Report to the Norwegian Ministry of Health

Vaccine-based mitigation of the 2014 Ebola Viral Disease (EVD) epidemic: Gap analysis and proposal for Norwegian initiatives

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Title:

Vaccine-based mitigation of the 2014 Ebola Viral Disease (EVD) epidemic: Gap analysis and proposals for Norwegian initiatives

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- "Production process for viral vector vaccines and technology transfer", page 19 and table 8 had the assumption that NIPH could fill multiple doses pr vial, which is not the case. The estimate for doses/month is adjusted from 250 000 – 1 500 000 doses/month to 25 000 – 150 000 doses/month.

Preface

The Norwegian Ministry of Health commissioned the Norwegian Institute of Public Health on 14th October 2014 to conduct an assessment of the possible contributions of Norway to the international efforts to contain and limit the ongoing 2014 Ebola viral disease (EVD) outbreak in West Africa through vaccines and vaccination.

This document presents a summary of the available information on vaccine development status as per November 1st 2014, including a gap analysis and proposals for initiatives that could be taken by the Norwegian government to ensure added value to existing international efforts and guidance to forthcoming activities.

Resource mobilisation and close communication with key international and West African partners are central in the potential implementation of the initiatives.

We stress that in order to achieve significant, timely and relevant contributions, there is a need to continously monitor the epidemic's developments, and be up-to-date with the latest scientific findings and ongoing international efforts; as this now occurs at an unprecedented speed, and therefore adapt any Norwegian response and support to where it can add the most value and be complementary to other efforts..

We have contributed to an early in-depth discussion note provided to the WHO on a key EVD vaccine development planning meeting on October 23rd in Geneva, Switzerland. Material from that note is also integrated here.

We have also engaged with the Norwegian scientific, regulatory and pharmaceutical industry stakeholders in vaccine development, and have received their direct and valuable feedback on proposed initiatives.

Our preliminary analysis strongly indicates that Norway has assets, competence and financial resources that can contribute to vaccine-based control of the epidemic, and we recommend that the Ministry of Health in collaboration with the Ministry of Foreign Affairs and potentially other relevant ministries will utilize this opportunity as a part of the overall Norwegian response to the epidemic. Depending on the epidemic scenario for early 2015, the benefits of if attempting to contribute to vaccine-based interventions seems to us to far outweigh the potential negative consequences of not intervening.

Oslo, November 2014

Gunnstein Norheim
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Executive summary

CHALLENGE

The ongoing Ebola Virus Disease (EVD) epidemic is the most serious public health emergency in modern times. EVD is an infectious disease that causes severe haemorrhagic fever, with an average case-fatality rate of 50-90%. From March to October 2014, 13 567 cases of EVD were recorded, with 4 941 reported deaths.

There are no commercially available cures or vaccines against EVD, and containment strategies may fall short from controlling the epidemic. There are no effective vaccines, nor readily available drugs that can treat the disease. EVD response efforts have focused on traditional infection prevention and control measures. These efforts have not contained the epidemic, and worst case scenarios indicate the need to explore the potential use of vaccines.

OPPORTUNITY

An effective vaccine has great potential to contain the EVD epidemic, if made available through vaccination campaigns in short time. Several candidates have demonstrated protection in nonhuman primates, two of which (ChAd3-EBO-Z and rVSV EBOV-GP) are being fast-tracked for clinical evaluation of safety and immunogenicity. Three additional candidates may enter clinical trials in 2015.

Targeted mobilization of Norwegian government resources is urgently required to support clinical testing, production and distribution of the prioritized EVD vaccines. Since March 2014, donors have disbursed over US$500m globally, and have pledged at least US$1.8bn, in response to the EVD outbreak. However, there are significant technology and funding gaps.

GAPS & BOTTLENECKS

Even with adequate safety and immunogenicity in clinical trials, sufficient quantities of the prioritized vaccines will be challenging to produce. 30,000 doses are needed for clinical trials as soon as possible. Over 10m doses will be needed for vaccination campaigns in Liberia, Guinea and Sierra Leone, and 37m doses if a ring vaccination strategy is to be deployed. Cumulative bulk production capacity by the two prioritized vaccine manufacturers can reach 26m by December 2015.

Large scale GMP vaccine production is instrumental for early epidemic control. It might be too early to assess whether global production capacity for vaccines will be sufficient, as dose estimates, manufacturing capabilities and logistical capacities are constantly changing. However, in a setting with limited number of vaccine doses, there will be trade-offs when it comes to fairness in distribution across and within countries.

There are additional, severe cold chain challenges and stability aspects of vaccines that require further exploration. All prioritized vaccine candidates have extreme cold chain constraints (-80 C) and transportation requirements. Beyond storage conditions, there are on-the-ground challenges with power supply, transport infrastructure, climatic conditions and availability of equipment. Some stability studies are being conducted by manufacturers but additional work is required to optimize cold chain solutions and formulations which can sustain warmer temperatures.

If the production cost of EVD vaccines is too high, their benefit potential might not be realized as prices may exceed affordability thresholds by endemic countries in the long term. Due the emergency of the situation, governments have signalled willingness-to-pay for EVD vaccines, given that industry has also committed to collaborative models.

A medium-term strategy for back-up candidates and platform technologies is lacking. In case of poor outcomes of the two prioritized vaccines candidates (ChAd3-EBO-Z and rVSV EBOV-GP), there will potentially be a gap in vaccine development efforts. The EVD epidemic has highlighted the need for technologies that can quickly be used to develop appropriate vaccines for new outbreaks. Intensifying development efforts across a broader range of vaccine candidates and platform technologies is crucial as a backup plan.

A long-term market shaping strategy is missing for the sustainable development of vaccines and medicines for infections such as EVD where there is insufficient commercial market space. An effective coordination mechanism is pivotal to ensure innovations are in line with health needs and emerging health threats.

NORWEGIAN STRENGTHS & COMPETENCIES

Norway has financial resources, research assets, manufacturing competence, policy and coordination experience. It can contribute to a vaccine-driven control of the EVD epidemic, and add value to the sustainable development of related biopharmaceuticals, where there is a growing global market space.

- ✓ **Financing** - Norway has built a track record of investments in global health research over the last 15 years. This is compounded by a long tradition of contributing to the global financing of vaccines and vaccination. Norway is in a strong position today to ensure consistency and a natural follow-up of its past financing efforts in R&D, purchase and distribution of vaccines.

- ✓ **Research** - Several Norwegian research groups and institutes have gained extensive experience in running clinical studies in LMICs. A number of research groups have also developed expertise in viral and cancer vaccine research.

- ✓ **Manufacturing** - Through the NIPH with its BSL-2 level GMP manufacturing facilities and contract manufacturing services, Norway has the competence to contribute to improved formulations, diminishing requirements for cold chain standards, and, in case of global emergency, global vaccine production bottlenecks. In recognition of these assets, the WHO has directed a capacity request to NIPH for *in vitro* stability testing.

- ✓ **Policy & coordination** - Norway has a record of commitment to the WHO and affiliated entities (e.g. GAVI Alliance). In the current EVD epidemic, NIPH has engaged in consultations coordinated by the WHO, supporting WHO's coordination and seconding one of its experts to the WHO. The WHO has invited the NIPH in a working group to coordinate vaccine trial efforts in Guinea.

PROPOSED INITIATIVES FOR NORWAY

Short-term measures:

- **Technically and financially support clinical phase II/III studies of the prioritized vaccines in Guinea,** where there are funding and technical contribution gaps. Ensure this is in collaboration with other European partners.
- **Support West African countries and the WHO to establish vaccine trial capacities and to set up appropriate supply chain platforms** in Guinea and in neighboring endemic countries.
- **Utilize Norwegian competencies in formulation and stability studies**, enabling scale up for mass production as early as possible, ensuring cold chain- and field- compatible vaccine distribution.
- **Closely monitor global production needs and utilize Norwegian competencies for EVD vaccine manufacturing,** if global capacity falls short following the dose-response results of the ongoing clinical phase I trials.
- **Support in-depth vaccine production and immunization cost studies** to guide vaccine pricing and immunization financing decisions, ensuring value for money to donors and affordable access to LMICs in the longer term.
- **Technically and financially support the establishment of a global market for EVD vaccines**, building on Norwegian institutional know-how on costing and financing aspects, and utilizing gold standard platforms for vaccine purchase, delivery and indemnification through, for instance, the GAVI Alliance and the World Bank.

Medium-term measures:

- **Identify back-up vaccine candidates and platform technologies to protect against poor clinical outcomes from the prioritized vaccine trials**. Strengthen the Norwegian Research Council and its GLOBVAC programme to ensure this, through a targeted announcement related to EVD and other serious infections with potential for bioterrorism or global dissemination.

Long-term measures:

- **Establish a sustainable international mechanism for the development of vaccines and medicines for infections such as EVD, where there are insufficient commercial markets**. Identify ongoing processes (e.g. the Global Research Collaboration for Infectious Disease Preparedness) and best practices from collaborative initiatives (e.g. partnerships for neglected diseases). Mobilize resources to set up the system, building on lessons learnt from related processes.

Contents

Introduction

As per 31st of October 2014, the Ebola viral disease (EVD) epidemic in West Africa had reached a cumulative 13 703 probable and suspected cases, with 4 920 reported deaths constituting an average case-fatality rate of 36%[1]. Other accounts have reported a case fatality rate of around 80%, and the WHO has categorized this epidemic as the most serious public health emergency in modern times.

The primary host for the Ebola virus is assumed to be the fruit bat; however EVD outbreaks are usually driven by human-to-human transmission. Efforts to limit and contain the epidemic focus primarily on traditional infection prevention and control measures[i]. With the near exponential growth in reported cases and mathematical modelling scenarios predicting from 500 000 to 1.4 million cases by end of January 2015 in West Africa, traditional infection prevention and control measures may fall short. The availability of EVD treatment centres and qualified HCW[ii] are most likely insufficient to stop the epidemic and vaccines have emerged as a possibly additive, preventive measure.

There are no licensed EVD vaccines. Several candidates have demonstrated protection against EVD in nonhuman primates (NHP) and the WHO has prioritized two of these for clinical testing[2]. Prior to 2014 all clinical development efforts of EVD vaccines had been discontinued, due to the inability to evaluate efficacy in human populations given the sporadic nature of EVD outbreaks[3]. The current outbreak gives an opportunity to evaluate vaccine efficacy, and there is an acute need for a vaccine. An effective EVD vaccine could contribute to outbreak control and future outbreak prevention, if rapidly distributed through mass vaccination campaigns.

A review of existing candidates, their clinical development status, bottlenecks in mass production and distribution as well as liability and long term financing is desirable to enable a best possible foundation for decision-making.

This report has been commissioned by the Norwegian Ministry to advise on measures and initiatives Norway should take in order to prevent as many EVD cases as possible and contribute to the global containment and limitation of the ongoing EVD epidemic (Annex 1).

The committee was composed by scientists, medical, pharmaceutical and financial advisors from the Norwegian Institute of Public Health and the Norwegian Directorate for Health, as described in Annex 2.

In order to engage with the Norwegian research community, regulatory bodies and pharmaceutical industry, a seminar was held on the 27th of October with over 50 participants representing domestic and international institutions. A summary of this seminar, institutions represented and key feedback by participants is presented in Annex 3.

An overview of meetings and teleconferences held with external Norwegian and international partners, as well as a list of submitted proposals for early stage preclinical vaccine concepts is listed in Annex 4.

