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Heterologous vaccine regimen: Stakeholder acceptance and implementation considerations

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ABSTRACT

Heterologous vaccine regimens deliver antigens through different vaccine components or vector types at sequential time points. Clinical development shows promising results and several candidates may be progressing to licensure in the coming years. This study aimed at exploring future acceptance and uptake of such regimens (also called heterologous prime-boost) and to identify implementation-associated benefits and challenges. Survey tools were developed based on findings from a previous literature search shared with the study team, and exploratory interviews with global stakeholders. An online survey and key informant interviews in six countries were conducted with stakeholders at national and sub-national level, including policy-makers, regulators and implementers. The interview guide and the online survey covered: (a) awareness of, and knowledge about, heterologous vaccine regimens; (b) rating of regimen-associated perceived benefits and challenges; (c) anticipation of possible challenges in relation to four hypothetical introduction scenarios; (d) potential acceptance benefits and challenges at the policy, health facility and recipient level. Sixty-two interviews were conducted at national level. The online survey was completed by 50 participants. Across the four introduction scenarios, respondents considered the highest potential for the introduction of heterologous regimens for immunoprophylaxis was among adolescents/adults for diseases against which no vaccines are currently available. Most reservations were related to logistics, record keeping, and recipient compliance. Adding a new heterologous vaccine regimen to the routine immunization calendar for children was considered feasible if it could generate an increased and longer-term immune response. Introduction in preparation of or following a disease outbreak was considered less favourably, with respondents stressing the difficulty of logistics in emergency situations, and the potential lag in the onset of protection. The recent approval of the first heterologous vaccine regimen for the prevention of Ebola Virus Disease will soon bring new light to the topic.

1. Introduction

The underlying principle of vaccination is to expose the immune system to an antigen to stimulate the development of an immune response. The exposure to a vaccine allows the body to memorize the antigen, which enables the immune system to quickly eliminate the pathogen when being exposed anew, and hence to protect the recipient from disease [1]. Immunoprophylaxis through single-shot vaccines and repeated injections of the same vaccine (homologous regimens) induce immunity that protects millions of people and animals against a range of infectious diseases associated with high morbidity and mortality, sometimes life-long [2]. However, certain infectious agents and conditions of public health concern may require a quantitatively and qualitatively enhanced immune response, which is difficult to achieve with traditional vaccination approaches [3–5].

Heterologous vaccine regimens are a promising approach to induce such a combined humoral and cellular response, by delivering similar antigens through different vaccine components or vector types. The expected key benefits are a stronger, broader and/or longer-lasting immunity [4–6]. The first vaccination initiates the targeted immune response, which is then reinforced with the later administration of another type of vaccine or vector. Vaccine types include: naked DNA vectors, different recombinant viral vectors,

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virus-like particles, nanoparticles and soluble proteins. Protective efficacy with this approach has been shown in several animal challenge studies and clinical trials [7–9].

Since 2004, over 100 pre-clinical and clinical trials with heterologous vaccine regimens have been conducted [10]. Targeted pathogens include: *Mycobacterium tuberculosis*, human immunodeficiency virus (HIV), simian immunodeficiency virus (SIV), *Plasmodium* species, *Listeria monocytogenes*, *Leishmania* species, hepatitis B and C virus, Herpes simplex virus, human papilloma virus and Ebola virus [10,11]. While heterologous regimens are one of the avenues that could improve immune responses, they might still need to be accompanied by additional factors to make the vaccine efficacious, such as immunogenic antigens and adjuvants [12].

Pharmaceutical companies are pursuing licensure and commercialization of the first heterologous vaccine regimens for Ebola virus and HIV [11,13]. Additionally, the approach may be beneficial for anti-cancer vaccines [14–16]. Such innovative vaccines are also expected to bring significant benefits to global public health if they can be successfully deployed in low and middle-income countries (LMIC), where the overwhelming burden of infectious diseases is concentrated [17]. However, the success of the future implementation of such vaccines will depend on planning and coordination among immunization stakeholders well ahead of any roll-out to address the potential barriers [14].

The present study was designed to provide an initial understanding of the future acceptance of heterologous vaccine regimens (non-product specific) amongst respondents at a national and sub-national level in six countries. We also aimed to identify the main perceived benefits and reservations regarding future implementation of heterologous vaccine regimens to add to the body of evidence needed for decision-making in view of licensure.

