DISCUSSION NOTE

# Roadmap considerations for DCVMN engagement in strengthening the supply chain in low- and middle-income countries

The innovation opportunities facing emerging country manufacturers have to be considered against a significant degree of uncertainty, which can include weak demand forecasting, erratic ordering schedules, dependence on material and supplier relationships as well as the configuration and infrastructure of the supply chain. Added to this are externalities such as disease dynamics including outbreaks and epidemics, greater demand for data, environmental factors and tender procurement methods. Such uncertainties and externalities are confounded by a sustained under-investment in preparedness in countries and inability to address the financial burden of outbreak and epidemic response[1].

The ability and capacity to embrace innovation remains a goal for many emerging country vaccine manufacturers, but they often lack resources for significant changes to their operations[2]. While up-front investments (subsidies) are one response, this should be weighed against manufacturers' ability and capacity to adapt and adopt new technology[3] . Technology transfers constitute one option to support capacity building for manufacturers with scientific knowledge facilitating the transfer process[4].

There are two significant constraints to a broad-based adoption of innovation. Firstly, emerging country vaccine manufacturers are diverse both in location across all developing regions, and in set-up with both privately-owned and state-owned companies, so seeking commonalities is not straightforward. Secondly, innovation and price pressure are competing goals and requires the understanding of international stakeholders that a balance is necessary for sustaining a healthy vaccine industry[5].

These constraints should be seen in a context where some manufacturers started supplying vaccines within the last decade and do not have significant experience in supply chain. Uncertainty may disrupt their operations with the risk of shortages or even exit from a particular market.

DCVMN members' feedback indicates their interest in pursuing ways to improve the vaccine supply chain, increasing their visibility in the international immunization community by developing specific proposals and innovations pertinent to emerging countries.

Assessment to date on the supply chain has centred on traceability, stockpiling and new packaging technologies where case studies and information exchange among members can influence the adoption of innovation in formulation, filling and packaging which would have a positive effect on the vaccine supply chain in countries.

## 1. Traceability

Traceability is a key feature in the implementation of immunization information systems, helping to plan and manage immunization activities and resources and ensuring that adequate quantities of vaccines are always available to meet demand[6]. It can streamline vaccine and ordering inventory, supply chain management, and safety monitoring, all directly of concern to manufacturers.

Health systems are increasingly integrating digital health which can lead to positive impact on immunization information systems, with immediate access to data on vaccine inventory, shortages and stock-outs. Gavi is already engaged in blockchain technology to track funds and vaccines. Within digital health there is a strong focus on mobile health (mHealth) using smartphones, whose ever expanding sphere of influence could enable it to become the future of global health[7].

The World Health Assembly has broadly determined that the use of appropriate digital devices for public

health can increase access to quality services, reduce maternal, child and neonatal mortality, increase health security and increase patient, family and community engagement[8]. WHO has published a guideline with recommendations on digital interventions for health systems strengthening, including the use of stock notification and commodity management.

While over 120 countries have reported having national digital health strategies, implementation concerns around digital health may be linked to the complexity of sustaining digital health, including the need for leadership and governance, digital infrastructure, interoperability frameworks, partnerships and financing. Digital health technologies are also potentially disruptive, leading to new kinds of partnerships between organizations in the health, knowledge and telecommunications sectors[9] .

So far, mHealth interventions have been largely on a pilot scale, many spearheaded by non-governmental bodies. The total market size of mobile health was estimated to reach US$23 billion by 2017, of which 42% was in the Asian Pacific, Latin American and African regions, with scaling up likely when governments embrace constructive policy for mobile health[10].

Barcoding significantly facilitates traceability and allows unit level data connection from manufacturer to end user, and is recommended by WHO on all vaccine packaging except for primary packaging following GS1 standards[11]. On vaccine tenders backed by Gavi financing and issued by UNICEF, it is required to have GS1 standard barcoding on secondary packaging by latest 31 December 2021[12].

There have been divergent views on barcodes on primary packaging (on the vaccine vial or ampoule); on the one hand, posing a technical challenge that could take several years to overcome, while a majority of manufacturers indicated implementation could occur within 4 years. Some emerging manufacturers are already pursuing barcoding on primary packaging to increase product security, given concerns about vaccines being diverted to parallel markets. This would also address secondary packaging being often discarded well before vaccination sessions, causing traceability to be lost before individuals are vaccinated. 2D matrix barcoding allows for fast and simple readability by downstream supply chain implementers and is already on primary packaging for vaccines used in developed/industrialized countries[13].

The demands on manufacturers to support traceability down to the individual being vaccinated will become pressing as countries scale digital health, and it is an opportune time for manufacturers to:

- understand the specific demand of country immunization systems, including digital health systems, in terms of the traceability of vaccines down to individuals being vaccinated;
- model the options for including barcodes using GS1 standards at the primary packaging level;
- estimate the potential fixed and operating costs involved;
- articulate financing options, which could include third-party grants to subsidize investment costs, advance market commitments to guarantee vaccine purchase volumes, the raising of vaccine costs, or potentially new financing innovations;
- showcase pilots in improving traceability.