[i] These include: isolation and treatment of patients in Ebola Treatment Centers, at home or in a community setting; contact tracing; safe burial ceremonies to reduce disease transmission.
[ii] including medical staff, laboratory staff, burial teams and facility cleaners

Ebola virus: Vaccine principles and candidates

Protective immune mechanisms against Ebola virus infection and disease

Protective immunity against Ebola virus is mediated by both antibody responses against the surface glycoprotein and T cell responses directed against a broader range of viral antigens[4,5]. The relative role of these immune responses is that antibodies against glycoprotein can prevent intracellular infection by blocking receptor-mediated binding and uptake into host cells (first line of defense), whereas T cell responses reduce clinical severity and death rates when infection already has been established (second line of defense). Both CD4+ Th1 helper cells and CD8+ T cells with ability to kill virus infected host cells contribute to viral clearance in this phase of the infection[6].

Although an ideal vaccine should induce both those arms of immunity, antibodies preventing the infection to be established are considered as the primary criteria for development of a successful vaccine against EVD[7]. The so far best established correlates of protection (COP) based on animal models, including NHP, are blocking antibodies and T cells capable of eliminating virus infected host cells[8]. This knowledge is strategically important in any accelerated vaccine development process, but specifically relevant in emergency situations like the EVD epidemic, where measurements of COPs may substitute time consuming and otherwise complicated and resource demanding protection studies[9].

Available vaccine candidates against EVD and priority of these

A spectrum of different EVD vaccine principles and candidates have been tested for immunogenicity and protection during the last decade, with positive results in several animal models, including NHP[10,11] (Table 1). This does not exclude the possibility that other platform technologies (e.g. synthetic peptides, vaccines targeting specific uptake in antigen presenting cells or recombinant proteins with suitable adjuvants) should be explored in the longer term. In the currect emergency, however, the WHO is focusing on the candidates already having promising data from challenge studies in animals and GMP product availability. The current development status and ability of these vaccine candidates to induce protective immunity is summarized in Table 2.

Table 1. Concepts for vaccines against EVD.

Vaccine concept	Basis for vaccine concept
Vector based, recombinant vaccines	Adenovirus (Ad); Vesicular Stomatitis virus (VSV); Vaccinia virus (MVA); Para-influenza virus; Cytomegalovirus (CMV)
Virus like particles (VLP technology)	Non-replicating Ebola virus like particles with VP40, GP and other antigens (without RNA).
Subunit vaccines	EBOV GP Fc fusion protein vaccines
DNA based vaccines	Plasmids expressing glycoprotein and nucleoprotein.

Among the most important selection criteria for further development and support were: strong preclinical immunogenicity and protection data based on evaluation in the nonhuman primate model (100% efficacy), single-dose immunization schedule, prospects for simple mucosal administration, and a substantial amount of GMP grade vaccine material already available.

Among these principles, two promising recombinant virus vector based vaccine candidates inducing antibodies against the surface glycoprotein have reached the clinical trial stage:

ChAd3-EBO-Z EBOV (developed by U.S. NIAID and GSK) and rVSV EBOV (developed by the National Health Agency in Canada and NewLink Genetics). A comparison of these two vaccine candidates is shown in Table 3.

WHO recently evaluated the prospects for rapid vaccine development against EVD and recommended that both vaccine candidates are prioritized in an accelerated development process[12]. WHO recommendations and increasing support from collaborators and the global community have facilitated the advancement of these vaccines into a comprehensive clinical trial program. The present challenge is timely and coordinated mobilization of resources to implement clinical testing, production, and distribution of efficient EVD vaccines. Table 2. Pre-clinical study findings on selected EVD vaccine concepts[13],[14].

Vaccine: Antigen	Vaccine concept	Immune responses	Animal model	Efficacy	Schedule
rAd5/3: GP (NP)	Virus vector Adenovirus	Ab CMI	Mice, GP NHP	100 % 100 %	1 x i.m
rVSV: GP	Virus vector VS virus	Ab CMI	Mice, GP NHP	100 % 100%	1 x i.m
VEE Replicon particle (VRP): GP	Virus vector Alphavirus	Ab CMI: CD8	Mice NHP	100 % Var.	3 x i.m.
HPIV-3: GP, NP	Virus vector Para-influenza virus	Ab CMI	Mice , GP NHP	100 % 100 %	2 x i.n.
mCMV-NPCTL: NP	Virus vector Cytomegalovirus	CMI: CD8	Mice	100 %	2 x i.p.
VLP (Baculovirus): GP, NP, VP30, VP40	VLP Virus like particle	Ab CMI	Mice, GP NHP	< 100 % 100 %	3 x i.m.
EBOV-GP-Fc: GP	Subunit Fusion protein	Ab CMI	Mice	< 90 %	4 x i.p.
DNA: GP, NP, VP35, VP40	DNA vaccine	Ab CMI	Mice, GP NHP	100 % Low	3 x i.m.
MVA and Ad26[iii]	Modified Vaccinia Ankara virus		NHP	100%	1 x each i,m.

The ChAd3-EBO-Z-ZEBOV vaccine uses a chimpanzee-derived replication deficient adenovirus vector with the GP gene from the Ebola virus inserted. After immunization with this recombinant vector system, efficient expression and presentation of this antigen to the immune system induces antibodies and T cells which by different mechanisms contribute to protection against infection and development of severe EVD. This vaccine concept has proven safe and efficient in inducing protective immunity against viral challenge (100 % efficacy) in several animal models, including NHP (macaques)[15],[16],[17]. The studies also showed that protection can be achieved by a single vaccine shot and promising mucosal administration.

Recently, a phase I clinical trial with a variant of the cAd-ZEBOV vaccine (cAd5) have also demonstrated safety and immunogenicity: Both significant and durable GP antibody levels as well as GP specific T cell responses of both CD4 and CD8 subsets were reported[18],[19]. Importantly, these immune responses correspond to the suggested correlates of protection (COPs) for vaccine induced protection against EVD, which strongly indicate that this vaccine

[iii] http://www.jnj.com/news/all/Johnson-Johnson-Announces-Major-Commitment-to-Speed-Ebola-Vaccine-Development-and-Significantly-Expand-Production

concept has protective potential in humans. Natural pre-immunity to an adenovirus vector is usually challenging in humans. Although the chimpanzee-derived form may reduce this problem, it is still not known what the natural pre-existing immunity towards this vector (ChAd3) is in the African population.

The rVSV-ZEBOV vaccine concept uses an attenuated, but not replication deficient, vesicular stomatitis virus vector, where one of its genes has been replaced by the glycoprotein gene from the Ebola virus. Immunization with this recombinant vector system results in antigen presentation of the Ebola glycoprotein itself, and limited replication of the vector virus containing this antigen[20]. Attenuated live recombinant vaccine vectors, in contrast to replication deficient vectors (cAd EBOV), can provide an advantage with respect to efficient antigen presentation leading to stronger antibody and T cell responses.

At the pre-clinical level, the rVSV vaccine concept showed promising results when tested in different animal models, including NHP. Mice were completely protected from challenge after vaccination using different administration routes[21]. NHP immunization with a blended vaccine consisting of three different VSV vectors expressing different Ebola and Marburg glycoproteins demonstrated a significant rise in GP antibodies and protection (100 % efficacy) against challenge with the respective viral strains[22]. The possibility to utilize alternative delivery routes (intranasal and oral delivery) for inducing relevant B cell and T cell responses and protection in NHP has also been reported[23]. Apart from high levels of immunity when used as a prophylactic vaccine strategy, the rVSV vaccine technology has also demonstrated post exposure protection against both the Ebola and Marburg virus when given after challenge in animal experiments[24].

The VSV vaccine technology has demonstrated protective efficacy and seems well tolerated in mice, guinea pigs and NHP. These viral vectors are replication competent, raising questions on safety and suitability for human use. However, the VSV vaccine platform has demonstrated both safety and efficacy in immunocompromised NHP without any side effects[25]. Pre-immunity to the VSV vector is not considered a problem in humans, since this pathogen is restricted to live-stock. In a practical setting VSV based vaccines show promise in terms of immunization schedules (one dose) and administration routes (systemic and mucosal administration).

Table 3. Comparison of the vaccine candidates ChAd3-EBO-Z and rVSV.

Features	ChAd3-EBO-Z ZEBOV GP (GSK)	rVSV ZEBOV GP (NewLink)
Ab CMI	GP antibodies CD4+ and CD8+ T cells	GP antibodies CD4+ and CD8+ T cells
Efficacy: prophylactic	100 %	100 %
Efficacy: therapeutic		Mice (24 hr.) and NHP (30 min.)
Schedule; Durability	One i.m. dose; Expanded: prime boost (MVA)	One i.m. dose
Vaccine dose	1 x 10E10 pfu	2 x 10E7 pfu
Administration route	Systemic (i.m.), mucosal (i.n.)	Systemic (i.m.), mucosal (i.n.)
Vector pre-immunity	Present but avoided (ChAd3-EBO-Z)	Not present
Safety in humans	Safe: replication incompetent	To be determined: replication competent

Clinical development for chAd3 and rVSV vaccine candidates

There are extensive plans for performing clinical trials for the two vaccine candidates in the most advanced stage of clinical development (see table 4), and funding has been recruited for nearly all of these except those being planned in Guinea. The first phase I trials are now ongoing among healthy adults in USA, UK and Mali with both the monovalent and the bivalent ChAd3-EBO vaccine among healthy adults. These are open-label, dose escalation studies. Similarly, a phase I trial with the rVSV vaccine has started in USA, in which healthy adults take part in a double-blind randomised placebo controlled dose-escalation trial. The first results from these studies ar anticipated in December 2014.

Table 4: Tabular overview of all clinical trials planned with the ChAd3-EBO-Z and rVSV vaccines. (WHO Consultation on potential Ebola therapies and vaccines, Sept 29-30th 2014)

Vaccine candidate	Sponsor	Site	Population	N	Phase	Trial type	Start date
cAd3 - EBO	NIAID	USA, Maryland	Healthy adults	20	I	Open-label Dose escalation	sep.14
cAd3 - EBO Z	Univ of Oxford NIAID Wellcome Trust	UK, Oxford	Healthy adults	60	I	Open-label Dose escalation	sep.14
cAd3 - EBO	NIAID	USA, Atlanta	Healthy adults	130	I	Open-label Safety high dose	okt.14
VSVΔG-ZEBOV	NewLink Genetics DOD	USA, Maryland	Healthy adults	117	I	Double-blind, RCT, Placebo controlled Dose-escalation	okt.14
cAd3 - EBO Z	UMD Wellcome Trust	Mali	Healthy adults	40	I	Open-label Dose escalation	okt.14
cAd3 - EBO Z	NIAID	USA, Maryland	Healthy adults	20	I	Open-label Dose escalation	okt.14
cAd3 - EBO	NIAID Wellcome Trust UMD Mali Ministry of Health	Mali	Healthy adults	40	I	Open-label Dose escalation	des.14
cAd3 - EBO Z	NIAID Wellcome Trust	Gambia	Healthy adults	40	I		jan.15
cAd3 - EBO Z	CDC	Nigeria	Healthy adults		I		?
VSVΔG-ZEBOV	NIAID NewLink Genetics	USA, Maryland	Healthy adults		I	Double-blind, RCT Placebo controlled Dose-escalation Boost day 28	?
VSVΔG-ZEBOV	Wellcome Trust	Germany, Hamburg	Healthy adults	20	II	Open-label Dose escalation	okt/nov-14
VSVΔG-ZEBOV	Wellcome Trust	Kenya/Gabon	Healthy adults	200	II	Open-label Dose escalation	okt/nov-14
VSVΔG-ZEBOV	Wellcome Trust	Switzerland, Geneva	Healthy adults	115	II	Open-label Dose escalation	okt/nov-14
cAd3 - EBO Z		Switzerland, Lausanne	Healthy adults	100	II	Open-label Dose escalation	okt.14
cAd3 - EBO Z		Mali, Ghana, Nigeria, Cameroon	Healthy adults/children	3000	II	Double-blind, RCT	jan.15
cAd3 - EBO Z		Sierra Leone, Liberia, Guinea	Healthcare workers	8000 - 12000	III	RCT or Stepped-wedge	jan.15
VSVΔG-ZEBOV		Sierra Leone, Liberia, Guinea	Healthcare workers	8000	III	RCT, Double-blind Stepped-wedge?	jan.15

It is estimated that for approval to enter into licensure by the US «Animal rule», safety and immunogenicity data in ~3000 subjects will be needed. This rule is relevant for pharmaceutical products targeting highly lethal pathogens, and applies if there is no other way to license a vaccine. The Animal Rule permits the Food and Drug Administration (FDA) to license human biological products or drugs on the basis of animal efficacy studies when human efficacy studies are not ethical or feasible.