2. Material and methods

2.1. Study design

A mixed methods approach was pursued including an online survey and key informant interviews in six countries. The interview guide for the country consultations and the online survey questionnaire were developed based on the findings from a literature search shared with the study team, and initial exploratory interviews with global stakeholders [6,10,11,18].

The interview guide focused on obtaining from the interviewees a detailed understanding of their opinions and perceptions regarding heterologous vaccine regimens. At the time of our research, the term used to describe the regimens was "heterologous prime-boost vaccination". This terminology has now been changed to "heterologous vaccine regimen" as we identified a risk of confusion with the administration of distant booster doses that can be necessary after a primary course of homologous or heterologous vaccination.

Particular attention was placed on awareness of, and knowledge about, the regimen, and perceptions on quality, safety and efficacy issues. Respondents were asked about their views on the benefits and challenges related to regulatory, implementation and logistical issues, acceptance and uptake at policy level, as well as benefits and challenges related to health care workers and the general public. To this end, the guide proposed four scenarios: introduction of heterologous vaccine regimens as: (1) an alternative to an existing childhood routine vaccine; (2) a new vaccine offered to adolescents and/or adults to protect against a disease for which no vaccine is currently available; (3) a replacement of an existing lower efficacy vaccine in advance of, or (4) in reaction to, an outbreak. So as to focus on the heterologous vaccine regimen acceptance, scenarios were selected to be generic, without adding variables that also may impact acceptance (such as health system setting or product characteristics).

The online survey was developed in English and was split into three sections, comprising 22 questions in total. The first section covered participant characteristics such as age, professional background, and self-declared level of knowledge about "heterologous prime-boost regimens"; the second section included the aforementioned scenarios, adapted to allow quantitative analysis. In scenarios 1 and 2, participants were asked to rate key benefits and challenges. In scenario 3 and 4, participants were asked to assess the minimal level of improvement in efficacy, longevity of protection, safety and total system cost savings that they would expect to consider introducing a heterologous vaccine regimen (versus an existing vaccine). The last section included questions addressing acceptance and uptake at different levels.

All survey tools were pre-tested before finalization and deployment. The exploratory interviews with global key informants were conducted (in person or by telephone) between January and March 2017. Country consultations took place between June and December 2017. The online survey was available through Limesurvey (https://www.limesurvey.org) from August to December 2017. Approximately 650 individuals with a stake in vaccination or global public health were directly invited to complete the survey via a personalized e-mail. Additionally, a link to the survey was published on TechNet, E-drug and Healthcare Information For All (HIFA), and was included in the One Health Platform Media Bulletin issued in October 2017.

2.2. Study area

Key informant interviews were carried out with stakeholders in the following selected countries: Chile, Germany, South Africa, Tanzania, United Kingdom (UK) and the United States of America (USA). These countries were selected based on current vaccine introduction guidelines [19] as well as the following selection criteria: (i) representing one of the four continents of North and South America, Europe, and Africa; (ii) having a functioning in-country National Immunization Technical Advisory Group (NITAG); (iii) achieving a 80% or higher Diphtheria tetanus toxoid and pertussis vaccination coverage rate (DTP3 [or tetravalent 3 or pentavalent 3]); (iv) having introduced an inactivated polio vaccine (IPV) program; (v) showing good scores in a recent Effective Vaccine Management (EVM) assessment; and (vi) having successfully introduced pneumococcal and rotavirus vaccines.

2.3. Study population

The main stakeholder groups for the assessment were: National Medicines Regulatory Authorities (NMRAs), Ministries of Health (e.g. vaccination programme managers, warehousing and supply chain managers), and implementers such as organizations involved in vaccine logistics and front-line health workers (immunization staff). In addition, representatives from non-governmental organizations (NGOs) involved in vaccination programmes, experts in immunology, vaccine and public health from not-for-profit research institutes, and representatives from donor organizations were included.

2.4. Data analysis

All interview transcripts underwent content analysis which involved looking across the data to identify and code broad initial themes [20]. An inductive approach based on Grounded Theory was used; this takes the actual data collected as its point of departure [21,22]. In subsequent rounds of analysis, each transcript was

worked through systematically and responses were "cross-coded" to the locations where they fitted thematically. Inter-linkages were then explored, and apparently contradicting statements juxtaposed with more widely held views.

