American Journal of Biomedical Science & Research

www.biomedgrid.com

ISSN: 2642-1747

Minireview



# Bacterial Delivery Vehicles for Mucosal Vaccines: A Promising Tool for Mass Vaccination

**Yakhya Dieye[1,2]*, Cheikh Momar Nguer[1], Fatou Thiam[1] and Abou Abdallah Malick Diouara[1]**

[1]*Applied Biotechnologies & Environmental Bioprocesses Research Group, Ecole Superieure Polytechnique, Cheikh Anta Diop University, Senegal*

[2]*Pole of Microbiology, Pasteur Institute of Dakar, Senegal*

***Corresponding author:** Yakhya Dieye, Applied Biotechnologies & Environmental Bioprocesses Research Group, Ecole Superieure Polytechnique, Cheikh Anta Diop University, Senegal and Pole of Microbiology, Pasteur Institute of Dakar, Senegal.

***To Cite This Article:*** *Dieye Y, Nguer CM, Thiam F, Diouara AAM. Bacterial Delivery Vehicles for Mucosal Vaccines: A Promising Tool for Mass Vaccination. Am J Biomed Sci & Res. 2022 17(3) AJBSR.MS.ID.002351,* DOI: 10.34297/AJBSR.2022.17.002351

**Received:** October 26, 2022; **Published:** November 03, 2022

## Abstract

Infectious diseases continue to be a leading cause of death especially in low-income countries. Vaccination is without doubt the best means to reduce the mortality and morbidity due to viral, bacterial, fungal and parasitic pathogens. Most of the infections are initiated at the mucosal surfaces that are in contact with the external environmental. Mucosal vaccination aims to deliver immunogens at the mucosa thereby activating the mucosal immune system and providing a protection at both the portal of entry for pathogens and the systemic compartment of the body. Recombinant bacteria represent a class of mucosal vaccine delivery platform that has a potential that need to be further explored. This short review discussed two type of bacterial mucosal vaccine delivery vehicles including attenuated pathogens and commensals. It summarizes the advantages and limits of each type and emphasizes the possibility of using these vectors alone or in combination for mass vaccination to reduce the burden of infectious diseases and prepare for pandemics like the recent Covid-19.

**Keywords:** Mucosal Immune System; Vaccine; Bacterial Delivery Vehicle

**Abbreviation:** APC: Antigen-Presenting Cell; G-MIS: Gut-Associated Mucosal Immune System; MIS: Mucosal Immune System; PAMP: Pathogen-Associated Molecular Pattern; PRR: Pathogen Recognition Receptor

## Introduction

Mankind has paid a heavy toll to infectious diseases throughout history. The scientific, social and economic progresses of the last two centuries have dramatically reduced deaths from infectious diseases. However, this benefit is unequally shared by human populations. While in developed countries well-structured health care systems enable an efficient management and care of infections, poor regions of the globe are still heavily affected by viral, bacterial, fungal, and parasitic diseases. Today the emergence of new and re-emergence of old diseases [1], the increase of antibiotic resistance [2], and the modern human lifestyle with unprecedented scales of travel and exchange of good have made infectious diseases an important health concern worldwide. Infectious diseases are typically controlled at three levels: prevention (vaccination), detection (diagnostic) and cure (therapy) of infections. Of these, vaccination is particularly important in that it prevents the occurrence of infections, especially when it takes place at the mucosae that are in contact with the surrounding environment.

Mucosae represent large surfaces of interaction between vertebrates and their external environment. They also constitute an entry route for various pathogens, including viruses, bacteria, and parasites [3]. Several of the most important infectious diseases worldwide are initiated at mucosal surfaces [4]. These include AIDS, tuberculosis and other respiratory infections, and diarrheal diseases. In total, it is estimated that 90% of infections in humans are initiated at the oral, nasopharyngeal, gut, or vaginal mucosa. Pathogen colonization and crossing through the mucosa are

prevented by several mechanisms. Primary mucosal protection is mediated by a physico-chemical barrier that involves several components, including epithelium, mucus layers, acidity in gastric mucosa, production of antimicrobial peptides and presence of commensals that compete with invading pathogens for the occupation of mucosal niches. Besides this physico-chemical barrier, and most importantly, mucosa possesses a dedicated mucosal immune system.