NIH and CDC have proposed two large clinical phase II/III trials in Liberia and Sierra Leone. Recruitment will start in Dec. -14/Jan.-15. The first efficacy data from these studies will be available in late March 2015 at the earliest. This data will determine if the vaccines could be licensed and recommended for mass vaccination.

Other vaccine candidates are also entering clinical trials, as seen in Table 5. The most likely candidate to catch up on the ChAd3-EBO-Z and rVSV vaccines is the prime-boost vaccine from Johnson and Johnson (Janssen), which are investing heavily in the area of scale up of EVD vaccines now. The Johnson and Johnson candidate vaccine is based on vaccination with one dose of each of two recombinant virus-vector-based vaccines both expressing the Ebola Kikwit glycoprotein; one based on modified vaccinia Ankara (MVA) virus and the other on an adenovirus (Ad26). The MVA vector comes from Bavarian Nordic (Denmark) and the Ad26 from Janssen (Crucell). Clinical trials for the study of safety and immunogenicity in healthy volunteers are scheduled for early January 2015 in Europe, USA and Africa. A cumulative production of one million doses of the vaccine regimen is expected within 2015[26].

Table 5: Pipeline of EVD vaccine candidates that are in an advanced development level.

Company	Vaccine candidate	Phase	Start date	Comment
Profectus	rVSV EBOV (Z) rVSV Marburg rVSV trivalent VesiculoVax®	Preclin (NHP)	Q1 2015	
Vaxart	Ad5 EBOV GP + TLR3	I	Q1 2015	Tablets
Johnson and Johnson / Bavarian Nordic	AdVac® + MVA-BN®	I	Q1 2015	2 dose
Inovio GeneOne Life Science Inc	DNA vaccine SynCon®	I	Q1/Q2 2015	
Protein Sciences	Protein vaccine	Preclin (NHP)	Q4 2014	

Estimates on vaccine doses needed to control the EVD outbreak

In order to take control of the epidemic and eliminate the virus from the human population, transmission has to be reduced by more than 50%, which can be achieved by an immunity[iv] exceeding 50 % [27]. Assuming a one-dose vaccination schedule, 100% vaccine efficacy for a minimum of one year and a 50% vaccination coverage in the general population (100% vaccination coverage in high risk groups)[v], our estimates (see table 6) show the minimum number of vaccine doses needed to reduce the transmission rate to < 1, hence arrest the exponential growth of the epidemic and control the outbreak in a one-year time frame[vi]. The total estimate is split into doses needed for research and development (clinical trials, stability studies) and emergency/public health use (pre-exposure).

Table 6: Estimates for required number of EVD vaccine doses as of Q4 2014

Estimates for required number of Ebola vaccine doses as of Q4 2014	
Stability studies, 250 doses pr. study	250
Clinical trials	≈ 15 000
R&D total	≈ 20 000
Pre-exposure vaccination, HCW in clinical settings	≈ 20 000
Pre-exposure vaccination, Community Ebola responders	≈ 17 500
Pre-exposure vaccination, Contacts providing home care of cases	≈ 16 000
Pre-exposure vaccination, population 21 mill, 50 % vaccination coverage **Children 9 mill** **Adults 12 mill** **Pregnant women 483 000** **People with HIV 146 000**	≈ 10.5 mill
Pre-exposure vaccination, all	≈ 10.5 mill
Total	**≈ 10.5 mill**

As the above table suggests, production will focus initially on doses for clinical trials and stability studies. There is a need for approximately 20 000 doses of each vaccine candidate as soon as possible. The number of required doses for clinical trials were given by NIAID/GSK and PHAC/NewLink Genetics [28]. A change in the numbers due to change in study design and number of trials, will not have a great impact on to the total number of doses needed in the long run.

[iv] Immunity refers to the percentage of the vaccinated population responding to a vaccine, whereas vaccination coverage refers to the percentage of the total population vaccinated. 50 % immunity therefore implies 100 % vaccine efficacy in 50 % of the population.

[v] Assumptions are based on the fact that the two prioritized vaccine candidates have demonstrated 100% protection in NHP after one dose; protective antibodies were found about one year after vaccination with VSV vector in NHP and with adenovirus vector in humans.

[vi] As of now there are limited data on short term and long term efficacy in humans. It will be necessary to re-calculate the number of vaccine doses needed to control the outbreak when this data is available. A less than 100 % vaccine efficacy will require more than 50 % vaccination coverage, and the number of doses needed to control the outbreak will increase. If two primary doses are required for protection the number of required doses needed to control the outbreak will double. The same will be the case if a booster-dose is required less than one year after the primary dose.

After licensure, there will be a pre-exposure vaccination need for approximately 10.5 million doses, assuming 100 % vaccine efficacy and 50 % vaccination coverage in Liberia, Guinea and Sierra Leone (100 % vaccination coverage in high risk groups). This estimate is based on a total population of 21 million for the three endemic countries. There may also be a situation that some will pressure for compassionate use before approval.

In addition to the general population group, the pre-exposure group is divided into three different groups with special risk of EVD (100 % vaccination coverage): national and international health care workers in clinical settings (e.g. doctors, nurses, cleaners); community Ebola responders (e.g. burial teams, contact tracers); contacts providing home care of patients with Ebola. Some of the HCW would be included in clinical trials.

Children, adults, pregnant women, and people living with HIV are groups that could be prioritized for vaccination or not, due to risk of infection and vaccine safety / efficacy data available for each specific group.

All numbers will change depending on updated plans for clinical trials and stability studies, the development of the epidemic and short term and long term clinical data in humans (vaccine efficacy, duration of protection, number of doses needed for short- and long-term protection).

When vaccine supplies become sufficient in the longer term, it will be ethically justifiable to offer the vaccines to the entire population in Liberia, Guinea and Sierra Leone, implying a doubling of the estimates. Further on mass vaccination might be necessary in the neighboring countries also (Guinea Bisseau, Senegal, Mali and Ivory Coast with a total population of 33.5 million). Nevertheless, long term dose estimates are not considered here since they are extremely questionable and most relevant for estimating post-exposure vaccination. Animal data on the rVSV vaccine suggest that post-exposure prophylaxis is possible when given very soon after exposure. It is uncertain whether the vaccine will induce post-exposure protection in humans, and there are other therapies under development that would probably be more relevant than the rVSV vaccine after Ebola virus exposure. Adequate capacity for vaccine distribution and administration are prerequisites for the provided dose estimates. Even if adequate safety and immunogenicity are demonstrated in planned clinical trials as described in the previous section, vaccines might not be available in sufficient quantities before 2015[29].

Production capacity challenges and opportunities for the prioritized EVD vaccines

Vaccine production capacity and delivery time

Global production capacity estimates (number of doses) for the ChAd3-EBO- and rVSV vaccines are constantly changing, and so are delivery time scenarios. Multiple bottlenecks around manufacturing capacity, demand estimates, cost estimates and logistical challenges – which are changing from week to week – are contributing factors to the uncertainty around production capacity. The table below presents an updated overview of current estimates, as per end October 2014.

Table 7: Estimates of vaccine production capacity and delivery time.

Manufacturer	rVSV production capacity (doses)	Delivery time scenario	ChAd3-EBO-Z production capacity (doses)	Delivery time scenario
NewLink Genetics[vii]	50 000 500 000 5 mill	Dec-2014		
	125 000 1.2 mill (bulk?) 12 mill (bulk?)	Q1-2015		
	250 000 2.5 mill (bulk?) 25 mill (bulk?)	Q2-2015		
GSK[§] (see Fig. 3)			11 500	Dec-2014
			24 000 – 310 000/month	Jan-2015- Aug-2015
			1 mill/month	Dec-2015
NIPH Norway	25 000/batch[viii] 100 000	Q2-2015		
	50 000/month	Q2-2015 -		
	150 000/month[ix]	Q2-4-2016 -		

It is important to define doses and the expression “bulk” in order to understand the challenge regarding the filling capacity world-wide, with some reports defining doses as filled vials whereas others only define «number of doses».

[vii] Depending on dose level determined to be effective. 1.0E+08, 1.0E+07 or 1.0E+06. NewLink Genetics data from sciencemag.org. §Reference to GSK data from sciencemag.org.
[viii] With existing filling line.
[ix] With new filling line

When viral vaccines are produced the product which has completed all processing stages up to, but not including, final packaging, is a bulk, i.e. the sterile preparation containing many doses prior to filling. The bulk is not ready for infusion and needs to be filled or transferred into final packaging, which may be vials or syringes.

As table 7 (and related references) suggests, GSK is clear on what amount of vaccines can be bulk and what the amount of filled doses is. Reports from NewLink seem less clear in terms of what amounts their doses represent. For instance, the 5 million doses in Dec-14 cannot be explained by traditional filling capacity. NewLink reports 60.000 to 70.000 vials of VSV-EBOV by the end of the year. Depending on the suitable dose level (from 10^6 to 10^8) these vials can represent 600.000 to 700.000 doses, or 6 to 7 million. In order to evaluate the relative impact of rVSV availability on the containment of the epidemic, it is critical to understand the optimal dose of the rVSV vaccine[30].

NIPH assets on vaccine manufacturing in BSL-2 and quality control testing

NIPH runs a contract manufacturing organization (CMO) for sterile manufacturing, suitable for handling biological products (Fig. 1). The facility has 1200m^2 cleanrooms, seven manufacturing units class B (sterile), one supporting manufacturing unit class C, five of seven units designed for containment of biohazards class 3 and Class A benches for aseptically processing. There are also supporting laboratories for non-sterile and sterile testing.