Quantitative data were summarized using descriptive statistics with Stata version 14 (StataCorp, College Station, TX, USA).

2.5. Ethical considerations

The study protocol was submitted to the Ethics Committee for Northwest and Central Switzerland (EKNZ). On 17 October 2016, the EKNZ formally waived the study from requiring ethical approval.

3. Results

3.1. Key informant interviews

Overall, 203 individuals in the six selected countries were contacted, of which 62 accepted to be interviewed. Of these, 22 were based in Tanzania, 10 in Chile, 9 in the UK, 8 in South Africa, 8 in the USA, and 5 in Germany.

3.2. Personal knowledge about "heterologous prime-boost vaccination regimen"

All respondents were interested to learn more about the "heterologous prime-boost vaccination regimen", but few were actively following the developments. Respondents identified scientific journals, conferences, newsletters and WHO information materials as main sources for quality information. One respondent stated "*This is a key resource in the fight against malaria, HIV, TB, hepatitis, influenza and various types of cancer. Basically, it's the solution for diseases where a potent immune response is needed. This level of potency simply can't be achieved by a single shot vaccination – it lets you make vaccines work where they don't otherwise*" (academic, UK). Respondents outside the scientific community and regulatory authorities were mostly little informed about the regimens, targeted diseases or the timelines by when such vaccines might become available for implementation.

3.3. Scenarios

Integration into the expanded program of immunization (EPI) schedule was seen as advantageous for achieving high vaccination coverage rates, with the caveat that any newly introduced vaccine can have an impact on already established vaccines. Respondents seemed more prone to consider heterologous vaccine regimens for adolescents and/or adults for diseases with no vaccine available. In scenarios proposing the regimen in preparation of, or as reaction to, an outbreak for a disease with an existing vaccine to be replaced, most respondents expressed reservations on suitability, and acceptance was considered to be dependent on improved effectiveness and duration of protection. Respondents expressed most interest in heterologous vaccine regimens that would allow protection against an outbreak that can be readily anticipated (for example, cholera). Vaccination of at-risk individuals or groups of infectious and/or non-communicable diseases (such as cancer) was also seen as potentially highly interesting, as a prolonged immune response would be expected.

3.4. Anticipated challenges of the heterologous vaccine regimen

Respondents stressed the importance of providing scientific evidence around the benefits of the regimens in terms of safety, efficacy and durability, independent of the targeted pathogen. In addition to the need for rigorous evidence, clear communication was identified as crucial. Respondents also spoke to cost-effectiveness and pricing, as well as vaccination record keeping – highlighting the importance of quality documentation, as well as the need for supervision and follow-up to ensure correct administration of the boost. Adequate tracking of the administration of any heterologous vaccine in the existing vaccination record systems was favoured, and highlighted as important. However, it was suggested that the high level of mobility of certain populations may require other solutions, as the different components of the heterologous regimen may not be administered at the same health facility [23,24]. An overview of the findings stratified by countries is presented in Table 1.

3.5. Online survey

Overall, 50 people from 16 countries fully completed the online survey, and another 25 submitted partially filled questionnaires, which were excluded from the analysis. One quarter of the survey participants were based in Switzerland (24%), followed by Tanzania (14%) and the USA (10%). Table 2 summarises the respondents' characteristics.

3.6. Self-declared knowledge about "heterologous prime-boost vaccination regimens"

Among the respondents, 16% considered themselves to be 'well-informed' about the principles of heterologous vaccine regimens, 28% reported to be 'informed' and 30% 'little informed', with 24% of participants declaring they were 'not informed' (data not available from 2% of respondents).

3.7. Perceived benefits of the heterologous vaccine regimen

When prompted about the perceived benefits, 86% of respondents rated efficacy of the vaccine regimen as a benefit (Table 3). Duration of protection was also rated as a benefit by 80%. On the other hand, the most reservations were related to the practicability (72%), and the total system costs including vaccines, handling and related activity costs (72%). Adherence to the protocol by health workers (62%) and compliance of vaccine recipients (62%) were also identified as potential challenges (Table 3).

