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Commentary

Using human papillomavirus (HPV) vaccine in controlled temperature chain (CTC): A solution looking for a problem? Or a solution to problems that are not systematically documented?

Dijana Spasenoska [a,b], Paul Bloem [a], Hiroki Akaba [a], Anna-Lea Kahn [a,c,d,*]

[a] Immunization, Vaccines and Biologicals Department, World Health Organization, Geneva, Switzerland
[b] Department of Social Policy, London School of Economics and Political Science, UK
[c] Swiss Centre for International Health, Swiss Tropical and Public Health Institute, Basel, Switzerland
[d] University of Basel, Basel, Switzerland

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1. Introduction

Human Papillomavirus (HPV) is a common sexually transmitted viral infection. Among the more than 200 known HPV genotypes, at least 12 types have been identified as oncogenic, leading to HPV-related cancer, with cervical cancer being the most prevalent. Cervical cancer is the fourth most frequent cancer in women globally, with an estimated 604,000 cases and 342,000 deaths in 2020. [1] HPV vaccine was proven highly effective in reducing the risk of infection and subsequent cancer development [2,3]. As of October 2023, HPV vaccination has been introduced in 138 countries, however, the vaccination coverage remains a challenge, with only one-fifth of girls worldwide receiving at least one dose of HPV vaccine. [4]

Several studies have reported on immunization programme barriers hindering the delivery of HPV vaccines [5]. Common barriers include: challenges in transporting vaccines; inadequate cold chain at the health facility levels; limited vaccine storage capacity at the district level; and the complexity of reaching girls who are not attending school. In addition, an inadequate workforce to support HPV immunization activities and limited funds for staff transportation and per diem allowances enabling vaccination sessions in schools and in the community were also reported barriers.

The cold chain entails the resources and procedures needed to ensure the proper, continuous storage and distribution of vaccines in temperature-controlled environment preserving the stability of vaccines from the time they are manufactured until the moment of vaccination. Lack of appropriate cold chain equipment and/or practices, weak transport infrastructures and restricted human and financial resources lead to difficulties in maintaining the required cold chain for the full journey of vaccines delivered through special strategies such as campaigns or school-based delivery. Accidental interruptions of the cold chain could occur at any point; from changes in temperatures in storage rooms and refrigerators, to the transfer of vaccines in a vaccine carrier from the district level to the health facility, to community outreach. Temperatures that are too high or too low can damage the vaccine causing loss of potency [6].

The Controlled Temperature Chain (CTC) is an approach to vaccine management which leverages the heat stability of a given product for the purposes of facilitated delivery without the constraints of the cold chain, for a specific number of days (usually 3 or more) and up to a threshold temperature (40°C) for a single excursion out of the cold chain, just prior to vaccine administration. This enables immunization programmes to overcome many of the challenges associated with the 'last-mile' of vaccine delivery in a standard 2–8 °C cold chain [7]. CTC as

* Corresponding author: 20 Avenue Appia, Geneva 1217, Switzerland.
E-mail addresses: spasenoska@who.int (D. Spasenoska), bloemp@who.int (P. Bloem), akabah@who.int (H. Akaba), kahna@who.int (A.-L. Kahn).

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a concept is innovative in two distinct aspects. First, it represents an innovation in how thermostability is recognized by regulatory authorities resulting in a more specific labelling on storage requirements. Second, it allows greater flexibility in delivery strategies allowing immunization vaccines to use and store thermostable vaccines out of the cold chain up to a certain temperature threshold. The CTC approach can only be adopted with vaccines that have been proven to have sufficient stability to allow for their removal from refrigeration, a validation that is attributed through regulatory approval processes and WHO prequalification.

There are HPV vaccines that are prequalified for CTC conditions allowing use out of the cold chain in ambient temperatures for up to four days. While it is evident that being able to deliver a vaccine out of the standard cold chain could potentially overcome barriers associated with cold chain inefficiencies and outreach logistics, there is a lack of documented evidence of programmes leveraging these advantages for HPV vaccination. The slow adoption of a CTC strategy for HPV vaccination has resulted in limited opportunities for research on the impact of CTC on HPV vaccine delivery [8]. In this paper, we ask a series of key questions that explore why it is difficult to build a case in favour of delivering HPV vaccines in CTC.

1.1. How do we measure the benefits of delivering the vaccines in CTC?

The first pilot CTC-HPV study was conducted in Uganda in 2017 [9]. A school-based delivery strategy was used in four districts, two of which maintained the standard cold chain, while the other two applied CTC. The study findings highlighted that measuring the benefits of delivering HPV vaccines in CTC can be complex.

Relying exclusively on quantitative population figures, such as coverage, does not easily capture the full range of benefits. Although the coverage in the two districts that used CTC was slightly higher compared to control districts, the data available did not allow for statistical analysis that could attribute this change with certainty to the CTC intervention [9]. Yet, the results from a survey conducted among health workers in these districts showed that 90 % ($n = 28$) of respondents credited CTC to enabling them to reach more girls, more easily.