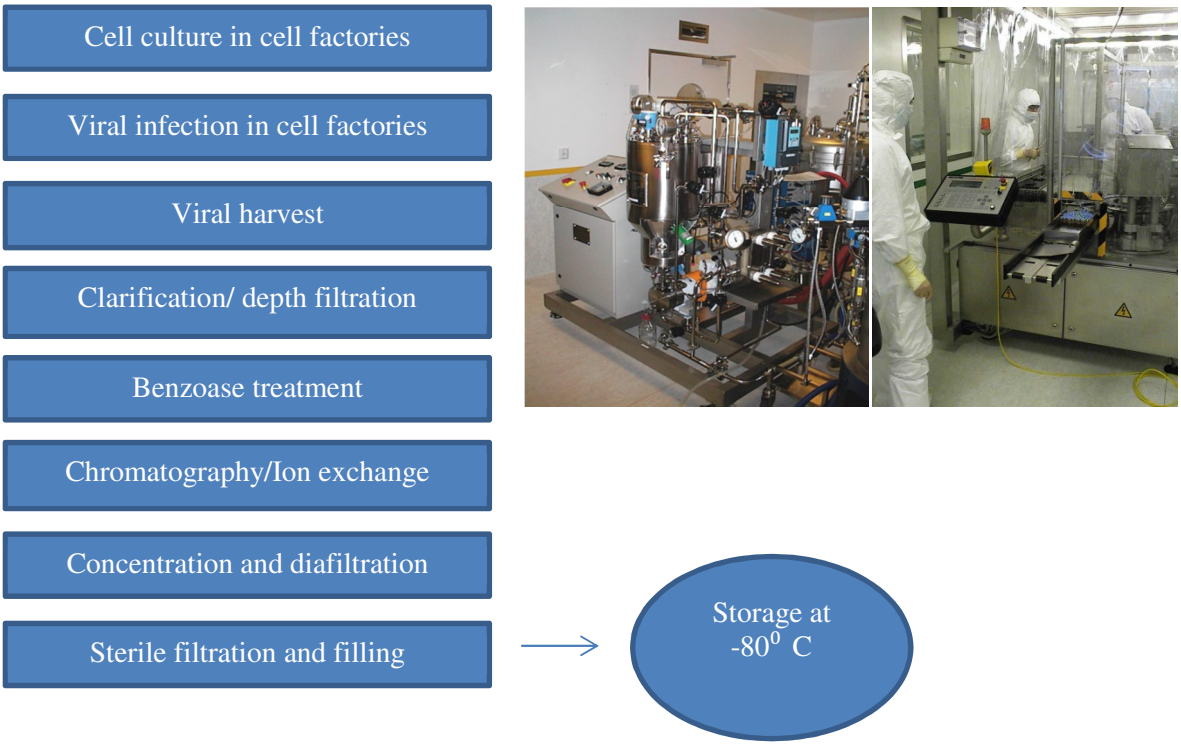
Major changes, improvements and investments were done to the NIPH facility in 2011 in order to become a large scale manufacturer of viral vaccines:

- Cleanroom for cell- and virus cultivation redesigned and improved
- Cleanroom for purification processes redesigned and improved
- The vendor contracts are all in place for raw materials /other materials and most of the central materials are available on storage/stock.
- The infrastructure and the production facilities are designed for scale-up production.
- Key production equipment is available and is qualified and used in regular production.
- “Disposable” technology is implemented, which will reduce lead time for validations and change of processes.
- Broad competence within development of virus vaccines, production of these and up-scaling. The use of cell factories is well known and these are often used for development of cell based human vaccines.
- Large scale production using cell factories which will give short lead time compared to reactor technology. Very few GMP facilities today possess as large capacity of cell factories. Competence within reactor technology is also in the facility for even further upscaling, but will have a longer lead time.
- Possibilities to use in-house and contracted QC services.

Production process for viral vector vaccines and technology transfer

Based on the limited information available in the literature, patents and media on processes for manufacturing the ChAd3-EBO-Z and rVSV viral vector vaccines, we have attempted to perform an exercise to see how large scale production of these virus vaccines in cell factories at NIPH could be performed. Adapting the tentative production scale-up of the two candidate vaccines with the equipment and know-how available with ongoing virus production for fish vaccines in the NIPH GMP plant, we have in Fig. 1 outlined how a process could be set up for the Ebola vaccine candidataes in the BSL-2 GMP facilities of NIPH or other potential sites.

Figure 1[x]: Assumed production process of ChAd3-EBO-Z and rVSV[31].



The first four steps and the concentration and diafiltration steps follow an ongoing production process in process by the aquaculture vaccine company Pharmaq. Pharmaq is the world's leading pharmaceutical company specializing in aquaculture, including injectable antiviral fish vaccines (www.pharmaq.no/products/injectable). Pharmaq rents production areas and offices in the NIPH GMP facility[xi]. Pharmaq and NIPH has therefore a close cooperation for large scale production of virus antigen using cell factory based processes; used as vaccines to prevent infections in farmed fish. The process is performed at GMP.

[x] Photos from the GMP manufacturing plant (fermentation and filling, respectively) at NIPH (A. Aase, NIPH).
[xi] NIPH is a provider of contract manufacturing services for several small and large companies, in Norway, Europe and USA. Pharmaq is one of these companies.

The process for ChAd3-EBO-Z and rVSV in figure 1 is described with additional purification steps with enzyme benzoase treatment and then chromatography (ion exchange). Both steps can be implemented at NIPH. Key success factors enabling technology transfer between production sites are:

- No intellectual property (IP) barriers
- All necessary methods, technology and knowledge are established and well documented
- Virus, cell cultures, methods, processes, and know-how can be shared without delays
- Equipment, facilities, logistics, material flow, quality control and quality assurance are in place at the new facility
- The facilities otherwise portfolio should not be an obstacle
- Economical support to handle loss while normal business is «on hold»

The production process scale up exercise has concluded that NIPH together with Pharmaq will be able to establish a cell factory based production at a scale of 200 – 400L virus suspension for purification within a short period of time. This estimate is based on an evaluation of production of the same virus vectors for other purposes, acknowledging the currently limited knowledge around the production processes for rVSV and adenovirus to ebola vaccines.

This may however confer a capacity to produce in bulk a virus suspension of 0.5-1 million doses per week, however the BSL-2 filling capacity is the major bottleneck (Table 8), and the output in terms of filled vials is up to 150 000 vials/month.

As filling capacity is also a common limitation of the two manufacturers producing ChAd3-EBO-Z and rVSV, filling of bulk virus suspensionat NIPH from other manufacturers could be a separate possible option to contribute to scale up for mass vaccination.

Table 8: Estimation of production scale and yield for rVSV vaccine at NIPH facilities[32].

Production parameter	Estimate
<u>Production yield, rVSV purified bulk prior to filling</u> Production yield rVSV [1)]: Dose based on primate [2)]:	 2,0 x 10^{11} PFU / L virus suspension 1,0 x 10^{6} PFU / kg
Estimated yield for a 70 kg person	2 500 doses/L virus suspension
<u>NIPH bulk capacity</u> Cell factory based – 200L: Double capacity: <u>NIPH capacity to release filled vials (assuming 1 dose vials)</u> 25 000-150 000 vials/month	 500 000 doses / week (bulk) 1 000 000 doses / week (bulk) 25 000 – 150 000 doses/month

Potential contributions to formulation affecting distribution

Based on available literature the ChAd3 EBO-Z and rVSV vaccines will need to be stored in -80°C freezers and transported on dry ice. After thawing, the vaccine will need to be stored at 4°C and used within 12-18 hours.

There are several challenges related to these storage conditions in West Africa. The power supply is uncertain and not always existing, transport and roads are not suitable for such equipment (freezers). Even if the vaccine is transported in boxes with dry-ice, the availability of dry-ice is very limited, and the climatic conditions are not compatible with the necessary handling of vaccines.

Studies should be done to explore the formulation and see whether anything can be done to stabilize or freeze dry the vaccine to be able to store at other conditions than -80°C. According to GSK, stability studies are ongoing with the production of the initial lots. As long as the vaccine is stored at -80°C, there is no concern about shelf life. Stability studies at -40°C and -20°C will begin shortly based on information from the latest SAGE meeting, and data will be available over the coming months (these are real-time studies). Formulation improvements to allow lyophilisation or liquid storage at refrigerator temperature (2-8°C) will begin in early 2015 and likely take six months to get stability results.

Dilution experiments should also be done to study whether the potency is acceptable when using fractional doses. However, as the virus is diluted away from the environment of tris/albumin, there is a high likelihood of it losing viability by pH change and by adhesion to the walls of the container, particularly if this is glass. The WHO has suggested testing of the use of protein-containing dilution fluids and potential advantage in using plastic vials to reduce loss of potency in vaccine vials.

The systems and capacity for quality control of biological products at NIPH could be used to assess urgent formulation, stability and control issues affecting the critical path to mass distribution of vaccines.

Assessment of the options

As previously demonstrated, NIPH has facilities, knowledge, technology and infrastructure to produce, fill and finish vaccines ready to be distributed within 6 months from start of the project, i.e. with the potential to deliver GMP quality vaccine doses by May 2015 at a quantity of up to 100 000 doses a month. However, this may not add a sizeable quantity additional to the volume already indicated by the producers, also taking into account that BARDA has reported that they have contractual arrangements with four GMP facilities that may be used for emergency needs.

This situation may change and in particular the Newlink vaccine production scale up may be vulnerable, also given the uncertainty of optimal dose. This may warrant the need for additional capacity.

NIPH's facilities, equipment and previous experience in stability studies can be used to conduct studies aiming at reducing the risk of product loss during shipment and distribution of EVD vaccines.

Aspects regarding fair distribution of vaccines

In a setting with limited number of vaccine doses, there will be dilemmas when it comes to fairness in distribution across and within countries. As clinical trials for EVD vaccines are currently under way, health authorities and ethical review committees in host countries should ensure that the proposed research is responsive to national health needs and priorities and that it meets the requisite ethical standards. The most affected countries should have equal, early access to vaccine, both in trials and for common use.

A WHO consultation on ethical considerations for use of unregistered interventions for EVD concluded that the principles used for setting priorities in resource-constrained settings should be applied to make choices about who will receive the intervention, which country will get what and on which criteria these choices will be made[33]. Criteria mentioned were:

- distributive justice
- reciprocity and social usefulness
- likelihood of positive impact on individual and public health, and best possible risk/benefit assessment based on available information
- minimal infrastructure and equipment to administer the vaccine
- capacity to monitor and manage side-effects and progress of treatment, and measuring outcome such as disease and immune response markers
- Possibility to ensure informed consent and freedom of choice regarding vaccination

Based on the principles above, priorities can be as follows:

Health care workers and community EVD responders (e.g. contact tracers)

Qualified HCW should have first priority while vaccine supplies are limited, as per the conclusions of the recent WHO meeting on EVD vaccines access and financing[34]. Prioritization of HCW is justified by their high occupational risk of getting EVD while treating others, and their social usefulness. HCW are essential in controlling the outbreak. In a clinical trial setting HCW will be easier to recruit and monitor than civilians, and they are in a better position to give informed consent to receive an experimental vaccine. National HCW should have the same ability as international HCW to get the vaccine, both in clinical trials and thereafter.

Contact tracers are not included among those who should be prioritized for vaccination in the summary report from the WHO meeting, which must be an oversight. Contact tracers are often mentioned together with burial teams under the annotation “Community Ebola responders”. Their risk of infection relative to other groups is likely to be elevated. Vaccination will help them deliver effective control interventions and increase motivation.

Contacts providing home care of EVD patients

Contacts providing home care of EVD patients should be offered vaccination as soon as a licensed vaccine is available, or earlier in a clinical trial setting. It will be challenging to implement and evaluate this vaccination approach as case numbers increases. The use of ring vaccination to surround and contain new foci of infection was discussed in the previously referred WHO meeting. This approach works well only if highly effective contact tracing is in place, which is not yet the case in the three most severely affected countries.

General population in affected countries versus non-affected neighboring countries

As vaccine supply expands, vaccine should be offered to the general population. In general, more lives could be saved by immunization prior to an epidemic peak rather than during the epidemics decline. In a setting with limited number of vaccine doses it might therefore be debated whether to prioritize affected or non-affected (neighboring) areas, in an attempt to contain the outbreak. This depends on the epidemic situation at the time when vaccine is available for mass vaccination.

The principles used to prioritize distribution of the limited number of doses should be transparent and involve both the global community as well as governments of the affected countries and communities in a participatory, inclusive manner[35].

Estimating EVD vaccine manufacturing costs and financing requirements for immunization

There is a great deal of uncertainty around the cost of production of the prioritied EVD vaccines, their manufacturing processes and scale up capacities by their developers. If the cost of these candidates is too high, their benefit potential might not be realized as prices will exceed affordability thresholds by endemic countries in the long term. Uncertainty itself is a major bottleneck to planning for introduction of these vaccines once they obtain regulatory approval. In the urgency of the situation, the global community has signaled willingness-to-pay for EVD vaccines given also the signals from industry about not-for profit models.

This section provides preliminary estimates of costs and financing requirements for vaccine production and introduction, acknowledging both the uncertainties around manufacturing processes, pricing strategies and purchase/procurement/delivery mechanisms; as well as the limitations around cost data availability by manufacturers at this stage.

