Asian Journal of Medicine and Biomedicine
eISNN: 2600-8173
https://journal.unisza.edu.my/ajmb

Asian Journal of Medicine and Biomedicine, Vol 6:1.

Open Access

Oral cholera vaccines; current perspective and future need; towards the development of novel DNA vaccine for Vibrio species.

Abdullahi Yusuf Muhammad[1], Atif Amin Baig*[1], Noor ul Ain[2], Mamona Badar[3], Chandrika Murugaiah*[4]

[1]Faculty of Medicine, Universiti Sultan Zainal Abidin, Malaysia,
[2]Faculty of Medicine, Universiti Malaysia Sabah, Malaysia,
[3]University of Westminster, London, UK
[4]School of Health Sciences, University of Management & Technology, Pakistan

Abstract

About one-third of the countries in the world are on the verge of a cholera outbreak placing over a billion individuals at risk. Water sanitation and health (WASH) programs and vaccination are preventive measures to eradicate cholera by 2030. While WASH takes a long time to implement successfully, vaccinations can reduce the cholera burden. 2030 is in less than a decade and yet the current WHO prequalified oral cholera vaccines (OCVs) failed to provide sufficient protective immunity to infants – the most affected age group in cholera outbreaks and cholera endemic regions, a shorter immunity in older children and adults, the requirement of multiple doses, and cold-chain for transport and storage are some of the limitations of OCVs and WHO recommends further research to provide better vaccines. DNA vaccine approach could be a potential approach in the future of cholera vaccines, providing ease of vaccine design and hence reducing production time; it is safer and cheaper, stable at room temperature, and can induce both humoral and cellular immune responses. Therefore, this can be a better alternative to over-dependence on vaccines' first and second generations.

Keywords: Vibrio cholerae, OCVs, DNA vaccines, Cholera

*Author for Correspondence

Cite as: Abdullahi Yusuf M., Atif Amin B, Noor ul Ain, Mamona Badar, Chandrika Murugaiah. (2022). Oral cholera vaccines; current perspective and future need; towards the development of DNA vaccine for Vibrio species. Asian Journal of Medicine and Biomedicine, 6(1),72-76.

DOI: https://doi.org/10.37231/ajmb.2022.6.1.476

An average of 3 million cholera cases are recorded, resulting in about 100,000 deaths yearly even under serious underreporting of the disease by the affected countries [1]. Cholera is an ancient global health concern that is caused by a facultative anaerobe, gram-negative bacilli with darting motility known as *Vibrio cholerae* [2]. *V. cholerae* is reported to have more than 200 serogroups, amongst which only 2 serogroups are reported to cause cholera infection: O1 and O139 serogroups [3]. Since the emergence of cholera in the early 1800s, seven pandemics were reported and the fifth and sixth pandemics are reported to be caused by a classical biotype of O1 serogroup. In contrast, the seventh pandemic is confirmed to be caused by the El Tor biotype of the same serogroup [4]. The strain responsible for the first four pandemics is considered to be unknown, and yet disputed that the classical biotype is responsible for the first six pandemics [2].

In Medium and Low-income countries, cholera is endemic, and outbreaks are frequent due to improper sanitation, inadequate access to clean drinking water, collapsed health systems, and poverty [3]. Cholera can be epidemic in some regions outside of the endemic regions, due to the existence of suitable climatic conditions for the growth of V. cholerae or natural disasters such as floods and earthquakes, which lead to outbreaks in these regions [5].

It can be directly transmitted through the fecal-oral route from person to person or from a contaminated water source or food to other individuals as an indirect transmission [6]. Cholera is known to cause conditions including severe vomiting and diarrhea which can eventually result in death if untreated [7]. Oral rehydration therapy is adopted first to correct the fluid imbalance followed by treatment of the infection to kill the bacteria. Early treatments include antibiotics but are replaced eventually with oral cholera vaccines (OCVs) due to the development of antibiotic resistance by the bacteria [8,9]. OCVs have been a promising alternative to antibiotics, but they failed to provide longer protective immunity in older individuals and insignificant immunity is observed in younger children. Other limitations include the cold-chain transport requirement and the requirement for multiple doses [4].

This article summarizes the current WHO licensed OCVs in 2022, their challenges, and the future perspective toward the DNA vaccine approach. This contributes to the roadmap for the eradication of cholera by 2030 [4]. Current preventive measures require improvement or most importantly a different approach to successfully eradicate cholera.