## Mucosal Immune System and Mucosal Vaccination

The Mucosal Immune System (MIS) is a very sophisticated and well-organized network of cells and immune districts that possess innate and adaptive branches with immune inductive and effector sites [5]. The innate branch of the MIS enables rapid detection of pathogens mainly through receptors such as the pathogen recognition receptors (PRR) that recognize components of pathogens called pathogen associated molecular patterns (PAMP) [6]. Following the detection of a pathogen, the innate MIS orchestrates a series of events that result in an inflammatory response that recruits immune cells to the site of infection and alerts the adaptive branch [7,8]. The adaptive MIS subsequently induces a response both locally, mainly by the secretion of IgA in the mucosa, and in the systemic compartment. Together, the coordinated activities of the innate and adaptive branches of MIS result in elimination of pathogens at the mucosa and neutralization in the systemic compartment of pathogenic microorganisms that succeeded in crossing the mucosal barrier. An important feature of the MIS is the concept of a common mucosal immune system: when a pathogen is detected in a particular mucosa, the adaptive immune response is mounted not only locally, but also in other remote mucosae [9]. This distal crosstalk between different mucosa provides a means of general surveillance of the organism. The best studied MIS is the gut-associated MIS (G-MIS) that is the largest immune organ. In contrast to the systemic immune system, the G-MIS is in permanent contact with molecules derived from food and also with an abundant gastrointestinal flora [10,11]. Therefore, G-MIS has to distinguish between

i. Food products against which no immune response should be induced,

ii. Commensal microorganisms that need to be controlled to prevent their translocation into the systemic compartment, and

iii. The pathogens against which a strong immune response should be induced for their elimination. These different functions require tight regulation of G-MIS. A defect in any of these functions can lead to different types of disease including auto-immune, allergy, metabolic and cancer disorders [12-14].

Mucosal vaccination that aims to stimulate the MIS in order to prevent colonization or invasion of the mucosa by pathogens appears to potentially be the most effective means of preventing infectious diseases. However, despite that most infections are initiated at the mucosa, only a few vaccines available to humans are mucosal vaccines [15]. Numerous attempts have been made to convert injectable vaccines for oral administration without success [16]. Several reasons could be proposed to explain this observation. Firstly, the systemic immune system has historically been better understood than the MIS. Secondly, in parenteral immunization the antigen directly accesses antigen presenting cells (APC) whereas in the mucosa it needs to be correctly sampled from a considerable number of foreign molecules against which no immune response is induced. Thirdly, antigens delivered to mucosa undergo degradation from enzymes and microorganisms decreasing the amount and quality of antigenic molecules that reach immune induction sites. Lastly, induction of a mucosal immune response requires to overcome mucosal tolerance which is important for maintaining mucosal homeostasis. Active ongoing research are addressing these limitations of mucosal vaccination. These efforts are justified by the many advantages that mucosal vaccination presents as an alternative to parenteral immunization [17]. Indeed, mucosal vaccination can possibly provide protection both in the mucosa, the site of pathogen entry, and in the systemic compartment. Additionally, mucosal vaccination is needle-free, cold-chain-free, and does not require qualified medical personnel. These features make mucosal vaccination particularly indicated for developing countries where infection diseases are most prevalent.