Potential market for EVD vaccines and required production capacity

Potential demand (doses) for EVD vaccines can exceed ~10 to 37 million[xii], suggesting that vaccine manufacturers globally will need to establish a production capacity of ~10 to 37 million doses per year. The lower end would be sufficient to meet the needs of the three endemic countries (basic scenario) whereas the higher end would be required to meet the needs of both endemic and neighbouring countries (intermediate, ring vaccination scenario)[xiii]. This crude estimate is based on the following assumptions:

Table 9: Assumptions used to estimate potential EVD vaccine market size

Market size	Description
Assumption 1:	Under a basic scenario, vaccines will be limited to the three endemic countries: Sierra Leone, Guinea and Liberia (19.8 million).
Assumption 2:	Under an intermediate scenario, a ring vaccination strategy will be adopted to additionally include: Guinea-Bissau, Senegal, Mali, Ivory Coast (53.3 million).
Assumption 3:	Vaccination coverage >50% of total population.
Assumption 4:	A reactive campaign strategy is adopted that is not followed by routine immunization.
Assumption 5:	Market size relates only to the public sector.

The actual market size beyond and above this crude estimate will depend on the appropriate strategy selected for preventing EVD. Specifically, a number of parameters affecting the design and time span of immunization efforts have not been factored in. Their consideration would alter the total market size estimate. These include: choice and timeframe of routine vs catch-up campaign immunization; vaccination cohort selection based on different vaccine schedules, age, risk or geographical distribution factors; benchmarking against different immunization

[xii] For simplicity of calculations, a 10 million dose benchmark is used for the basis scenario although the estimated doses in previous sections are approximately 10.5 million. Moreover, a 37 million dose benchmark is used for the intermediate, ring vaccination scenario, even though this might be unrealistic in the short term.

[xiii] Potential market can reach 140 to 290 million (extreme scenario) if all countries at risk of EVD introduce EVD vaccines in their routine immunization programmes with 50% to 100% coverage targets. Countries include: Democratic Republic of the Congo, Guinea, Uganda, Côte d'Ivoire, Gabon, Congo, South Sudan, Nigeria, Cameroon, Central African Republic, Ghana, Liberia, Sierra Leone, Angola, Togo, United Republic of Tanzania, Ethiopia, Mozambique, Burundi.

coverage targets and drop out rates; choice of EVD control vs elimination objectives; consideration of private sector markets in endemic countries; consideration of global travel markets including tourists as well as healthcare and aid personnel; stock-piling requirements and wastage factors.

Cost of production

The potential cost of production can exceed US$20m – US$74m. The former amount represents the cost of production required to meet the needs of the three endemic countries (basic scenario), while the latter represents the cost of production required to meet the needs of both endemic and neighbouring countries (intermediate, ring vaccination scenario). This is an extremely simplified, crude estimation of costs, based on published evidence on costs of production and a number of assumptions presented below.

Evidence by the GAVI Alliance suggests that bulk production and fill-finish for vaccines may require on average cash flows of US$50m to US$500m, with ~ 60% fixed costs; 25% semi-fixed (per-batch) costs; and 15%variable costs[36]. Another study estimating the cost of production of a hypothetical live attenuated dengue vaccine suggests that costs can reach US$1.75m for 15 million doses per year[37]. And in an older study it was shown that the cost of production of a plasma-derived hepatitis B vaccine varied from US$20 to US$0.10 per dose as production increased from small quantities to 20 million doses per year[38].

Evidence suggests that vaccine manufacturing has economies of scale, and the closer to full capacity, the lower the cost per dose due to fixed and semi-fixed cost per volume decreasing. However, published evidence on costs of vaccine production is extremely limited. Such costs are closely guarded by manufacturers and, in the case of new vaccines, they rarely become known to the public sector. Vaccine pricing therefore often takes place without a link to the cost of production, focusing primarily on what the markets will bear and setting prices in line with the avoided costs of treatment[39].

In the absence of manufacturing process specifics by the vaccine developers at this stage, and in light of limited evidence in the public domain, the above estimate is built on a number of assumptions.

Table 10: Assumptions used to estimate potential EVD vaccine cost of production

Costs of production	Description
Assumption 1:	The manufacturing process of an EVD vaccine is similar to that of a hypothetical dengue vaccine, where it has been demonstrated that cost of manufacturing can reach US$1.75 for 15m dose production per year.
Assumption 2:	Production cost per dose remains steady as production volume increases.
Assumption 3:	Under a desired cost+ pricing scenario, total cost of production would not exceed US$2 per dose – a reasonable cost ceiling for affordable pricing in low income country settings.
Assumption 4:	Costs of R&D and marketing are excluded[xiv].

[xiv] Under 'normal settings', i.e. three to six year timeframes for clinical phase I/II/III development and stringent regulatory authority requirements, non-capitalized clinical development costs for vaccines can vary from US$192m – 206m (Rotarix and RotaTeq respective estimates) to US$361m (estimates for multiple biopharmaceuticals). According to NIPH own estimates from past vaccine trials in African country settings, small scale production for clinical phase I and II trials (N=200-300) can cost US$1-2m per country.

Costs of production	Description
Assumption 5:	Scale up production can be accomplished in modestly sized process equipment, where production capacity is already in place, including sterile filling and GMP.
Assumption 6:	Technology transfer or other IP licensing costs are excluded.
Assumption 7:	Registration dossier submission costs are excluded.
Assumption 8:	Additional laboratory and clinical studies required by stringent regulatory authorities or to satisfy alternative storage temperatures or formulations are excluded.
Assumption 9:	Costs are not capitalized.
Assumption 10:	No time-to-finish is included and costs are not discounted.

It is important to highlight that the consideration of factors excluded by the above assumptions will likely alter the true cost of production. For instance, the complexity of the technology used will affect cost and ease of scale up, compounded by the potential need for different formulations across countries and age groups[40]. Choice of technology will also affect bulk production capacity. For instance, in the case of flu vaccines, the production of 60m egg-based doses requires ~US$600m in a 140k s.m. facility, while 100m mammalian cell culture based doses require US$150m. In contrast, 75m insect cell-culture based doses require US$40 - 225m in a smaller, 40k s.m. facility, depending on the production approach[41]. Number of bulk production lines required and their location, as well as raw material and equipment requirements, skills and labour requirements can all increase production costs significantly. On the other hand, economies of scale due to large volume production and stock-piling requirements can decrease production costs substantially.

Cost of vaccine introduction

The potential cost of vaccine introduction can exceed US$21.4m – US$78.6m. The former amount represents the cost of vaccines purchased to meet the needs of the three endemic countries (basic scenario), while the latter represents the cost of vaccines purchased to meet the needs of both endemic and neighbouring countries (intermediate, ring vaccination scenario). As in the case of production costs, this is an extremely simplified, crude estimation of vaccine introduction costs, based on a number of assumptions presented below.

Table 11: Assumptions used to estimate potential EVD vaccine cost of introduction (purchase costs only).

Vaccine introduction	Description
Assumption 1:	Potential market size ~10 to 37 million (basic and intermediate scenario respectively).
Assumption 2:	Immunization coverage target at 50% given a 100% efficacious EVD vaccine
Assumption 3:	Only direct costs of vaccine purchase are included, excluding procurement, freight and other supply chain costs.
Assumption 4:	Direct costs are in proxy to US$2.14 vaccine introduction cost per capita, which is the high cost per capita end of previous meningococcal vaccine reactive campaigns[xv][42] and estimated MenAfriVac™ preventive campaign cost estimates[xvi][43].

[xv] Such as the reactive polysaccharide vaccination campaign in 2009 in Niger and Nigeria, with 7 million individuals targeted costing US$15m; and the reactive meningococcal polysaccharide vaccine campaign in response to the 2007

Vaccine introduction	Description
Assumption 5:	Vaccine introduction costs per capita cannot be less than the manufacturing cost per dose and must be in line with the cost+ pricing markup above the baseline production cost. The vaccine introduction cost per capita proxy of US$2.14 under assumption 3 is therefore in line with the US$2 desired production cost per dose ceiling under assumption 3 in the cost of production section.

The actual vaccine introduction costs beyond and above this crude estimate will depend on the choice of immunization coverage targets and the scale of the campaigns implemented, the sequence of targeting population cohorts and, ultimately, the final price of the EVD vaccines. They will also depend on choice of purchasing, procurement and delivery partners, as well as buffer stock requirements set by the WHO. For instance, if purchased through the GAVI Alliance and procured through UNICEF SD and standard WHO stock requirements, full vaccine introduction costs could exceed US$38.4m (basic scenario) and US$139.1m (intermediate scenario), following a number of additional cost assumptions:

Table 12: Assumptions used to estimate potential EVD vaccine cost of introduction, including procurement and freight costs.

Additional intro costs	Description
Assumption 1:	Freight (shipment and delivery) costs similar to the Yellow Fever Vaccine that also has particular supply chain requirements: ~25% under basic scenario (based on 2012 actual freight costs for YF vaccines through GAVI/UNICEF SD: 33% Sierra Leone; 22% Liberia; 19% Guinea). ~23% under intermediate scenario (in addition to the three endemic countries, also based on 2012 actual freight costs for YF vaccine through GAVI / UNICEF SD for Guinea-Bissau (35%) and Mali (25%); based on 2012 lowest actual freight cost of 13% for YF vaccine through GAVI / UNICEF SD in the case of Senegal and Cote D'Ivoire).
Assumption 2:	Cost of safety boxes and syringes 5% (based on ceiling set by GAVI in vaccine co-financing requirements for low income countries).
Assumption 3:	Wastage rate of 10%.
Assumption 4:	Buffer stock requirement 25% (based on WHO minimum stock requirement for routine vaccines in GAVI countries).
Assumption 5:	Procurement services fee 4% (based on UNICEF SD average procurement service charges).
Assumption 6:	Procurement buffer 10% (based on UNICEF SD's standard financial security requirement).

epidemic in Burkina Faso, targeting 4 million people and costing US$3.5m (based on direct costs only, i.e. average cost per dose and purchase cost, excluding shipment and delivery costs).

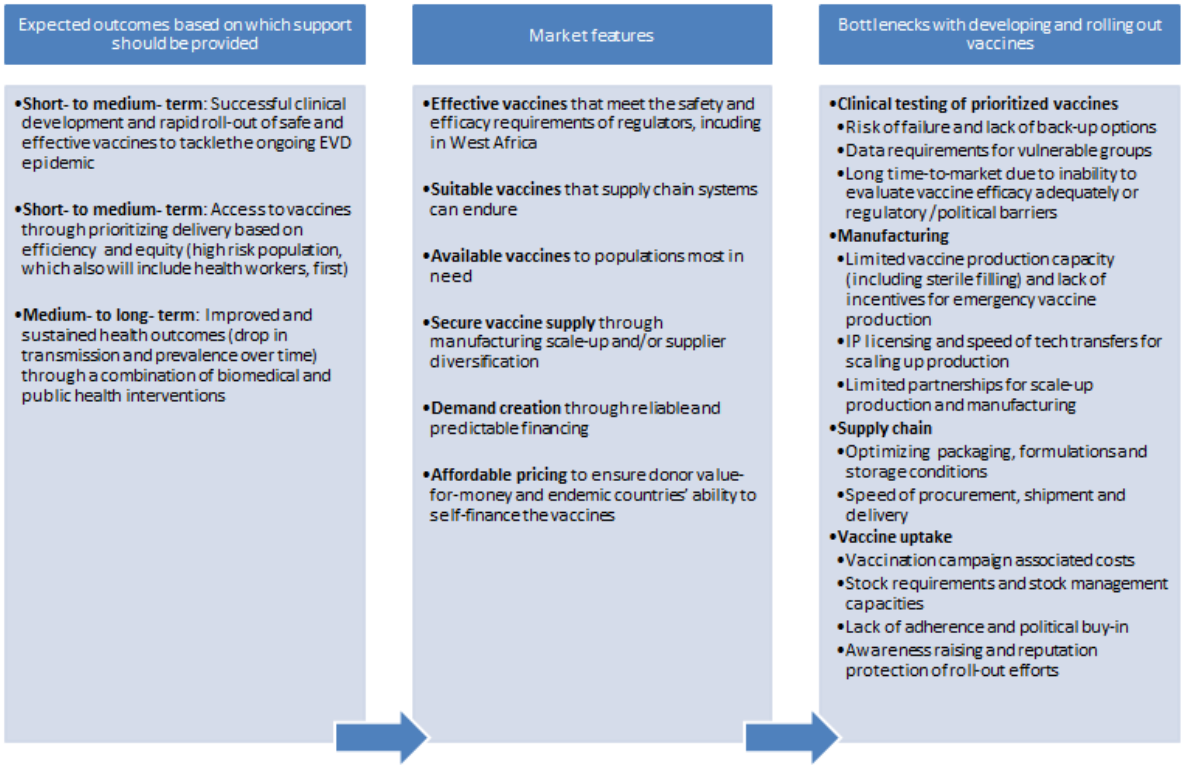
[xvi] Cost of introduction estimates for a country of 12 million ranged from US$12.1m to US$15.1m, based on direct costs only, i.e. average cost per dose and purchase cost, excluding shipment and delivery costs.