After the pathogen gain entrance into an individual's body, the bacteria will initiate survival factors to withstand the hostile environment of the human gut before it successfully colonizes itself. The major survival factor is a class of outer membrane protein U (OmpU), which ensure resistance to bile content and antimicrobial peptides [10]. Once the establishment stage is complete, the bacteria begin invasion and colonization mechanisms aimed at penetrating the mucolytic layer of the small intestine [2]. In the same study, it is reported that the penetration is aided by mucolytic enzymes which lyse the mucous layer, and a single flagellum that propels the bacteria into the dense mucosal layer. The bacteria's pili enable the attachment of the organism to the microvilli of the small intestines [11].

Cholera toxin (CT) producing *V. cholerae* releases the toxin, which is the major virulence factor of the bacteria and causes the characteristic symptoms of cholera infection [2]. CT comprises five B subunits which are responsible for the binding of the bacteria to the GM1 ganglioside of the epithelial cells of the gut to form a complex and subsequently lead to the uptake of the bacteria by the cell and a single A subunit which upon entrance of the bacterium into the cell it is activated and results in the upregulation of adenylate cyclase and hence increase cAMP levels leading to the secretion of high amounts of electrolytes and water into the large lumen resulting in diarrhea and vomiting [12].

In 2001 WHO prequalified Dukoral, and it is the first OCV to be prequalified by WHO and has been used in over 60 countries. Dukoral consists of formalin-inactivated or heat-inactivated Inaba and Ogawa of both classical and El Tor biotypes of O1 serogroup with cholera toxin B (CTB) [9,3]. Due to the presence of CTB, a buffer is required to protect the vaccine from acid degradation, as such the vaccine is co-administered with a buffer and the requirement for a buffer is a setback to Dukoral [13]. A decade later

after the prequalification of Dukoral, WHO prequalified Shanchol which is a modification of Dukoral, a bivalent vaccine consisting of killed whole cells of O1 and O139 serogroups without the CTB subunit, to eliminate the undesirable buffer requirement [3]. Due to major cholera outbreaks a year before the prequalification of Shanchol, to increase the production of the global OCV, Eubiologics in South Korea begin the production of OCV similar to Shanchol in a composition called Euvichol and was prequalified by WHO in 2015. Thiomersal is removed from the usual vaccine composition of Euvichol, packed in plastic materials, and named Euvichol plus and licensed in 2017. Euvichol plus has been the major OCV in the global stockpile [14].

Other OCVs exist but are only licensed nationally, but not WHO qualified. These vaccines include mOraVax which is similar in composition to Shanchol and Euvichol and is licensed in Vietnam, OraVAx which is a modeled Shanchol plus rCTB licensed in China and the Philippines, and Vaxchora which is a live attenuated form of OCV comprising of Inaba strain of classical biotype of O1 serogroup [14,15].

Vaccines are the major approach to eradicating cholera globally due to the difficulty of establishing a Water, Sanitation, and Hygiene (WASH) program worldwide. So while this program widens, vaccines can serve as a preventive measure in preventing cholera. Unfortunately, the current OCVs prove insufficient in combatting cholera, due to their limitations in providing immunity to younger children, who are the most affected age group in endemic cholera regions and during outbreaks. Moreover, the cold-chain requirement and the need for multiple doses make them inefficient towards the goal. And hence future perspectives are highly encouraged [4, 16].

DNA vaccines approach provides a rapid design and modifications in the design, eliminates the need for purification of the pathogenic bacteria, and can induce both humoral and cellular immune responses providing an advantageous approach in the future of cholera vaccines [17]. Specific antigens of interest that prove to be a potential vaccine candidates can be rapidly designed and used to create DNA vaccines that could provide solutions to the limitations of OCVs.

Current OCVs prequalified by WHO and other nationally licensed belongs to either first or second generation of vaccines (table 1). Moreover, they are slight modifications of one another or have similar composition, similar techniques, and production procedures. Hence, a different approach will widen the understanding and provide alternatives for developing more effective vaccines for all vibrio species. DNA vaccine will be a potentially effective approach in developing better cholera vaccines, as it is safe, easy to design, and able to induce both humoral and cellular immune responses.

Table 1: WHO prequalified OCVs

	Vaccine type/Subunit	Serogroup	No. of doses	Age range	Route of administration	Duration of protection	WHO prequalification	storage	Limitation
Dukoral	Killed-whole cells & cholera toxin B	O1 serogroup	2	2 years and above	oral	2 years (6months in younger children	2001	2° to 8°C	Buffer is needed, requires cold storage, shorter protection in younger children, multiple doses required and hence increase in transportation cost
Shanchol	Killed-whole cells only	O1 and O139 serogroup	2	1 year and above	oral	Up to 5 years	2011	2° to 8°C	requires cold storage, shorter protection in younger children, multiple doses required and hence increase in transportation cost
Euvichol	Killed-whole cells only	O1 and O139 serogroup	2	1 year and above	oral	Up to 5 years	2015/17	2° to 8°C	requires cold storage, shorter protection in younger children, multiple doses required and hence increase in transportation cost

Acknowledgment: We would like to acknowledge the grant from Universiti Sabah Malaysia with the grant number of UMS-DN20093.

