Editorial

Time to tap the potential of synthetic conjugate vaccine technology as the future of conjugate vaccine market

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Vaccination is the most successful health intervention till date and hence it has taken a centre- stage of global health in recent times. This is evident with the significant impetus on increasing immunization coverage of traditional vaccines, increasing focus of global agencies on vaccine affordability and delivery, and finally, significant support to the research on new and affordable vaccines through various funding agencies. Out of the several licensed vaccines and several vaccine candidates in advance stages of development, the conjugate vaccines (CVs) target a significant portion in terms of lives saved and reducing years of life lost or lived with disability.[1] Currently licensed CVs have been able to target infections due to many pathogenic bacteria viz., Haemophilus influenzae type b (Hib), Neisseria meningitidis serogroups A, C, Y and W, Pneumococcal CVs covering up to 13 serotypes of Streptococcus pneumoniae and most recent addition of an effective Salmonella enterica serovar Typhi CV. Several other CV candidates covering higher valancies than the currently licensed vaccines and others targeting new disease areas e.g. Group A streptococcus, Group B streptococcus, Sal. enterica serovar Paratyphi, Klebsiella pneumoniae, Clostridium difficile, Shigella spp. and Staphylococcus aureus CVs etc. are in advance stages of pre-clinical or clinical development and many of them hope to see the market in 2020's. More than 3 million global deaths can be potentially averted using the CVs.[1] However, the above benefit comes with a significant proportion of cost associated with overall immunization coverage. As the CV manufacture is comparatively complex in terms of multiple steps and significant analytical testing required to release a vaccine batch for sale in the market as compared to many other vaccines, the cost of various CVs is substantially higher than most of the other vaccines used in national immunization programs.[2,3] The price of each of the CV in private market is further high and is prohibitively expensive for enough coverage in developing countries where the respective disease burden is highest. Due to the above and various other business, political and technical reasons, in many cases, the introduction of a new CV in developing countries takes even up to decades from the date of initial licensure in any country. Examples of such important vaccines include the introduction of Hib CV containing vaccines, multivalent pneumococcal and meningococcal CVs.[4]

To minimize this gross inequity in access of vaccines including that of CVs, there have been significant global efforts in last two decades.

The efforts range from advocacy, polity, pull and push approach including funding for research, creating access as well as market demand through e.g. advance market commitment etc.[5–7] The increased focus of important global health stake holders (e.g. WHO, GAVI alliance, National health agencies etc.) on the improving vaccine access to all needy people has also played a vital role. One of the key drivers in these whole efforts are the improved focus on novel research to help develop broadly protective and affordable CVs. The traditional approach to manufacture a CV is to use a bacterial fermentation-based technology to produce bacterial capsular polysaccharide (PS) which led to licensure of several successful CVs. However, the traditional approach to manufacture CVs has various limitations e.g. it mandates and demand the handling of highly pathogenic organisms that too at very high fermentation volumes giving rise to significant bio-safety risks and hence requirement of highly stringent manufacturing facilities which is one of the key drivers to the high cost for CV manufacturing. Further, due to the inherent variation in the bacterial strains used, different biological processes during bacterial growth and multiple downstream purification steps, the PS tends to be generated with a significant variation in terms of chemical structure, molecular size, host cell impurities etc. This leads to batch to batch variations and hence failure of various batches to meet the desired quality specifications. Further, the natural PS is required to be size degraded to an optimal size for desired immunogenicity before being used for the conjugation with a suitable carrier protein. The conjugation chemistry for each of the PS needs to be optimized separately according to the chemical structure of the respective PS. Each of the chemistry modifies the structure of PS during conjugation potentially impacting the immunogenic epitopes to varied extent based on type of conjugation chemistry used.[8] Due to the above limitations and complexities associated with the conventional CV manufacturing approach, there have been a good amount of research in developing alternative approaches to manufacture CVs e.g. organic synthesis, enzymatic synthesis, bacteria- and plant-based in vivo bioconjugation and non-covalent conjugation approach etc. [9–13] The focus of the present article is the advances in synthetic CV (SCV) approach. SCV research has been mainly driven by the significant advances in the organic chemistry in last few decades which led to increased capabilities to synthesise larger molecules than the pharmaceutically important small molecules. The SCV research based on organic synthesis has been broadly directed towards two types of conjugate molecules namely fully synthetic conjugates and semi-

synthetic conjugates. The semi-synthetic CVs comprise of synthetic oligosaccharide (OS) corresponding to a short fraction of bacterial PS which is conjugated to carrier protein of bacterial origin used in conventional CVs. While the latter being a construct of synthetic OS molecules and synthetic immunogenic peptides corresponding to the bacterial carrier protein. Semi-synthetic CV research is much more advanced in terms of development of different vaccine candidates than the fully synthetic CV candidates.