Financing requirements for the production and introduction of EVD vaccines

Based on the above estimates of market size, vaccine production and vaccine introduction, and taking into account all assumptions previously laid out, the total financing requirements for EVD vaccine production and immunization efforts should exceed ~US$ 41.4 – 58.4m (basic scenario)[xvii] and ~US$ 152.6 – 213.1m (intermediate scenario)[xviii].

Shaping the space of financing EVD vaccine production and immunization requires a definition of expected outcomes, based on which support should be provided; a specification of the market features financing efforts aim to secure; and an identification of bottlenecks with developing and rolling out the EVD vaccines. In alignment with analyses and key messages in previous and consequent sections of the report, figure 2 summarizes these requirements:

Figure 2: Expected outcomes, market features, and bottlenecks shaping EVD vaccine production and vaccination campaign financing requirements.



Direct funding to industry for manufacturing and pooled funding to a multilateral vaccine purchasing agency might appear to be the fastest and most cost-efficient solution, given the urgency of developing and rolling out EVD vaccines in a hurry. However, direct funding should depend on the level of availability and transparency of data provided by industry on manufacturing costs, and the final price manufacturers will set for their products. In the absence of a diversified supplier based in the short term, such transparency might be difficult to achieve, in which case the consideration of other financing mechanisms will be important, such as advance market commitments at the international level or bulk purchases according to a tiered pricing scheme at the national level.

[xvii] Low end: US$20m (production) + US$21.4m (introduction direct costs only); High end: US$20m (production) + US$38.4m (introduction costs including procurement and freight)
[xviii] Low end: US$74m (production) + US$78.6m (introduction direct costs only); High end: US$74m (production) + US$139.1m (introduction costs including procurement and freight)

Gap analysis and proposed initiatives for vaccine-based EVD interventions

Indication of gaps

Previous sections have demonstrated evidence and challenges around EVD vaccine candidates and their clinical development status, estimates of doses needed, bottlenecks in mass production and distribution, cost estimates and financing requirements for manufacturing and vaccination campaigns. The gap analysis hence focuses on further studies required for regulatory approval of a vaccine for use in the entire population, as well as activities not covered by ongoing partners. Potential gaps in the international response for development and implementation of a vaccine against EVD are summarised in Table 13.

Table 13: Gaps identified for vaccine-based EVD interventions

Topic for gap analysis	Gaps identified
Pre-clinical development and pilot GMP production of promising vaccine candiates	Long-term strategy for encouraging development of affordable vaccine candidates seemingly suitable for mass vaccination in regions at risk for EVD.
Clinical trials	Effect of booster doses and different prime-boost vaccine vectors Immunogenicity and safety in vulnerable population groups: -Children -Pregnant women -Patients diagnosed with TB and/or HIV infection Post vaccination pharmacovigilance surveillance (safety of rVSV) Lot to lot comparison of immunogenicity Involvement of all three most affected countries in trials
Large scale GMP vaccine production sufficient for early epidemic control	Vaccination of the at risk general population in the 3 most affected countries transalates to a need of >10 million doses of vaccine. Once clinical phase II/III trials deem either of the vaccines to be safe and effective, the demand for vaccine will likely be high; depending on the epidemic setting. Production of vaccine doses required for mass vaccination is not synchronized with phase II clinical trial results. Filling capacity of rVSV viral vector vaccine appears inadequate.
Distribution of vaccines	Plan and consortium for ensuring super-cold-chain in place in the three countries New formulations of vaccines which will endure higher temperatures
Market mechanisms	Vaccine production / immunization costs and financing requirements - purchase arrangements and market shaping strategies
WHO coordination	Following severe budget challenges, the WHO has now reduced capacity to maintain the role intended for this international public health emergency.

Relevant Norwegian assets and competences

Norway has financial resources, research assets, manufacturing competence, policy and coordination experience. It can contribute to a vaccine-driven control of the EVD epidemic, and add value to the sustainable development of related biopharmaceuticals, where there is a growing global market space.

In terms of financing, the Norwegian government has invested heavily in global health research over the last 10 to 15 years, both in Norway and in Low and Middle Income Countries (LMICs). This is compounded by a long tradition of contributing to the global financing of vaccines and vaccination. Norway is in a strong position today to ensure consistency and a natural follow-up of its past financing efforts in R&D, purchase and distribution of vaccines.

In terms of research, several research groups and institutes have gained experience in running large clinical studies and field trials in LMICs, in collaboration with LMIC institutions, and there are some centres which have undertaken phase I and phase II vaccine trials in Norway[44]. A handful of research groups have also developed expertise in viral or cancer vaccine research.

In terms of manufacturing, as a detailed presentation of NIPH competencies in production demonstrated previously, Norway has the competence to contribute to stability testing and improved formulations, diminishing requirements for cold chain standards, and, in case of global emergency, global vaccine production and filling bottlenecks[xix]. In recognition of these assets, the WHO has directed a capacity request to NIPH for in vitro stability testing.

In terms of policy and coordination, Norway has a record of commitment to the WHO and affiliated entities (e.g. GAVI Alliance). In the current EVD epidemic, NIPH has engaged in consultations coordinated by the WHO, supporting WHO's coordination and seconding one of its experts to the WHO. The WHO has invited the NIPH in a working group to coordinate vaccine trial efforts in Guinea[xx].

Table 14: Alternative clinical trials for EVD vaccines in Guinea

Alternative 1: The Guinea Frontlinen Worker Study	Alternative 2: The Guinea Ring Vaccination Trial	Alternative 3: The Guinea Booster Trial
➢ Healthcare workers, burial teams, community surveillance teams and other frontline workers in MSF treatment centers in Guinea (Conakry, Guéckédou and Macenta Transit Centre) ➢ N = 1000 ➢ Single-arm cohort design with historical controls. Offering of at least one vaccine (ChAd3-EBO-Z and/or rVSV) at each treatment center ➢ Outcome: Incidence of EVD, safety	➢ All primary contacts to confirmed EVD cases living in the catchment areas to Conakry, Guéckédou and Macenta Transit Centre identified by surveillance teams. ➢ Ringvaccination (vaccine type not defined) ➢ N = 600 index cases ➢ Outcome: incidence of EVD, safety	➢ Healthy volunteers > 17 yrs old at nursing and teaching training colleges in Conakry. ➢ N = 80 ➢ Three-armed, randomized controlled trial (ChAd3-EBO-Z vs rVSV vs ChAd3-EBO-Z+rVSV) ➢ Outcome: Immune responses, safety for both prime and boost vaccination

[xix] If the worst case scenario of EVD cases is realized (500 000-1.4M cases by end of January 2015) - whereby global access to vaccine doses will become extremely limited - it is vital to ensure that the most affected areas in West Africa will be prioritised. Ensuring access to a vaccine for healthcare workers, independent of nationality, will most likely be a main rationale for distribution. Having a manufacturing facility capable of bulk manufacture and final fill of up to 150 000 ten-dose vials per month would be a highly valuable asset, under such a severe case scenario.

[xx] Following the decision taken by the participants at the October 23 2014 high-level meeting on EVD vaccine Access and Financing, the WHO Director-General, Dr Margaret Chan, invited to a teleconference on Tuesday 28 October. Dr Kader Konde, Chairman of Guinea Ebola Research Commission, Executive Director, Center of Diseases Research in Guinea, proposed three alternative clinical trials for EVD vaccines in Guinea presented in table 14 of the report.

Proposed initiatives to be supported by the Norwegian government

Based on our gap analysis and assessment of Norwegian assets and competences, we propose that the Norwegian government supports the following initiatives:

Table 15: Proposals and rationale for initiatives to be taken by the Norwegian government.

No	Proposal	Rationale
1	Support clinical vaccine trials in Guinea or neighboring West African countries with ChAd3-EBO-Z and rVSV vaccines, including among children and immunosuppressed individuals	Ensure early access to vaccines in Guinea in addition to Liberia and Sierra Leone where studies are already planned. Explore booster effects
2	Strengthen the capability of the WHO Geneva to ensure timely and clear coordination of clinical trials, regulatory approval, mass production and distribution	Support licensing and approval processes Avoid duplication of efforts Ensure participation of West-African countries Secondment of a Norwegian vaccine development expert to strengthen WHO's capacities.
3	Contribute to ongoing pharmaceutical development of EVD vaccines by assisting in formulation studies enabling scale up for mass production and field-compatible vaccine distribution	Assist in faster and more suitable formulations than delivery at minus 80°C Assist in making as many doses as needed available as early as possible Assist in stability testing
4	Assess the global manufacturing capacity for the rVSV vral vector vaccine when dose requirements are established after phase I studies, and consider establishing time limited production of the rVSV viral vector vaccine at the NIPH BSL-2 GMP facility if other options are not more cost-effective.	At the current point in time it is not clear whether there is a need to strengthen VSV manufacturing capacities, but this should be revisited when dose requirements are assessed after phase I.
5	Assist in the development, investment and logistical requirement for setting up an appropriate super-cold-chain in Guinea	Assist West African countries and the WHO in enabling mass vaccinations
6	Support in-depth vaccine production and immunization cost studies to guide vaccine pricing and immunization financing decisions, ensuring value for money to donors and affordable access to LMICs	Ensure transparent and evidence-based costing and financing of the production of the prioritied EVD vaccines. If the cost is too high, the benefit potential in the long term will not be realized, as prices will exceed affordability thresholds by endemic countries.
7	Contribute to establishing WHO-coordinated procurement mechanims for EVD vaccines through GAVI or the WB and in agreement with WHO	Ensure the most cost effective use of public funds
8	Initiate GLOBVAC/NRC research programme on enhancing vaccine research for infectious diseases with low-probability but severe public health consequences	Encourage research on vaccines for diseases where there is no immediate commercial market, but which have a high negative health and security impact if spreading
9	Establish a sustainable international mechanism for the development of vaccines and medicines for infections such as EVD, where there are insufficient commercial markets	Identify ongoing processes (e.g. the Global Research Collaboration for Infectious Disease Preparedness) and best practices from collaborative initiatives (e.g. partnerships for neglected diseases). Mobilize resources to set up the system, building on lessons learnt from related processes

Potential benefits of proposed initiatives

The proposed initiatives confer benefits both on short term and longer term perspectives.