References

1. Bi, Q., Ferreras, E., Pezzoli, L., Legros, D., Ivers, L. C., Date, K., Qadri, F., Digilio, L., Sack, D. A., Ali, M., Lessler, J., Luquero, F. J., Azman, A. S., & Oral Cholera Vaccine Working Group of The Global Task Force on Cholera Control (2017). Protection against cholera from killed whole-cell oral cholera vaccines: a systematic review and meta-analysis. The Lancet. Infectious diseases, 17(10), 1080–1088.
2. Sharmila, T., & Thomas, T. A. (2018). Pathogenesis of Cholera: Recent Prospectives in Rapid Detection and Prevention of Cholera. In (Ed.), Bacterial Pathogenesis and Antibacterial Control. IntechOpen.
3. Wierzba T. F. (2019). Oral cholera vaccines and their impact on the global burden of disease. Human vaccines & immunotherapeutics, 15(6), 1294–1301.
4. Cholera vaccines: WHO position paper – August 2017. Vaccins anticholériques: Note de synthèse de l'OMS – août 2017. (2017). Releve epidemiologique hebdomadaire, 92(34), 477–498.
5. Jutla, A., Whitcombe, E., Hasan, N., Haley, B., Akanda, A., Huq, A., Alam, M., Sack, R. B., & Colwell, R. (2013). Environmental factors influencing epidemic cholera. The American journal of tropical medicine and hygiene, 89(3), 597–607.
6. You, Y. A., Ali, M., Kanungo, S., Sah, B., Manna, B., Puri, M., Nair, G. B., Bhattacharya, S. K., Convertino, M., Deen, J. L., Lopez, A. L., Wierzba, T. F., Clemens, J., & Sur, D. (2013). Risk map of cholera infection for vaccine deployment: the eastern Kolkata case. PloS one, 8(8), e71173. https://doi.org/10.1371/journal.pone.0071173
7. Pietroni M. (2020). Case management of cholera. Vaccine, 38 Suppl 1, A105–A109.
8. Pietroni M. (2020). Case management of cholera. Vaccine, 38 Suppl 1, A105–A109.
9. Holmgren J. (2021). Modern History of Cholera Vaccines and the Pivotal Role of icddr,b. The Journal of infectious diseases, 224(12 Suppl 2), S742–S748.
10. Pennetzdorfer, N., Höfler, T., Wölflingseder, M., Tutz, S., Schild, S., & Reidl, J. (2021). σE controlled regulation of porin OmpU in Vibrio cholerae. Molecular microbiology, 115(6), 1244–1261. https://doi.org/10.1111/mmi.14669
11. Harris, J. B., LaRocque, R. C., Chowdhury, F., Khan, A. I., Logvinenko, T., Faruque, A. S., Ryan, E. T., Qadri, F., & Calderwood, S. B. (2008). Susceptibility to Vibrio cholerae infection in a cohort of household contacts of patients with cholera in Bangladesh. PLoS neglected tropical diseases, 2(4), e221.
12. Silva AJ, Benitez JA (2016) Vibrio cholerae Biofilms and Cholera Pathogenesis. PLoS Negl Trop Dis 10(2): e0004330.
13. Shaikh, H., Lynch, J., Kim, J., & Excler, J. L. (2020). Current and future cholera vaccines. Vaccine, 38 Suppl 1, A118–A126.
14. Levine MM, Chen WH, Kaper JB, Lock M, Danzig L, Gurwith M. PaxVax CVD 103-HgR single-dose live oral cholera vaccine. Expert Rev Vaccines 2017; 16:197–213
15. Holmgren J. (2021). An Update on Cholera Immunity and Current and Future Cholera Vaccines. Tropical medicine and infectious disease, 6(2), 64. https://doi.org/10.3390/tropicalmed6020064
16. Mogasale, V., Ramani, E., Wee, H., & Kim, J. H. (2016). Oral Cholera Vaccination Delivery Cost in Low- and Middle-Income Countries: An Analysis Based on Systematic Review. PLoS neglected tropical diseases, 10(12), e0005124. https://doi.org/10.1371/journal.pntd.0005124
17. Li, H., Zhang, W., & Dong, C. (2018). Crystal structure of the outer membrane protein OmpU from Vibrio cholerae at 2.2 Å resolution. Acta crystallographica. Section D, Structural biology, 74(Pt 1), 21–29.