3.8. Scenarios

For scenario 1 (heterologous vaccine regimen replacing a routine childhood vaccine) the total system costs (38%), and logistics (30%) were considered important for acceptance. For the second scenario (heterologous vaccine regimen introduced as a new vaccine for adolescents and/or adults for a disease with no alternative vaccine), the three key challenges were: the total system costs (36%), acceptance by the target group (30%) and recipients' compliance (22%). When prompted with the third scenario (asking respondents to indicate the desired level of improvements needed to be achieved through the regimen to replace an existing vaccine before an outbreak of a disease for which a vaccine is already available), respondents desired substantial improvements in the longevity of protection (74%) and efficacy (64%; Fig. 1a). Substantial improvements in safety and reduced total system costs were rated as 'less important' for this scenario and mentioned at comparable frequency as 'any improvement' in these dimensions (Fig. 1a). In scenario 4 (asking respondents to rate characteristics needed for a heterologous vaccine regimen to replace an existing vaccine in reaction to an outbreak of a disease for which a vaccine is already available) respondents rated a substantial improvement in efficacy

Table 1
Summary of findings on the heterologous vaccine regimen from all 62 interviewed key informants across the six study countries.

		Responses to the heterologous vaccine regimen in the four scenarios					
Country (N = number of respondents)	Level of knowledge (self declared)*	1. Childhood vaccine	2. Adults/ adolescents	3. Outbreak as prevention	4. During outbreak	Critical issues to uptake and reservations	Main perceived challenges
Tanzania (N = 22)	Not well informed	High expectations, especially for malaria	Strong interest but rather focused on disease benefit linked to HIV and TB so as to have a more productive workforce	• Benefits linked to how easily the "at risk" population could be identified • Duration of effect considered the key benefit	Concern about logistical and technical complexity (if compared to a single dose vaccine)	• Availability of cost-benefit analysis and effectiveness studies from similar contexts • Visibility of benefit in terms of burden of disease • Need for infographics to convey how it works • Training for health workers and logistics managers • Involvement of local leaders in communication to general public	• Cost • Strength or weakness of the health system
USA (N = 8)	Well informed	Benefits linked to target audience, children easily reachable	Responses linked to difficulties to reach these target groups	• Skeptical that people would make two visits • High expected drop-off rate	Dismissive of the feasibility	• Availability of evidence • Procurements and logistics for two products would need to be addressed • Communications should focus on benefits in terms of disease rather than the vaccination platform/approach	Balancing the complexity with the need to be transparent when it comes to communications
UK (N = 9)	Experts well informed Implementers not well informed	If the first and second vaccination would be just two doses this was seen to be an improvement of some childhood vaccines	Even a small improvement with this target group could bring a very big impact	• Would have important benefits if the fear of the outbreak were very real • Benefits linked also to how far an outbreak can be anticipated	Very hesitant about feasibility	• Need to actively prepare NITAGS • Communication campaigns would be needed developed with and for health workers and community members • · Will be critical to find convincing ways to convey the complexity (lessons learned from OPV in India)	· Implementation challenges • Need to prepare the health system
Chile (N = 10)	Not well informed	High expectations of the benefits for this target group	If the first and second vaccination would be just two doses it was thought adherence in this target group could be increased. HPV proving to be very difficult.	Clear benefits if prime is protective, especially for community immunity	Anticipated to be very difficult	• Availability of evidence • Cost • Health worker training and buy-in • Education of community	• Need for evidence • Involvement of local opinion leaders to inform general public • Should not risk to fuel the emerging anti-vaccine lobby
South Africa (N = 8)	Not well informed	High expectations of the benefits for this target group to prevent childhood diseases	Disease benefits and to reach adolescents, improve coverage and adherence	• Some benefits seen to achieve greater protection, but need for stronger communication • One dose was considered preferable	High skepticism	• Availability of evidence around heterologous vaccine regimen (benefits, safety, costs etc.) • Approval and acceptance at policy level • Cost-effectiveness • Immunization schedule • Management of vaccine	• Need for evidence • Communication and advocacy • Trainings
Germany (N = 5)	Moderately well informed	Not considered very likely that could be	Benefits and feasibility seen to be greatest for	• Concerns this would be a costly scenario	Concern about complexity		• Implementation challenges