## Bacteria As Delivery Vehicles for Mucosal Vaccines

Several types of delivery systems for vaccines and therapeutics at mucosal surfaces have been, and are still being, investigated. These delivery systems include killed or live bacteria and viruses, transgenic plants, liposomes and microparticles that can be targeted to the mucosal immune induction sites [17,18]. Bacterial vectors are one of the most studied delivery systems [19]. It is interesting to note that the only bacterial mucosal vaccines approved for use in humans are killed or attenuated strains of Vibrio cholerae and Salmonella enterica serovar Typhi [20]. In these attenuated bacterial mucosal vaccines, immunization is sought against the pathogen administered to the mucosa [21]. Therefore, the almost complete pool of antigens from the pathogen is delivered to the MIS at the route of entry used by the pathogen. The situation is quite different in the context of bacterial mucosal vaccine delivery system in which a recombinant bacterium is used to deliver to the MIS one or a small number of heterologous antigens from a pathogen that infects the organism by the mucosal or parenteral route. This highlights an important challenge for development of bacterial mucosal vaccine delivery systems. Ideally, the vaccine carrier should be designed such that the immune response is preferably, or at least substantially, directed against the delivered heterologous antigens. Bacterial mucosal delivery vehicles present several advantages.

First, bacteria used as carrier can reach and colonize mucosal surfaces and by this means can access MIS induction sites. Secondly, genetic engineering tools and technologies that are available make possible construction of recombinant bacteria that

i. Efficiently synthesize the desired molecules in situ, protecting them from degradation in the mucosal environment and thus favoring supply of a sufficient amount of antigen to the immune induction sites

ii. Specifically interact with APC

iii. Simultaneously deliver adjuvants

iv. Induce the desired type of immune response. Thirdly, bacteria can be cultured in fermenters making production of vaccine strains a cost effective, easy, and highly reproducible process. Live bacterial vaccine carriers can be classified in two groups:

a. attenuated pathogens.

b. commensal, non-pathogenic bacteria.

These two types of vehicles interact differently with the host immune system and therefore possess different advantages and limitations.

### Attenuated Pathogens

Attenuated pathogens that are used for vaccine delivery harbor mutations that prevent them from causing disease to the host. However, they retain the [22] ability to survive the stresses encountered in the mucosa and to multiply to some extent in host tissues. This category of vaccine carrier is detected by the MIS almost similarly as a fully pathogenic microorganism and by this displays intrinsic adjuvant properties. Attenuated bacterial pathogens present heterologous antigens which they deliver in a context of strong activation of both innate and adaptive branches of the MIS. This is exemplified by Salmonella, the best studied prototype of bacterial mucosal vaccine delivery vehicle [23]. Salmonella's interactions with the host have been extensively studied making it possible to select mutations that decrease or eliminate the possibility of causing diseases. Studies with Salmonella delivery vehicles showed induction of systemic and mucosal antibody comparable or even better in mice deficient for innate immune signalling than in wild type rodents [22,24]. This observation demonstrates the strong immunostimulatory capability of Salmonella vaccine carriers. But live attenuated pathogens present two main drawbacks. First, the strong response against their components makes it difficult to use these vehicles repeatedly. It has been shown that prior exposure to Salmonella results in a decreased ability of a recombinant Salmonella carrier to subsequently colonize host tissues compromising its efficacy as vaccine delivery vehicle [25]. Secondly, it is often difficult to find an adequate balance between attenuation and ability to multiply enough in host tissues. Ensuring a complete attenuation of a bacterial pathogen requires several mutations that negatively affect its fitness in host tissues and compromise its ability to synthesize and deliver sufficient amounts of antigens.

### Commensals and Non-Pathogenic Bacterial Vaccine Carriers

Commensal bacteria are members of mucosal flora that are involved in several host functions and are indispensable for mucosal homeostasis. They contribute to energy harvest and storage from the diet [26] and to prevention of gastrointestinal tract (GIT) colonization by pathogens. Additionally, gut microbiota participates in normal development and regulates the G-MIS [11]. Because of these important functions, commensals are recognized by the MIS but regulatory mechanisms permit tolerance toward members of the flora [27]. A rupture of this tolerance is the cause of several autoimmune diseases. Commensals and non-pathogenic mucosal vaccine carriers present the advantage of not requiring mutation to be used as delivery vehicles. Members of the host flora are fully capable and multiplying in the mucosa and can continuously deliver substantial amounts of antigen. Additionally, since a weak immune response is induced against these carriers, the possibility of immune reaction against heterologous antigens they deliver is increased. Moreover, this category of vaccine carrier can potentially be repeatedly used without affecting the immune response to the antigen they deliver. All these features make commensal and non-pathogenic delivery vehicles more indicated for use in infants and immune-compromised individuals. The main limitations of this category of vaccine carrier pertain to their poor inflammatory capability and the need to overcome the immune tolerance they are subjected to. The most studied bacteria from this category of vaccine delivery vehicle belong to the group of lactic acid bacteria [28]. Most of these bacteria are members of human microbial flora or have been consumed with food products for centuries.

