions, they do not cause infections. A disruption of the natural defense barriers allows opportunistic colonizers to gain access to otherwise sterile

sites and trigger inflammation and damage. Eliminating one of the colonizers will almost never reduce the risk of developing infections from opportunistic pathogens. Once the defense mechanisms are compromised, a new colonizer would gain access to the site and cause inflammation. During the 1940s, in the pre-antibiotic era, native colonizers such as *S. pneumoniae* and *Haemophilus influenzae* were the leading cause of nosocomial pneumonia [2]. Following the introduction of antibiotics in medical practice, *Staphylococcus aureus* emerged as the leading etiological agent during the 1960s [3]. Colonizers, and consequently the causative microorganisms, changed but the incidence of nosocomial pneumonia did not decrease. Following the widespread use of pneumococcal vaccine, similar consequences were observed [4]. This study once more indicates that vaccines against opportunistic colonizers are ineffective in preventing infections.

However, the predominant worry is not the failure of vaccines against opportunistic pathogens. Widespread use of vaccines against members of the human microbiome or the normally non-pathogenic environmental microorganisms has the potential to unpredictably change our microenvironment [5]. More importantly, administering large amounts of antigens parenterally to humans, despite no tangible benefits, is a major ethical issue.

Authors' response

Jordi Rello and Anton Klingler

We appreciate the interest by Arslan and Vahaboğlu in our manuscript. Unfortunately, we respectfully disagree with the assertion that invasive *P. aeruginosa* infections were more common in IC43-vaccinated compared to placebo-injected ventilated ICU patients in our phase II

report of a new, recombinant protein (OprF/I)-based vaccine against this opportunistic pathogen. As presented in the article, there was no significant difference observed in confirmed infection rates when randomized vaccination groups and placebo were compared overall with the pre-planned statistical test (Fisher-Freeman-Halton) [6]. The post-hoc comparison of all merged IC43 vaccination groups together against placebo by Arslan and Vahaboğlu

* Correspondence: ferhatarlandr@hotmail.com
Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Istanbul Medeniyet University, Istanbul, Turkey



using Fisher's exact test in a one-sided manner is statistically highly disputable and we are convinced that the observed infection rates do not allow the conclusion that IC43 neither increases nor reduces the risk of invasive *P. aeruginosa* infections.

In addition, the presented phase II study investigated two doses and two formulations of the IC43 vaccine against *P. aeruginosa* in ventilated ICU patients for immunogenicity as primary, and safety and efficacy as secondary, outcome measures. Consequently, as emphasized in our discussion, the study was insufficiently powered for evaluation of efficacy in terms of *P. aeruginosa* infection rates and the study methodology likely had biased detection of infections [1].

We oppose Arslan and Vahaboğlu's statement that administration of antigens is a major ethical issue, as therapeutic benefit/risk assessment is the key concept of clinical development and regulatory drug approval. In contrast to the authors' statement, there is evidence that vaccination against opportunistic pathogens can be successful, as demonstrated by a recent meta-analysis on the effectiveness of a 23-valent pneumococcal vaccine in the elderly [7].

Years into the development of effective vaccines against nosocomial infections, *P. aeruginosa* continues to cause serious infections, particularly in the critically ill, immunocompromised, and those with burn wounds, with cystic fibrosis or contact lens-associated bacterial keratitis [8]. Our data provide a rationale that vaccination against nosocomial *P. aeruginosa* infection may improve clinical outcome in mechanically ventilated patients exposed to nosocomial infections and warrants further testing in a pivotal Phase II/III study.

Taken together, we strongly believe that considering the problem of nosocomial infections, the prominent role of *P. aeruginosa* in this setting, antibiotic resistance, an aging population and population dynamics with a predicted doubling in population, a vaccine against *P. aeruginosa* is urgently needed. Indeed, MDR *P. aeruginosa* is classified as a "serious threat" by the CDC [9], and innovations to develop adjunctive therapies, such as a vaccine, should be a research priority.

Acknowledgement

We would like to thank Editage (<http://www.editage.com>) for English language editing.

Funding

No funding source.

Availability of data and materials

All data generated and/or analyzed during this study are included in this article.

Authors' contributions

HV wrote the article. FA contributed to the design of the study and interpreted the relevant manuscripts. HV performed the statistical analysis. Both authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

Not applicable.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Published online: 05 May 2017

References

1. Rello J, Krenn C-G, Locker G, et al. A randomized placebo-controlled phase II study of a pseudomonas vaccine in ventilated ICU patients. *Crit Care*. 2017; 21:22.
2. Smillie WG, Duerschner DR. The epidemiology of terminal pneumonia: II. The selectivity of nasopharyngeal bacteria in invasion of the lungs. *Am J Hyg*. 1947;45:13–8.
3. Kneeland YJ, Price KM. Antibiotics and terminal pneumonia. *Am J Med*. 1960;29:967–79.
4. Ortqvist A, Hedlund J, Burman LA, et al. Randomised trial of 23-valent pneumococcal capsular polysaccharide vaccine in prevention of pneumonia in middle-aged and elderly people. *Lancet*. 1998;351:399–403.
5. Brown SP, Cornforth DM, Mideo N. Evolution of virulence in opportunistic pathogens: generalism, plasticity, and control. *Trends Microbiol*. 2012;20: 336–42.
6. Freeman GH, Halton JH. Note on an exact treatment of contingency, goodness of fit and other problems of significance. *Biometrika*. 1951;38(1–2):141–9.
7. Falkenhorst G, Remschmidt C, Thomas H, et al. Effectiveness of the 23-valent pneumococcal polysaccharide vaccine (PPV23) against pneumococcal disease in the elderly: Systematic review and meta-analysis. *PLoS One*. 2017;12(1):e0169368.
8. Priebe G, Goldberg J. Vaccines for *Pseudomonas aeruginosa*: a long and winding road. *Expert Rev Vaccines*. 2014;13:507–19.
9. Sievert DM, Ricks P, Edwards JR, et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2009–2010. *Infect Control Hosp Epidemiol*. 2013;34:1–14.