(*continued on next page*)

Table 1 (*continued*)

Country (N = number of respondents)	Level of knowledge (self declared)*	Responses to the heterologous vaccine regimen in the four scenarios				Critical issues to uptake and reservations	Main perceived challenges
		1. Childhood vaccine	2. Adults/ adolescents	3. Outbreak as prevention	4. During outbreak		
		integrated in EPI Lack of clinical trials on children	this scenario	• Recognized that those who consider themselves at risk would be more likely to come back for the second vaccination		• Striking balance between need to inform communities and the risk to cause unnecessary confusion • Importance of having the figures available of the potential impact of having a vaccine for these big killer diseases	• Cost vis-a-vis current vaccines/other interventions • Important to demonstrate that confusing the first and second vaccination would not be dangerous for vaccinees

*Familiarity with scientific concept underpinning heterologous vaccine regimens.

(60%) as more important than the longevity of protection (48%; Fig. 1b).

3.9. Importance of disease control potential for acceptance at policy level

In order to assess the benefits and challenges of a heterologous vaccine regimen at policy maker level, respondents were questioned about the acceptance of a heterologous vaccine regimen for disease control. Most respondents (72%) identified a novel solution to control a disease currently lacking a vaccine as of very important' for acceptance. Another 16% rated it as 'important', while 2% found this 'less important'.

Heterologous regimens were also considered favourably in a situation where they could substantially contribute to the achievement of disease elimination targets in a timeframe of 10 years: 62% of the respondents considered this outlook as 'very important' for acceptance, and a further 22% found this 'important', with 6% rating it as 'less important'.

3.10. Importance of economics for acceptance at policy level

Total system costs were identified as one of the main perceived challenges for the introduction of a heterologous vaccine regimen. Some participants had expectations about reduced costs; however, costs were also seen in relation to the potential benefits of the heterologous vaccine regimen: 10% of respondents reported that even a 50% cost increase would be acceptable ('not important'), and for 12% of respondents costs were deemed 'less important'. On the other hand, some respondents found it 'very important'

Table 2
Characteristics of respondents (N = 50) to online survey on heterologous vaccine regimen.

Respondent's characteristics	Percentage (n)
Male	60 (30)
Age range (years)	
20–29	6 (3)
30–39	28 (14)
40–49	30 (15)
50–59	24 (12)
60+	12 (6)
Employment	
Academia/research	30 (15)
Non-governmental organisations	24 (12)
Ministry of Health at national/sub-national level	10 (5)
Vaccine logistics (supply chain, production, etc.)+	10 (5)
National medical regulatory authority	4 (2)
Physician/nurse or health care provider+	4 (2)
Vaccination programme senior staff (e.g. manager)	4 (2)
Others*	14 (7)
Currently based in:	
Switzerland	24 (12)
Tanzania	14 (7)
USA	10 (5)
South Africa	6 (3)
Belgium	4 (2)
Ethiopia	4 (2)
France	4 (2)
Guinea	8 (4)
Spain	4 (2)
United Kingdom	4 (2)
Others€	18 (9)
Membership or contributor to advisory vaccine groups	28 (14)

+Implementer
*Donor agency (1), UN organization (1), working in animal health (1), retired WHO staff (1), clinical research company (1), pharmaceutical public health consultant (1).
€One participant from each of the following countries: Cameroon, Germany, Liberia, Mali, Republic of Korea, Thailand; 3 participants did not answers the question (included in the analysis).

Table 3
Fraction of respondents (N = 50) rating different aspects associated with a heterologous vaccine regimen as beneficial, challenging or unknown.

Aspect	Beneficial	Challenging	Don't know	No answer
Efficacy/immune response	86%	4%	6%	4%
Duration of protection	80%	4%	14%	6%
Practicability: logistics and administration	16%	72%	6%	6%
Total system costs*	8%	72%	14%	6%
Adherence to protocol/guidelines by health workers	24%	62%	4%	10%
Adherence by vaccination recipients	18%	62%	14%	6%
Safety	24%	24%	36%	16%

* The total system cost perspective includes the costs of vaccines, vaccination handling and related activities.