2. Stockpiling

Stockpile investments are an integral part of comprehensive disease control strategies, providing countries with the capacity for rapid response to shortages or emergency situations, such as outbreaks of yellow fever and meningococcal meningitis[14] . Stockpiles address insufficient quantities of vaccines being available on spot markets, the need for very fast deployment and difficulties in foreseeing outbreaks ahead of time.

The shift in the global health landscape, with increased pressure from climate change, population increases and mass urbanization, heightens the risk of large-scale outbreaks and urban epidemics, continuously re-defining the role and size of vaccine stockpiles[15]. The WHO Blueprint R&D includes 8 categories of priority diseases, of which 6 were in the midst of outbreaks at the same time in 2018[16]. There are calls to consider stockpiles for all vaccines with elimination goals and help prevent and control endemic or epidemic diseases given inefficiencies in vaccine supply chains[17]. The focus of CEPI on outbreak response already

signals the need for investigational stockpiles of candidate vaccines against the diseases it has targeted[18].

Gavi, which already supports cholera, yellow fever and meningococcal vaccine stockpiles, is working to mitigate the risk of outbreaks including creating the right market conditions to bolster vaccine stockpiles. Gavi also provided an advance purchase commitment for an Ebola vaccine, ensuring its immediate availability and the eventual creation of a stockpile for future outbreaks. WHO has opined that the setting up of the cholera vaccine stockpile has transformed a vicious cycle of low demand, low production, high price and inequitable distribution to a virtuous cycle of increased demand, increased production, reduced price and greater equity of access.

UNICEF manages four stockpiles for outbreaks and humanitarian emergency situations – measles and MR, oral cholera, yellow fever and meningococcal vaccines - as well as an mOPV stockpile for both bulk and finished product. The measles and MR vaccine stockpiles are managed in coordination with the Measles Rubella Initiative (MRI) and polio stockpiles in coordination with the Global Polio Eradication Initiative (GPEI). The advantage of global stockpiles is common governance with an accountability framework based on good partnership to overcome a "first-come, first-served" approach[19].

Some stockpiles are static, not shipped until an outbreak or epidemic occurs. Rotating stockpiles are shipped for routine immunization programmes and specific volumes should be available within 72 or 96 hours as stipulated in UNICEF tenders. The oral cholera vaccine stockpile was specifically set up on a rotating stock basis. The rotating yellow fever stockpile has 6 million doses available for shipment from manufacturers. This differentiation between static and rotating stockpiles, based on programmatic use, is critical for epidemics of concern, including Ebola, Marburg, MERS, SARS, Zika, dengue, chikungunya, avian and pandemic influenzas, cholera, measles, meningitis and yellow fever. Whether stored as bulk and/or finished product depends on vaccine characteristics, time to fill and finish and the urgency for shipment. All stockpiles run the risk of product expiry, also if product does not meet countries' required remaining shelf-life conditions it is subject to loss and the additional costs of destruction.

While there is considerable investment in vaccines tied to elimination strategies and on outbreak response, short-term shortages and stock-outs of vaccines disrupting routine immunization activities are widespread. Between 2010 and 2015, countries in all regions of the world and of all income groups experienced regular stock-outs of key vaccines, causing interruptions of immunization services. This implies that many countries do not even hold sufficient buffer stock in the event of shortages or sudden increased demand. Effective stock management is one of the criteria for an effective vaccine supply chain[20]. Financing stockpiles is a critical factor as manufacturers consider stockpiles as product already purchased.

The likelihood of vaccine stockpiling becoming more prominent impels emerging country vaccine manufacturers to assess and determine their conditions and best practices for retaining and expanding stockpiles, specifically to:

- collect more information on global and regional stockpiling policies for both creating and financing stockpiles;
- determine main components for manufacturers in creating, financing and maintaining stockpiles;
- identify potential efficiencies and financing options in stockpile management.

3. New packaging technologies

Gavi, WHO, BMGF, PATH, UNICEF and CHAI have formed an alliance creating a vaccine innovation prioritization strategy (VIPS) to drive vaccine product innovation to better meet country needs and support immunization coverage and equity goals. The goal is to prioritize innovations in vaccine product attributes to provide greater clarity to manufacturers and partners to make investment decisions.

VIPS has prioritized 5 upstream and 4 downstream innovations, of 24 assessed, based on health impact, coverage and equity impact, safety impact, economic costs and potential breadth of innovation use, with cost issues of upmost importance from country perspectives[21] . Of these, MAPs, cPADs, dual-chamber

delivery devices, combined VVM and TI and barcodes are considered packaging innovations. Barcoding has been widely discussed in the context of traceability above.

MAPs may be a priority as a case has been made for the MR vaccine[22]. WHO has published a target product profile for MR-MAP. There are issues, however, that need resolution around patches containing vaccines especially related to clinical, regulatory, manufacturing and scale-up activities. Key considerations for MAP manufacturing for vaccines used in low-resource settings include the scalability of production processes and costs per unit when produced at large scale[23]. Manufacturers have expressed concerns around accountability in case of product failure – whether the patch mechanism or the vaccine is at fault, for example.