In the short term, Norwegian initiatives will accelerate EVD vaccine development efforts, ensuring lives saved and added value to the international emergency response to mitigate the ongoing EVD epidemic. Specifically, the proposed initiatives will:

- Contribute to a faster clinical development pathway to document safety and immunogenicity of either ChAd3-EBO-Z or rVSV vaccines among citizens of West Africa.
- Save lives by improving access to these vaccines through contributions to mass production and distribution, given that these vaccines prove safe and effective in clinical trials.
- Contribute to international emergency response to contain or mitigate the ongoing EVD epidemic.

In the longer term, Norwegian initiatives can improve global health preparedness capabilities, by sustaining product development efforts against EVD, ensuring greater health security and improved access to affordable and suitable EVD biopharmaceuticals for LMICs.

Financing requirements for proposed initiatives

Approximately NOK 100m will be required for the proposed Norwegian initiatives. Table 16 provides a budget breakdown by proposed initiative.

Table 16: Funding requirements for proposed initiatives

No	Cost breakdown per proposed initiative	Budget estimate per proposed initiative
1	**Support clinical vaccine trials in Guinea or neighboring West African countries**	**NOK 20m-40m**
	Fixed cost (equipment and consumables; labor; administrative overheads)	*NOK 12m - 24m*
	Semi-fixed cost (per MSF treatment centres and catchment areas)	*NOK 5m - 10m*
	Variable cost (per clinical trial cohort design arm)	*NOK 3m - 6m*
2	**Strengthen WHO to coordinate clinical trials, reg approval, production, distribution**	**NOK 1m -5m per year**
	Seconded Researcher Annual Full-Time-Equivalent (FTE) (1 to 3 persons of variable seniority levels)	*NOK 0.8m - 4.5m per year*
	Variable costs (1 to 3 travels per month)	*NOK 0.2m - 0.5m per year*
3	**Formulation and stability studies for production and field-compatible distribution**	**NOK 2m**
	Formulation testing at -80C	*NOK 0.5m*
	Dose manufacturing	*NOK 1m*
	Stability testing	*NOK 0.5m*
4	**Assess manufacturing capacity for rVSV and consider production at NIPH**	**NOK 7m -10m (TBC)**
	Fixed cost (facility and equipment; labor; factory overheads; administrative overheads)	*NOK 4.2m - 6m*
	Semi fixed (per batch) cost	*NOK 1.75m - 2.5m*
	Variable cost (raw materials, vials, packaging)	*NOK 1.05m - 1.5m*
5	**Support setup of appropriate super-cold-chain in Guinea**	**To Be Confirmed (TBC)**
	Assist West African countries and the WHO in enabling mass vaccinations (More details needed depending on stability studies for ChAd3-EBO-Z and rVSV)	*TBC*
6	**Contribute to establishing -coordinated procurement mechanims for EVD vaccines**	**3 MNOK**
	Fixed fees-for-services in FTEs (technical advisory, policy analysis, administrative support and coordination)	*NOK 1.2m - 2.4m*
	Variable costs (1 to 4 travels)	*NOK 0.2m - 0.6m*

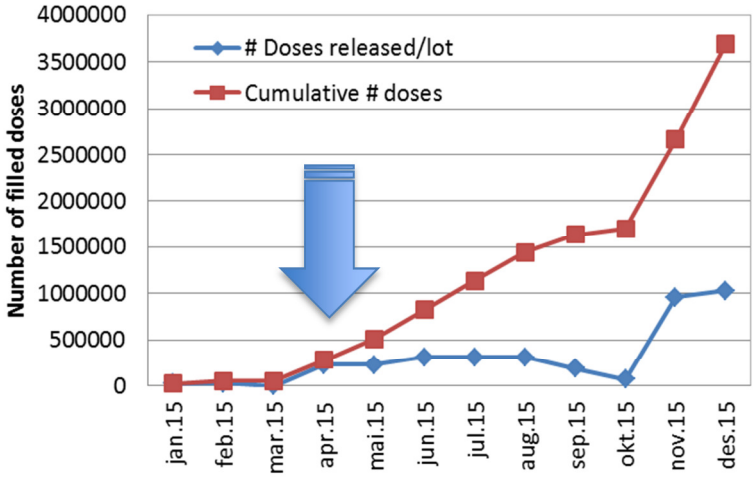
No	Cost breakdown per proposed initiative	Budget estimate per proposed initiative
7	**Vaccine production/immunization cost studies to guide pricing & financing decisions**	**NOK 1.5m – 2m**
	Research design (selection of most appropriate industrial methodology for production cost estimates; demand forecast modelling; vaccine introduction cost modelling) and write-up of findings and publication	*NOK 0.3m - 0.5m*
	Data collection and analysis (interviews, database mining, literature review)	*NOK 1.1m – 1.5m*
8	**Initiate GLOBVAC/Norwegian Research Council related research programme**	**NOK 30m**
	Grants to programme beneficiaries	*NOK 29m*
	Programme management	*NOK 1m*
9	**Establish a sustainable international mechanism for the development of vaccines and medicines for infections such as EVD**	**NOK 3m**
	Fees for expert consultations	*NOK 1.2m - 2.4m*
	Variable costs (travels, meetings, conference in Oslo)	*NOK 0.2m - 0.6m*

Risk assessment of proposed initiatives

Risks associated with not supporting initiatives in regard to vaccine development

It is relevant in preparedness planning to also consider the risk of not doing any interventions. If one of the two vaccine candidates rVSV or ChAd3-EBO-Z are demonstrated to be safe and effective in the phase IIb/III studies in Liberia and Sierra Leone, the earliest this would be known is around March-April 2015. The timeline of number of doses available of the ChAd3-EBO-Z vaccine is shown in Figure 3 alongside this go-no-go decision timepoint. The number of vaccine doses that would be needed at this time is dependent on the vaccination strategy, however access for the general population will soon become an expectation (>~10 million doses needed) and there will likely be a significant time gap before this need will be met.

Figure 3: Time gap from potential licensure for mass vaccination and until significant ramping up of production capacity[xxi].



[xxi] Projected capacity to produce and release doses for clinical use of the ChAd3-EBO-Z vaccine grom GSK/NIH (number of doses released per month). The arrow indicates earliest possible timepoint that vaccine may be deemed safe and effective in prevention of EVD, on the basis of phase II/III trials.

The main risks associated with the proposed initiatives are presented below, however in the immediate term most of these are mainly related to clinical trials in Guinea and the lack of available doses of EVD vaccine.

Risks associated with manufacturing vaccines at NIPH facility

The major risks associated with setting up the manufacturing process for the rVSV vaccine are as follows, assuming IP issues are solved in advance:

- Process scale up takes longer time than anticipated
- Doses are not completed in time to a make significant impact since other manufacturing facilitates may have covered the needs.
- Phase I/II trials shows vaccine is not safe and/or effective, and vaccine cannot be used or implemented

These risks will have to be balanced against the underlying preparedness scenarios used; either based on the worst case or best case scenarios.

Risks associated with performing clinical trials in Guinea

Health systems performance

Prior to the 2014 EVD outbreak, Guinea allocated 6.3% of GDP for healthcare. The number of physicians or nurses per 10 000 inhabitants were 1 and < 0.5, respectively (www.who.int/country/gin/en). Since the Ebola outbreak, the fear of contracting EVD has kept several of the national healthcare workers from going to work. A large trial will need human resources and these will have to be recruited from already existing personnel. This could be a potential challenge regarding treatment of EVD patients as well as patients with other illnesses (e.g. malaria)

Malnutrition is a serious problem, with a 2012 study reporting rates of chronic malnutrition ranging from 34% to 40% depending on region. The EVD epidemic has made food supplies even scarcer and 70% of the population lives in absolute poverty (less than $1 per day). 1.4-2.0% of the population between 15-49 years is HIV positive and only 50% of them receive antiretroviral therapy. The incidence of tuberculosis is 150-200/100 000 inhabitants and 23% of them are also HIV positive (www.who.int/country/gin/en). This is a concern for immune responses to both vaccine candidates. For the rVSV candidate there is also a safety concern, since the vaccine consists of replicating virus and may infect immunocompromised patients. The replicating ability of the rVSV candidate also causes concern regarding the potential to infect cattle, since the vesicular stomatitis viral disease is common in cattle. In addition, fever is a common side effect in other replicating viral vaccines, which is a disadvantage in the current situation in West Africa where fever also can be the first sign of EVD, malaria or other infectious diseases. Healthcare workers with vaccine induced fever will be forced into quarantine.

The WHO-UNICEF estimates the vaccination coverage of the National Immunization Schedule to be 62-76%[45]. There is some uncertainty as to wether this is due to the weak healthcare and infrastructure, vaccine sceptizism or both. Before the Ebola outbreak, Guineans had little faith in national healthcare in general. This has not improved in the current epidemic. The skepticism towards the existence of EVD is high. Civil unrest is a major concern, especially

when vaccination occurs in the general population.The lack of a cure for the disease, and the high mortality in the treatment centers, make people afraid of seeking help. This could be a potential problem for a clinical trial.

Introduction of a new vaccine, especially one not extensively tested in humans, is a major challenge both concerning the attitude towards the Ebola vaccine candidates, but also for the maintenance of the already implemented immunization schedules. In addition, the litteracy rate among adults over 15 years of age is only 18% in women and 43% in men (www.who.int/country/gin/en), making proper information around the safety and efficacy of the vaccine candidates as well as the studies crucial.

General infrastructure and relevance for clinical trials

Approximately 35% of the population in Guinea lives in urban areas (WHO country profile). Poor road infrastructure has made many communities outside of the capital inaccessible[46]. The railway from Conakry to Kankan ceased operating in the mid-1980s, and domestic air services are intermittent. There is some river traffic on the Niger and Milo rivers. Horses and donkeys pull carts, primarily to transport construction materials. Despite the opening in 2005 of a new road connecting Guinea and Mali, most major roadways remain in poor repair. Electricity may be unreliable and there is an increased need for alternative power sources such as diesel aggregates.

Monitoring of possible trial candidates in rural areas can therefore be demanding. Trials conducted in the MSF treatment centers will be easier. Vaccine distribution is challenging, especially considering the cold-chain issues discussed in earlier sections.

Anticipated challenges

The suggested clinical trials in Guinea would likely confer challenges as listed in Table 17. These can in part be mitigated by utilising all existing research infrastructure and selecting the best national partners, capacity building of local staff and by ensuring that sufficient staff with GCP experience participates on-site from a country with experience.

Table 17: Anticipated challenges with clinical trials in Guinea

Challenge	Challenge - related issues
MSF capacity to run clinical trial in addition to regular work (Only for study 1+2)	➢ Vaccination ➢ Blood samples ➢ Clinical assessment of possible side-effects or symptoms of disease ➢ Quaranteene of HCW who get a fever within 24 days following vaccination (only for study 1)
Logistics	➢ Transportation of vaccines into Guinea ➢ Storage of vaccines at arrival[xxii] ➢ Distribution to MSF centers
Ethical approval hurdles	➢ Ethical approval by the National Ethics Committee in the Republic of Guinea
Information flows	➢ Distribution of information on vaccines, trials, follow-up and possible disadvantages
Motivation issues	➢ International and national HCW and civilian motivation for vaccination and follow-up
National capacity to run clinical trial	➢ Capacity to conduct vaccination of civilians in both rural and urban areas ➢ Collect and analyze blood samples of study participants ➢ Clinical assessment of possible side-effects or symptoms of disease
Value of data	➢ Potential confounding issues for data generated in The Guinea Ring Vaccination Trial

[xxii] Both the vaccine candidates in the proposed studies in Guinea will need to be stored in -80°C freezers and transported on dry ice. After thawing, the vaccine will need to be stored at 4°C and used within 12-18 hours. The availability of dry-ice is very limited in Guinea, and the climate is unfavorable for vaccine handling. According to MSF, purchase and installation of -80° freezers is not possible at a large scale, but -20° is feasible. Temperature conditions need to be negotiated with manufacturer.