## Conclusion

Vaccination is without doubt the best means to address the threat posed by infectious diseases worldwide. Mucosal vaccines delivered by recombinant bacterial vectors by the attributes they display represent a powerful tool for preventing infection by viral, bacterial, and parasitic microorganisms. The two types of bacterial delivery vehicles described in this article can be used for this purpose. Depending on the targeted pathogen, an attenuated pathogen or a commensal vector can be used. Alternatively, the two vectors delivering the same antigen(s) can be combined in order to benefit from their respective advantages. Another option could be to alternate vaccine delivery by the two categories of vehicle in a prime-boost immunization regimen. Although additional work is needed to make recombinant bacterial platform usable in humans, this effort can be expedited. The Covid-19 crisis showed that the

available scientific tools combined with technological innovation enable accelerated design and manufacture of vaccines [29]; One of the lessons learned is the need of preparedness to efficiently respond to pandemics. In this regard, bacterial mucosal vaccine delivery platform represents an interesting option that deserve more attention. This platform can be used to synthesize in situ, supply antigens and activate different compartments of the MIS. This vaccination system can be manufactured at very low cost, stored in the absence of a cold-chain, and administered without the intervention medical professionals. These attributes make bacterial mucosal delivery system an ideal strategy for mass vaccination in LIC and for global response to pandemics.