WHO considers the benefits of cPADs as delivering a correct dosage, vaccine wastage is better controlled, less handling of the vaccine takes place, reduced logistics workload and reduced time by health workers to deliver vaccination. These benefits have been verified in Indonesia and Timor Leste where hepatitis B is delivered in a cPAD (UnijectTM) out-of-the-cold-chain in hard to reach areas[24] . In spite of the fact that both tetanus toxoid and hepatitis B vaccines in a UnijectTM have been prequalified by WHO, global demand has been very low because of the higher vaccine price, compounded by insufficient attention to overall costs. WHO in late 2014 also pre-qualified the pentavalent vaccine in a cPAD[25], but the manufacturer stopped production of the pentavalent in 2017.

Dual-chamber delivery devices for lyophilized vaccines can simplify the reconstitution process. MR dual-chamber injection devices reduce open vial wastage at any volume and can lead to an increase in MR vaccine availability[26] . Of potential interest is the development by a research laboratory in India of a dual-chamber device for a heat-stable rotavirus vaccine that can stay out of the cold chain for 4 months at 45°C.

While not an immediate priority of VIPS, BFS multi-monodose polymer containers have been shown to be the least expensive option for oral vaccines in terms of total cost of delivery and second to glass vials for injectable vaccines in multi-dose forms. Given the advantage for oral vaccines, rotavirus and cholera manufacturers are already adopting BFS technology.

Improved packaging and presentation reduce stress on vaccine supply chains, through reduced volume packaging. There may be opportunities to reduce the packaging footprint in the cold chain. A smaller box for the safe delivery and storage of vaccines has been developed, halving the size of packaging, allowing twice as many doses to be shipped at once and occupying half the storage space, while removing all plastic to make it eco-friendly[27] .

From surveys and interviews with DCVMN members during 2019, it was clear that manufacturers had not actively participated in the prioritization processes of VIPS, but should be consulted more actively in discussions around packaging innovations. This is particularly important as manufacturers will bear the costs of required innovations and need to have the opportunity to voice the options they see on the practicalities, costs and financing of adopting innovations given the price pressure vaccines are under.

The development of new packaging and delivery technologies requires partnership between vaccine and technology manufacturers, with key considerations being programmatic suitability include cold chain volume, costs, IP rights and health impact[28]. More broadly, continued innovation in the vaccine industry can best be supported via a comprehensive and shared agenda across key stakeholders, with a view on demand clarity, value communication, economic incentives, collaboration and data sharing and early consultation on innovation design[29] . Countries also need to have better opportunities to express their preferences and articulate demand for different products which they see as relevant in improving access and coverage rates[30] .

Innovations in packaging which includes primary containers are largely aimed at increasing the ease of vaccination by health care workers while reducing vaccine wastage and in some reducing storage volumes. Manufacturers have to be more active in partnering with innovation developers to ensure that innovations

are feasible and cost-comparable with current technologies, specifically to:

- review the multiple innovations being developed by global stakeholders;
- become fully familiar with MAPs, cPADs, dual-chamber delivery devices, reduced packaging footprints and BFS;
- determine if additional innovations might be pursued by manufacturers;
- intervene in design, prototyping and piloting phases;
- identify any IP issues;
- estimate the projected fixed and operating costs of selected innovations;
- signal potential financing options for the introduction of innovations.

Conclusion

Manufacturers have a significant stake in the vaccine supply chain as their reputations rest on the effectiveness of their vaccines at the point of vaccination. Manufacturers from emerging countries are diverse in nature, being from distinct regions of the world and being either privately or state-owned. They agree, however, on finding ways to positively impact the vaccine supply chain through innovations they can bring to vaccine production stages specifically in traceability, stockpiling and the introduction of new packaging technologies.

The overall context in looking at the next decade includes a global move to digital health which can provide significant opportunities for improving the vaccine supply chain. Here, the labelling of primary packaging to include 2D barcodes will likely become a requirement in the near future and manufacturers adopting this first may likely gain considerable market share. It is considered that major opportunities lie ahead for digital health innovators, assuming payers continue to value the gain from digital technologies[31]. A second driver will be the increased demand for stockpiling vaccines, both as a measure to address shortages and stock-outs as well as for preparedness for outbreaks and epidemics. A third driver will be technological innovations that significantly improve the workload and time investment of health workers in vaccination and reduce vaccine wastage.

Key aspects for manufacturers to consider are the wider use of barcoding to enhance traceability, including the application to primary packaging, the increased use of stockpiling including buffer stocks, and new packaging technologies that include new primary containers. The implication is that emerging manufacturers need to be engaged more actively in global stakeholders' forums, not as information recipients but as equal partners in determining the best ways forward for improving the vaccine supply chain to reduce the current inequities in vaccination.

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