The survey found that the full impact of the innovative delivery strategy was often not apparent due to an unreliable baseline of comparison in view of erroneous cold chain practices. Incorrect practices for conditioning and use of ice packs were observed in the non-CTC districts, undermining programme confidence in vaccine integrity, due to the risk of degraded potency, and inaccurate closed vial vaccine wastage calculations. While majority of health workers were able to recognize that CTC helped them save time because they did not need to prepare nor renew conditioned ice packs, allowing them to stay longer in the field and not be dependent on refrigeration and freeze capacity, the advantages gained from reducing the exposure of the vaccine to the high-risk sub-optimal practices, such as freezing conditions, was not measured or captured.

1.2. Are current cold chain resources and practices adequate and sufficient?

Inadequate and insufficient cold chain refers both to the physical infrastructure (e.g. number and type of functional refrigerators) and the practices (e.g. knowledge of health workers to maintain and monitor the cold chain).

The cold chain requirements for the pulsed delivery of the HPV vaccine, where vaccines are administered to a large population over a short period in repeated waves, result in a surge in storage requirements and could temporarily increase the burden on the cold chain. It is plausible that in countries where this delivery strategy is used, the burden on the physical cold chain is minimal and with careful planning can be accommodated for. Yet, national post introduction evaluation reports, shared with the World Health Organization, suggest that countries have reported cold chain capacity limitations such as refrigerators being out-of-service, lack of refrigerators in remote health facilities, insufficient cold storage space, and unreliable power grids that can prevent effective vaccine storage and ice-pack preparations for outreach strategies.

However, inadequate cold chain also refers to the limited knowledge and practices of persons handling the vaccines and maintaining the cold chain (e.g. inadequate number of ice packs or insufficiently conditioned ice packs), as these might result in undetected freeze or heat exposure, especially during service delivery. The risk could be elevated, particularly in countries that face high staff turnovers and staff shortages resulting in limited training of new human resources. Staff practices, as well as training and supervision needs, are not well documented or reported and it is difficult to estimate accidental interruptions. The lack of documentation of these barriers is challenging the ability to determine the magnitude of barriers that could be addressed through CTC.

1.3. Are freeze exposures of the vaccines monitored sufficiently?

Monitoring of freeze exposure of freeze-sensitive HPV vaccine helps preserve confidence in vaccine potency and ensure corrective action is taken when potency is compromised. Freezing of vaccines is a result of not only the exposure to freezing temperatures, but also other conditions such as time spent in those conditions and movement. The highest risk of freeze damage occurs during transport when vials can come into contact with incorrectly conditioned ice packs (e.g. frozen ice-packs) [10]. The currently recommended method to confirm suspected freeze exposure is through a shake test which requires time and access to a freezer, making it especially incompatible with an outreach context. Through the use of freeze tags, devices used to monitor the exposure of vaccines to freezing temperatures, freeze conditions could be detected. Yet, their use in vaccine carriers in the last mile is inconsistent across countries and within countries. Thus, the magnitude of the burden of freeze exposure during transport is unknown as it is not systematically monitored. CTC has the potential to eliminate the risk of freeze exposure during the last-mile as the vaccines can be delivered in ambient ($> 0^{\circ}C$) temperatures.

1.4. Is sufficient importance placed on workforce workload?

The school-based delivery strategy used for HPV vaccination is the most commonly used and most efficient delivery strategy for the vaccine, but it is associated with more intensive resources and preparation. It may result in additional costs related to outreach logistics such as costs attributable to vaccine transport and per-diem for health workers delivering the vaccine. [11] Reflecting these costs accurately is not always straightforward. For instance, health workers have reported that they can be ill equipped to manage the required logistics (e.g. lack of spare parts to repair motorcycle or lack of protection from the rain) or spare the time away from their other duties, but the burden of resolving these challenges falls on them, often without corresponding incentives or compensation. Hence, in resource constrained settings, the time and logistical implications of properly meeting service delivery expectations represent a further load on already overburdened health workers and a source of accumulated demotivation.

2. Conclusion

This series of questions reveal the lack of documented evidence and measures available to determine and appreciate the full benefit of CTC in HPV vaccination programmes. There are apparent evidence gaps regarding barriers associated with immunization programme performance. If the magnitude of barriers is not appreciated through the current measures used, then it is not possible to quantify the benefit of using innovative immunization technologies and practices. Thus, the value and appropriateness of the design of the CTC approach and its subsequent uptake are limited to the assumptions made about the

strengths and weaknesses of the immunization programme performance.

While CTC is not the 'silver bullet' or the only solution to increase HPV vaccination coverage, it could lead to increased efficiencies during the 'last mile' of service delivery, especially in fragile settings. Moreover, we should also consider the risk of inadequate cold chain practices for vaccine potency. This impact is rarely documented. In order to better assess these opportunities and risks, we recommend expanding the immunization research agenda to include implementation research examining and quantifying barriers to effective HPV vaccination, as well as to identify and develop indicators that would accurately reflect the suitability of current practices. This will also contribute to better understanding the challenges underpinning low HPV coverage and the appropriate actions needed to increase it. By confirming the need and potential benefit of interventions like CTC through compelling evidence, we can ensure that the right practices are adopted and implemented for optimized impact.

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Dijana Spasenoska: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Paul Bloem:** Writing – original draft, Writing – review & editing. **Hiroki Akaba:** Writing – original draft, Writing – review & editing. **Anna-Lea Kahn:** Conceptualization, Data curation, Funding acquisition, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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No data was used for the research described in the article.

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