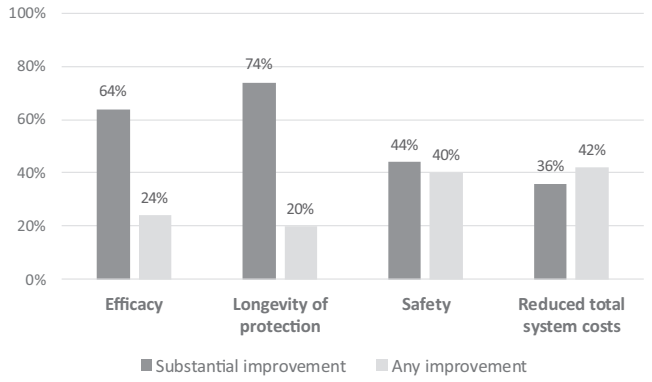

Fig. 1a. a: Respondents' (N = 50) expectations of the "amount" of improvement a heterologous vaccine regimen would need to provide before an outbreak (Scenario 3).

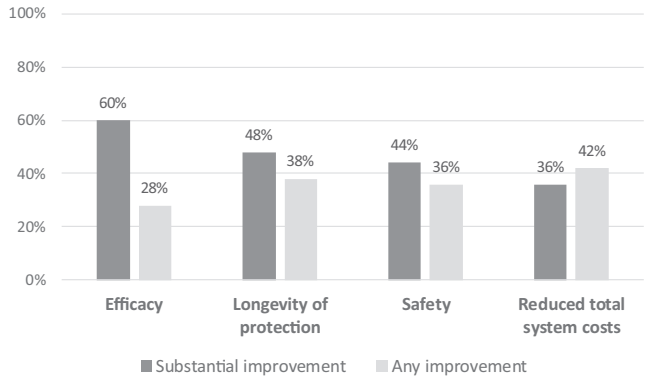

Fig. 1b. b: Respondents' (N = 50) expectations of the "amount" of improvement a heterologous vaccine regimen would need to provide in reaction to an outbreak (Scenario 4).

(22%) or 'important' (40%) for the cost to remain comparable even in the context of additional benefits in terms of safety, and efficacy or durability (Table 4).

3.11. Acceptance and uptake at health facility level

Most survey respondents considered ease-of-use/uncomplicated management of a heterologous vaccine regimen (68%) and the possibility to use existing supply chain systems (70%) as 'most important' for acceptance at health facility level. On the question of vaccination records, respondent views differed: while some identified a comprehensive or additional registry as 'very important' (28%) or 'important' (35%), others (37%) commented that they did not see any need for a separate registry and that an adaptation of the existing registries would be sufficient. Lastly, respondents rated health worker capacity building, logistics including record-keeping and clear safety information for health workers as equally important.

3.12. Acceptance and uptake at recipient level

Increased efficacy and duration of protection were rated as equally important for acceptance at recipient level (65%). Time efforts to receive the complete vaccination and costs were rated as 'less important'. Of note, 80% of the respondents highlighted the importance of clear information material about the new vaccines and all related practical aspects.

4. Discussion

The study showed that respondents anticipated rather high benefits of the heterologous vaccine regimen, most importantly a longer lasting and stronger immunity compared to existing vaccines. However, a number of respondents wrongly assumed that a heterologous vaccine regimen would mean fewer shots when compared to existing vaccines. Although the ideal vaccine for any

Table 4
Fraction of respondents (N = 50) rating different aspects related to the acceptance of the heterologous vaccine regimen concept in view of disease control and economic factors.

Disease control If a heterologous vaccine regimen would…	Very important	Important	Less important	Not important	No answer
…make elimination targets possible within the next 10 years?	62%	22%	6%	0	10%
…present the unique solution for a disease that so far lacks any vaccine?	72%	16%	2%	0	10%
…lead to increased herd immunity effect, thus higher population impact	50%	32%	4%	0	14%
Economics					
If a heterologous vaccine regimen would…					
…cost slightly less compared to the existing vaccination regimen?	14%	40%	22%	8%	16%
…cost 50% less than for an existing vaccination regimen?	60%	22%	2%	2%	14%
…cost the same as an existing vaccination regimen, but there were additional clinical benefits in safety, efficacy or durability?	22%	40%	14%	4%	20%
…cost 50% more than an existing vaccine but there were additional clinical benefits in safety, efficacy or duration?	34%	10%	12%	10%	38%

disease would be a single oral dose, it needs to be carefully conveyed that for the heterologous vaccine regimen at least two vaccinations are required to achieve the desired immunity [10,11]. The study also revealed an acute awareness of the importance of health system preparedness to mitigate implementation challenges and avoid delays between vaccine licensure and actual delivery to target populations [14]. Respondents directly involved in vaccination program planning and implementation voiced reservations about the complexity of introducing a heterologous vaccine regimen; it appears important to further understand these reservations in detail to develop a tailored response.