Conclusions

The current report has provided information on the following EVD-vaccine related topics:

- Available vaccine candidates and their clinical development status
- Assessment of doses required for prevention and control of the ongoing EVD epidemic, and expected challenges for mass vaccination campaigns
- Assessment of global vaccine production capacities for ChAd3-EBO-Z and rVSV vaccines
- Description of relevant assets and research competence available in Norway
- Evaluation of the vaccine market mechanisms and preliminary estimates of costs and funding requirements beyond mass vaccination and control of the 2014 epidemic
- Gap analysis and proposal for initiatives to be taken by Norway
- Risks associated with performing clinical trials in Guinea during the EVD epidemic
- Need to contribute to strengthen local capacity in vaccine testing, vaccination rollout and disease control

We conclude that the Norwegian government should consider the following initiatives:

- Support clinical vaccine trials in Guinea or neighboring West African countries with chAd3 and rVSV vaccines, while ensuring that local capacity to undertake such trials is strengtened
- Strengthen the cability of the WHO Geneva office to ensure timely and clear coordination of clinical trials, regulatory approval, mass production and distribution
- Contribute to ongoing pharmaceutical development of EVD vaccines through formulation studies enabling scale up for mass production and field-compatible vaccine distribution
- Assess the global manufacturing capacity for the rVSV vral vector vaccine when dose requirements are established after phase I studies, and consider establishing time limited production of the rVSV viral vector vaccine at the NIPH BSL-2 GMP facility if other options are not more cost-effective.
- Financially and technically support the development and logistical setup of an appropriate super-cold-chain in Guinea
- Contribute to establishing coordinated procurement mechanims for EVD vaccines
- Support in-depth vaccine production and immunization cost studies to guide vaccine pricing and immunization financing decisions, ensuring value for money to donors and affordable access to LMICs.
- Initiate research programme focussing on enhancing vaccine research for infectious diseases with low-probability but severe public health consequences
- Establish a sustainable international mechanism for the development of vaccines and medicines for infections such as EVD, where there are insufficient commercial markets

The cost of the proposed initiatives would amount to a total of approximately 100 MNOK.

Annex 1: Mandate from the Norwegian Ministry of Health

DET KONGELIGE
HELSE- OG OMSORGSDEPARTEMENT

Nasjonalt folkehelseinstitutt
Postboks 4404 Nydalen
0403 OSLO

Deres ref	Vår ref	Dato
	13/2803-	14.10.2014

Vurdering av mulige norske bidrag til vaksine-basert bekjempelse av Ebola-epidemien – oppdrag til Folkehelseinstituttet

Epidemien av Ebola-sykdom i Vest-Afrika har per 10. Oktober 2014 forårsaket over 4000 dødsfall. Antallet tilfeller har økt tilnærmet eksponentielt i de siste to månedene, og tiltak for å stoppe epidemien har til nå fokusert mest på tradisjonelt smittevern som tidlig identifikasjon [redacted] vaksiner bør derfor intensiveres parallelt med at tradisjonelle smitteverntiltak implementeres i stor skala. En effektiv vaksine vil være et avgjørende bidrag dersom denne blir bredt tilgjengelig tidlig nok. Det finnes ingen tilgjengelig godkjent vaksine mot Ebola, men det er flere kandidater som er under utvikling.

Folkehelseinstituttet bes innen 1. november 2014 om å:

- Beskrive ulike prinsipper for Ebola-vaksiner
- Beskrive status for ulike vaksinekandidater, herunder hvilke kliniske utprøvinger som er i gang eller som er finansiert
- Vurdere og beskrive behov for ytterligere kliniske studier
- Gi et estimat på antall doser, produksjonsskala og tidsscenario for at en vaksineleveranse skal kunne påvirke utvikling av epidemien
- Beskrive global produksjonskapasitet for vaksinene som er i fase I utprøvning og hva som er flaskehalser for å oppskalere produksjonen
- Ta stilling til hvilke initiativ Norge bør ta eller støtte opp om for at en effektiv vaksine skal bli bredt tilgjengelig innen kortest mulig tid
- Gi en vurdering av sannsynlighet og konsekvenser for de ulike risikoer som finnes

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Saksbehandler
Sverre Berg Isaksen
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innen hvert av de foreslåtte initiativ, samt hvordan disse kan møtes.

- Beskrive hvilke forutsetninger Norge bør legge inn med tanke på rettferdig fordeling av vaksiner (forebygge flest mulig tilfeller)
- Ha dialog med relevante norske fagmiljø og aktører som er relevant for utvikling, utprøvning og regulatorisk godkjenning av vaksiner, samt distribusjon til kliniske forsøk og oppskalering av vaksineproduksjon
- Ha dialog med WHO, internasjonale forskningsgrupper med relevant vaksinekompetanse, samt legemiddelindustri

Folkehelseinstituttet bør basere sitt arbeid på konklusjonene fra WHO sitt ekspertmøte 29.-30-9.2014. I dette møtet ble det vurdert hvilke tiltak som pågår for å evaluere og produsere sikre og effektive vaksiner mot Ebola så raskt som mulig. Møtet konkluderte med at det er mulig å [redacted] utviklingsløpet. Dersom disse og andre viser at en eller flere vaksiner er sikre og i stand til å indusere antistoff mot Ebola-virusets glykoprotein, vil det være behov for større beskyttelsesstudier. Dersom disse viser at vaksine(r) er effektiv(e), vil det være ønskelig å masseprodusere og implementere vaksinen(e) i affiserte regioner.

Dersom Norge skal iverksette tiltak for å bidra til denne utviklingen er det vesentlig å ha god kunnskap om hvilke vaksinekandidater og prinsipp som finnes tilgjengelig og kapasitet til utvikling og produksjon.

Med vennlig hilsen

Elin Anglevik (e.f.)
avdelingsdirektør

for Sverre Berg Lutnæs
seniorrådgiver

Annex 2: Overview of members in the evaluation group

Name	Position, background	Department, institution
John-Arne Røttingen	Division Director, MD PhD, Professor	Division for Infectious Disease Control, NIPH
Gunnstein Norheim	Scientist, MSc Pharm PhD	Department for bacteriology and immunology, Division for Infectious Disease Control, NIPH
Kristin M. Schoultz	Department director	Department for biomanufacturing, Division for Infectious Disease Control, NIPH
Fredrik Oftung	Senior scientist, cellular immunology	Department for bacteriology and immunology, Division for Infectious Disease Control, NIPH
Berit Sofie Wiklund	MSc Pharm, vaccine procurement and distribution	Department of vaccine, Division for Infectious Disease Control, NIPH
Dimitrios Gouglas	Adviser, global health access and innovations	Department for international public health, NIPH
Sara Watle	Paediatrician, vaccine programme	Department of vaccine, Division for Infectious Disease Control, NIPH
Eirik Bakka	MSc Pharm, preparedness	Norwegian Directorate for Health
Halvor Sommerfelt	Professor, MD, clinical vaccine trials	Secondary position at Division for Infectious Disease Control, NIPH. Main affiliation at the Centre for Intervention Science in Maternal and Child Health (CISMAC) at the University of Bergen

Acknowledgements
We appreciate valuable input and feedback from Hanne Nøkleby (NIPH), Lisbeth M. Næss (NIPH), Svein Rune Andersen (Norwegian Medicines Agency), and Klaus Bryn as well as external lecturers and participants at the open scientific meeting on October 27th in preparation of in this report.

Annex 3: Summary of Oct. 27th Ebola vaccine seminar and key feedback

Title: «Vurdering av mulige norske bidrag til vaksine-basert bekjempelse av Ebola-epidemien» [English title: «Assessment of potential Norwegian contributions to vaccine-based mitigation of the Ebola epidemic»]

Venue: Lovisenberg Hospital, Oslo, 27 October 2014

Speakers: John-Arne Røttingen, NIPH; Svein Rune Andersen, NoMA; Fredrik Oftung, NIPH; Sara Watle, NIPH; Berit S. Wiklund, NIPH; Kristin Schoultz, NIPH; Birger Sørensen; Agnete Fredriksen, Vaccibody; Dimitrios Gouglas, NIPH; Ripley Ballou, GSK.

Panel discussion: Gunnstein Norheim, NIPH; Sissel Overvoll, MSF; Karianne Johansen, LMI; Svein Rune Andersen, NoMA; Eirik Rødseth Bakka (chair), Norwegian Directorate of Health

Responses to proposals for Norwegian contributions

General response

- WHO leadership and coordination is essential.
- Strengthening of health care systems is the most important measure at this stage, and vaccine development should not remove focus from infection control measures that are already available.

Response to vaccine candidates

- All vaccine candidates, both first line and back-up is based on the same technology, e.g. viral vector platforms. This constitutes a risk.
- Norway should prioritise the two vaccine candidates that have reached a developmental stage that enables an actual effect on the ongoing epidemic. As should international efforts organised by WHO.
- Spending resources on preclinical development of Norwegian projects should not be prioritised. There is no shortage of vaccine candidates and a potential Norwegian vaccine will come too late.
- The potential Norwegian vaccine platforms presented are unlikely to be completed in time to provide any real contributions to the ongoing epidemic. Pre-clinical development through NFR-GLOBVAC financing is a more viable basis for future epidemics.
- Response to clinical trial proposals
- Norway should support clinical trials. It is important that all studies are coordinated by WHO to provide a supplement to comparative studies and stability studies from vaccine manufacturers.
- Norway should support phase II studies, but phase II studies with vaccines stored at -20°C and 2-8°C could be unnecessary and a potential waste of available time and vaccines. Stability issues should be investigated in stability tests focusing primarily on quality control, or potentially in animal trials.
- Further pre-clinical trials for the two main vaccine candidates should not be prioritised. Sufficient pre-clinical data is probably already generated as the vaccines are entering

clinical trials. Other aspects of pre-clinical trials which are prerequisites for marketing authorisations are likely to be initiated by the patent holders.

Response to manufacturing proposals

- It is important that NIPH is able to document necessary capacity for GMP scale-up, and especially whether a shift from fish vaccines to human vaccines is plausible. If NIPH filling capacity is limited this should be emphasised.
- If vaccine production at NIPH is a realistic opportunity, this could be of use. However, this must be compared to the value of spending resources on other measures.
- Response to proposals on logistical support
- The demand for a -80°C logistical capacity will depend on whether the vaccine can be stabilised at higher temperatures. Nevertheless, the preliminary clinical trials will require such capacity.
- The main issues regarding storage conditions are whether long term storage can be done at -20°C rather than -80°C, and whether short term storage can be done at 2-8°C rather than -20°C.

Feedback on other projects to support

- Pharmacovigilance in mass vaccination is a challenge. There is a demand for an evaluation of whether the affected countries have adequate capacity for pharmacovigilance surveillance.
- International cooperation between vaccine manufacturers to provide technology transfer, ensuring rapid and effective vaccine production. Cooperation can be established as a network of technical experts from the various vaccine manufacturers.
- Build on established R&D networks and consortia, such as IMI, to enable public-private partnerships.

Annex 4: Proposals for early stage preclinical vaccine or adjuvant concepts

The following unsolicited proposals for pre-clinical or clinical research related to the mandate received from the Ministry of Health on October 14th 2014 were submitted to the NIPH.

Date received	Concept	Contact
15.10.2014	Polypeptide-based vaccines	Birger Sørensen
24.10.2014	Recombinant proteins	Bjarne Bogen, University of Oslo
29.10.2014	Betaglucan as adjuvant and immunostimulant	Jan Raa

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