The research focus on SCV approach is not new. The foremost work relevant to synthetic conjugate vaccines dates back to late 1970s and 1980s which included organic synthesis of single, 2 and 3 repeating units of Hib PS.[14,15] Another important early study included proof of principle animal immunogenicity of the synthetic Hib OS conjugates in mouse and monkey models in 1990s.16 But it was not until November 2003, when the first semi-synthetic HibCV was developed and licensed for sale in Cuba by pioneering research of Bencomo and co-workers and later achieved pre-qualification by WHO.[17,18] During last 3 decades, the interest in carbohydrate synthesis and hence development of different SCV candidates has been increasing. Several academic and industry research laboratories have developed or have been working on development of various semi-synthetic CV candidates e.g. those against several pneumococcal serotypes, meningococcal serogroups, *Escherichia coli*, *K. pneumoniae, C. difficile, Staph. aureus, Shigella spp., Sal. Typhi, Burkholderia mallei, Pseudomonas* aeruginosa, Group A and Group B Streptococcus serotypes etc.[11,13,19-22] The synthetic approach to developing CVs has several advantages when compared to the conventional PS based approach. Following are the few main advantages, namely, there is no need to handle pathogenic or recombinant microorganisms, hence avoiding the related bio-safety issues and the stringent manufacturing facility requirement. The technology can be optimally used with bacteria which are difficult to grow in lab or from which it is tedious to get purified PS/antigen of desired specifications and optimal yield. Further, the synthetic OSs have significant advantage in terms of batch to batch consistency, no host cell impurities, easy modification of antigenic structure or specific OS length and incorporation of in-built linker to the OS. The in-built linker in turn help higher conjugation yields, highly defined conjugates and easy adaptation of conjugation reactions with different antigens as the same chemistry can be applied through the defined in-built linker. Removal of free OS from the conjugated OS is much easier due to the size difference between the two entities. Lastly, the molar ratio of the OS molecules linked to each carrier protein molecule is much higher than corresponding bacterial PS CVs which is an important immunological feature. There may be potential stability benefits from shorter OS conjugates as compared to large PS based conjugates although it needs to be proven in detailed systematics studies.

The above advantages with SCVs have been proven in several studies,[11] however, the SCV technology has few downsides, especially, the time required for synthesis of the OS as compared to bacterial PS with desired specifications is relatively longer. Although, this limitation could be minimized with the advancements in organic chemistry alongside increasing capabilities at chemical entity manufacturing organizations. Further, a proper scheduling of the batch manufacturing could help reduce the production of finished product based on the assessment of the vaccine market need in advance. Another important quality attribute for CVs is the residual impurities, which need to be tested in the purified OS for several different chemicals used in the process of organic synthesis. However, due to multiple purification steps in the whole organic synthesis and downstream conjugation steps, the residuals impurities would potentially fall in acceptable range which need to be tested and confirmed for consistency for each synthesis scheme. Lastly, the manufacturers of conventional CVs would be hesitant to make a shift from the existing to SCV production technology which would require modification in the existing manufacturing facility or building up a new facility for organic synthesis along with recruitment of specialized skilled manpower, which is not commonly available in conventional vaccine manufacturing organizations. Nevertheless, the investment could pave the way for a big leap towards future generation of CVs i.e. SCVs. Currently, SCVs show promise to be a good and viable alternative to conventional CVs and a significant research and development is required to bring-in enough confidence in the vaccine manufactures for adaptation of this technology. This requires good support for funding the research and especially for clinical development of the SCV candidates which are currently in research phase. The two recent and important developments in the field of SCVs are the successful completion of Phase 1 clinical trial of Shigella flexneri type 2a vaccine candidate[23] and CARB-X funding support to Vaxillon AG to develop a multi-valent semi-synthetic vaccine against Carbapenem resistant K. pneumoniae.[24] The technology is further being explored for development of non-conjugate synthetic vaccines and biotherapeutic molecules to combat various other disease targets e.g. anti-fungal, anti-cancer molecules etc. [11,25]which further strengthens and validates the potential of application of synthetic technology for human health in near future. In conclusion, the advantages of the SCV technology outweigh the conventional approach to manufacture CVs and has tremendous potential to serve as a plausible platform to answer the inequitable access of CVs for the developing world. This requires a renewed focus and desired funding from the scientific fraternity, industry and other relevant stakeholders.

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Conflict of interest

The authors declare no conflict of interest.

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