With regards to logistics, a key topic was to avoid confusion between doses and wastage, e.g. through separate packaging. Training of health staff and the establishment of a simple record keeping system were also highlighted. Providing an introduction concept including materials, trainings etc. to regulatory authorities will be required to facilitate licensure [19].

It is also noteworthy that participants had a range of views on aspects such as total system costs. If the regimen were to bring substantial benefits (addressing non-preventable pathogens, improved durability, superior efficacy), cost-effectiveness rather than cost alone would be a decisive factor. Respondents considered slightly higher and even significantly higher costs were acceptable should such public health benefits be achieved. However, it remains unclear whether such considerations were specifically related to heterologous vaccine regimens or to new vaccines more generally.

While some respondents were confident that a heterologous vaccine regimen would not require any different communication than a well-established vaccine, others urged cautious communication, and stressed the need for clear, transparent, consistent and timely messaging as well as alignment with communication efforts related to other vaccines to prevent confusion and vaccine hesitancy. Studies have revealed that the established vaccines, despite extensive testing over decades, were subject to shifts regarding the perception of their safety, while public attention and expectations towards vaccine safety have substantially increased [25,26]. This further highlights the importance of carefully developed communication ahead of implementation [27]. Other studies have shown communication to be one of the many factors influencing vaccination willingness, alongside accessibility, health worker engagement and personal or parental knowledge [28–30]. It is therefore recommended that not only the general public but also grassroots level health workers, patient groups etc. need to be adequately informed in context, as they are vital component in efforts to achieve high vaccination coverage in low- and middle income countries [31,32].

Our assessment has several limitations. The fact that countries and respondents were purposively selected limits the generalizability of the findings. The response rate may have been affected by the novelty of the topic being addressed and the targeting of relatively senior experts for key informant interviews in each constituency, who may be less prone or available to respond. Secondly, the implementation scenarios may have been difficult to visualize or conceptualize for study participants or were far removed from their reference context. Although the heterologous vaccine regimen was widely expected to be associated with improved vaccination outcomes, profound evidence and knowledge on the consequences of incomplete vaccination, dose reversal (second vaccination before first) or delays between vaccinations, will contribute to perceived safety concerns. In light of these findings, communication needs to be pragmatic to ensure that the evidence is well presented before, during and after the introduction of a heterologous vaccine regimen. Finally, some respondent insights appear rather general in nature. Their expectations could equally well have been applicable to other types of vaccine innovations and therefore may not be unique to the heterologous vaccine regimen.

Approval of the first heterologous vaccine regimen for the prevention of Ebola Virus Disease in Europe on the 1st of July 2020 (https://www.ema.europa.eu/en/medicines/human/EPAR/zabdeno) will allow to further assess the acceptance and implementation of these innovative regimens.

5. Conclusions

Respondents were interested in a heterologous vaccine regimen which offers the prospect of controlling major diseases – as a potential solution for diseases for which currently no vaccines exist. This notwithstanding, participants expressed reservations towards feasibility, costs, logistics at health facility level and the compliance of recipients, and rated these aspects as critical – especially on the part of country-level implementers. To address these challenges, diverse aspects will need to be considered: from packaging, to training of health staff, and the establishment of a suitable way of record-keeping.

A well-orchestrated communication effort will be required to adequately and proactively prepare policy-makers, regulatory agencies, implementers and the public for the advent of this new approach and inform them about the safety, immunogenicity, efficacy and cost-effectiveness of heterologous vaccine regimens. Early engagement and an open discourse with stakeholders at all levels will be indispensable for acceptance and implementation.

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7. Authorship

All authors attest they meet the ICMJE criteria for authorship.

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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