## References


1. David E Bloom, Steven Black, Rino Rappuoli (2017) Emerging infectious diseases: A proactive approach. Proc Natl Acad Sci USA 114(16): 4055-4059.
2. Antimicrobial Resistance Collaborators (2022) Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet 399(10325): 629-655.
3. Fengling Feng, Ziyu Wen, Jiaoshan Chen, Yue Yuan, Congcong Wang, et al. (2022) Strategies to Develop a Mucosa-Targeting Vaccine against Emerging Infectious Diseases. Viruses 14(3): 520.
4. Victor Araujo Correa, Amanda Izeli Portilho, Elizabeth De Gaspari (2022) Vaccines, adjuvants and key factors for mucosal immune response. Immunology 167(2): 124-138.
5. Jerry R McGhee, Kohtaro Fujihashi (2012) Inside the mucosal immune system. PLoS Biol 10(9): e1001397.
6. Ji-Hyun Jang, Hee Woong Shin, Jung Min Lee, Hyeon Woo Lee, Eun Cheol Kim, et al. (2015) An Overview of Pathogen Recognition Receptors for Innate Immunity in Dental Pulp. Mediators Inflamm: 794143.
7. Stogerer T, Stager S (2020) Innate Immune Sensing by Cells of the Adaptive Immune System. Front Immunol 11: 1081.
8. Trine H Mogensen (2009) Pathogen recognition and inflammatory signaling in innate immune defenses. Clin Microbiol Rev 22(2): 240-273.
9. Bernadeta Pietrzak, Katarzyna Tomela, Agnieszka Olejnik Schmidt, Andrzej Mackiewicz, Marcin Schmidt (2020) Secretory IgA in Intestinal Mucosal Secretions as an Adaptive Barrier against Microbial Cells. Int J Mol Sci 21(23): 9254.
10. Daisuke Tokuhara, Yosuke Kurashima, Mariko Kamioka, Toshinori Nakayama, Peter Ernst, et al. (2019) A comprehensive understanding of the gut mucosal immune system in allergic inflammation. Allergol Int 68(1): 17-25.
11. Shi N (2017) Interaction between the gut microbiome and mucosal immune system. Mil Med Res 4: 14.
12. Nathalie Juge (2022) Relationship between mucosa-associated gut microbiota and human diseases. Biochem Soc Trans: BST20201201.
13. Mingxin Li, Fang Wang (2021) Role of Intestinal Microbiota on Gut Homeostasis and Rheumatoid Arthritis. J Immunol Res: 8167283.
14. Lu Wang, Shiqi Wang, Qing Zhang, Chengqi He, Chenying Fu, et al. (2022) The role of the gut microbiota in health and cardiovascular diseases. Mol Biomed 3(1): 30.
15. Ed C Lavelle, Ross W Ward (2022) Publisher Correction: Mucosal vaccines - fortifying the frontiers. Nat Rev Immunol 22(4): 266.
16. David A Sack (2019) Enhancing immune responses to oral vaccines: still an enigma. Lancet Infect Dis 19(2): 122-123.
17. Ed C Lavelle, Ross W Ward (2022) Mucosal vaccines - fortifying the frontiers. Nat Rev Immunol 22(4): 236-250.
18. J Wallis, Shenton D P, Carlisle R C (2019) Novel approaches for the design, delivery and administration of vaccine technologies. Clin Exp Immunol 196(2): 189-204.
19. Chengchao Ding, Junfei Ma, Qingli Dong, Qing Liu (2018) Live bacterial vaccine vector and delivery strategies of heterologous antigen: A review. Immunol Lett 197: 70-77.
20. Médéric Diard, Erik Bakkeren, Verena Lentsch, Andrea Rocker, Nahimi Amare Bekele, et al. (2021) A rationally designed oral vaccine induces immunoglobulin A in the murine gut that directs the evolution of attenuated Salmonella variants. Nat Microbiol 6(7): 830-841.
21. Kim A Woodrow, Kaila M Bennett, David D Lo (2012) Mucosal vaccine design and delivery. Annu Rev Biomed Eng 14: 17-46.
22. Noemi Lupo, Veronika Novakova Tkadlečková, Max Jelkmann, Flavia Laffleur, Gergely Hetényi (2019) Self-emulsifying drug delivery systems: In vivo evaluation of their potential for oral vaccination. Acta Biomater 94: 425-434.
23. Kenneth L Roland, Karen E Brenneman (2013) Salmonella as a vaccine delivery vehicle. Expert Rev Vaccines 12(9): 1033-1045.
24. Qing Liu, Xuegang Shen, Xiaoping Bian, Qingke Kong (2020) Effect of deletion of gene cluster involved in synthesis of Enterobacterial common antigen on virulence and immunogenicity of live attenuated Salmonella vaccine when delivering heterologous Streptococcus pneumoniae antigen PspA. BMC Microbiol 20(1): 150.
25. José Martín Ruvalcaba Gómez, Zuamí Villagrán, Juan José Valdez Alarcón, Marcelino Martínez Núñez, Lorena Jacqueline Gomez Godínez, et al. (2022) Non-Antibiotics Strategies to Control Salmonella Infection in Poultry. Animals (Basel) 12(1): 102.
26. Marcelo José Barbosa Silva, Matheus Batista Heitor Carneiro, Brunna dos Anjos Pultz, Danielle Pereira Silva, Mateus Eustáquio de Moura Lopes, et al. (2015) The multifaceted role of commensal microbiota in homeostasis and gastrointestinal diseases. J Immunol Res: 321241.
27. Ji Youn Yoo, Maureen Groer, Samia Valeria Ozorio Dutra, Anujit Sarkar, Daniel Ian McSkimming (2020) Gut Microbiota and Immune System Interactions. Microorganisms 8(10): 1587.
28. Szatraj K, Szczepankowska AK, Chmielewska Jeznach M (2017) Lactic acid bacteria-promising vaccine vectors: possibilities, limitations, doubts. J Appl Microbiol 123(2): 325-339.
29. Vivek P Chavda, Qian Yao, Lalitkumar K Vora, Vasso Apostolopoulos, Chirag A Patel, et al. (2022) Fast-track development of vaccines for SARS-CoV-2: The shots that saved the world. Front Immunol 13: 961198.