SCIENTIFIC COLLOQUIUM

on heterologous prime-boost vaccination

SUMMARY REPORT

29 SEPTEMBER 2017
FACULTY CLUB UNIVERSITY OF LEUVEN • BELGIUM
Preface

Infectious diseases, like Malaria, tuberculosis and HIV, continue to be a leading cause of death among humans, especially in developing countries. Current vaccination approaches have failed against these pathogens mainly due to their inability to induce effective immune responses.

Heterologous prime-boost vaccines could be an avenue to tackling infectious diseases where protection and/or longer-lasting immunity has not been successfully achieved with other approaches. However, while promising with respect to addressing unmet medical needs, heterologous prime-boost, like most novel medical tools, is accompanied by manufacturing, regulatory, logistical and deployment challenges.

Colloquium concept and programme

In order to establish policy pathways for the successful development and implementation of heterologous prime-boost strategies, general consensus about the potential medical benefits of such strategies is urgently needed. To that end, the One Health Platform brought together some 80 academics, public health professionals, industry and regulatory agency officials at the first colloquium on heterologous prime-boost vaccination in Leuven, Belgium, on 29 September 2017. This event came very timely as it is envisaged that the first heterologous prime-boost vaccine will become available in the very near future.

An international panel of scientific experts from different disciplines and backgrounds provided the latest scientific insights and advances, while the colloquium programme was designed in such a way as to maximize the exchange of ideas and to foster audience participation.
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Theoretical basis and need of heterologous prime-boost vaccination

David Masopust, Professor at the Department of Microbiology and Immunology of the University of Minnesota, provided the theoretical basis of heterologous prime-boost vaccination from the perspective of a basic T-cell immunologist. T cells are attractive candidates against so far intractable infections like malaria, TB, and even HIV, which have not yielded to humoral-based vaccination approaches.

Employing T cells in the context of an HIV vaccine has raised enthusiasm, in large part because of the difficulty to raise broadly neutralizing antibodies against HIV and because CD8 T cells recognize more conserved epitopes and can control infection once established. This led to the STEP trial with homologous prime-boost vaccination with what was considered a good T cell vaccine, on the basis of the magnitude of the memory T cell population in the blood of the vaccinees. However, the results were highly disappointing, with no efficacy signal.

Dr. Masopust asked the audience the crucial question: “Is this a failure of concept or is this a failure of execution?” He continues: “What is the definition of good when it comes to magnitude?”

David Masopust

“For a T cell vaccine to achieve rapid recognition and rapid control, magnitude (or efficiency of surveillance) matters, as does T cell quality and anatomic location.”

“For a T cell vaccine to achieve rapid recognition and rapid control, magnitude (or efficiency of surveillance) matters, as does T cell quality and anatomic location.”

David Masopust

Dr. Masopust reminded the audience that upon a homologous boost to a vaccine inducing good humoral and good T cell immunity, including neutralizing antibodies against the vector used in the vaccine, the humoral response can essentially block antigen presentation to the T cells. With heterologous prime-boost vaccination, the antigens seen by the T cells are packaged into a vector with different outer-surface determinants, serologically distinct from the priming vector. Abundant presentation of the antigens to the pre-existing memory T cells can occur, leading to a robust anamnestic response. Dr. Masopust used results from heterologous prime-boost vaccination studies of mice and macaques to demonstrate the potential of this approach, and provided clear evidence of the synergy that can be seen upon heterologous prime-boost vaccination.

In essence, Dr. Masopust demonstrated that abundant memory CD8 T cell quantity can be achieved through heterologous prime-boost vaccination strategies, with the efficiency of memory generation increased with boosting, and without proliferative or functional senescence. He demonstrated that heterologous prime-boost induces T cell responses that retain qualities of proliferation and differentiation potential, and are present at target locations, concluding that heterologous prime-boost is most probably the best strategy for T cell vaccines to achieve rapid recognition and rapid control of pathogens.

“IT’S DISAPPOINTING THAT IN 2017, WE ARE STILL ASKING WHAT IS THE ADVANTAGE OF HETEROLOGOUS PRIME-BOOST. THE ANSWER IS OBVIOUS: YOU GET MUCH STRONGER ANTIBODY AND T CELL RESPONSES.”

Adrian Hill
After briefly reviewing the range of vaccine designs and approaches that have been used against HIV yet failed to provide effective immune responses, Mathias Kroll, VP, Head of Global Business Development at Bavarian Nordic, reviewed some of the extensively used vectors in the medical and veterinary fields. He mentioned that heterologous prime-boost strategies can combine live vectors, DNA/RNA and recombinant adjuvanted proteins in any combination and order, and can be applied for infectious disease and cancer therapy to allow for a strong (CD8) T cell immune response. Dr. Kroll argues that viral vectors in particular efficiently expand T cell response and affinity, providing a response largely focused on the encoded antigen.

Dr. Kroll focused on the Vaccinia virus, adenovirus and measles virus vectors as key examples demonstrating the pros and cons of heterologous prime-boost vaccination. These offer attractive platforms for the development of heterologous prime-boost-based vaccines due to their relative ease of manipulation and propagation, large insertion capabilities, excellent safety profiles, and induction of good humoral and T cell immune responses. An interesting finding was the asymmetrical impact of the sequence of vaccination on the efficiency of the boost. This had been discussed earlier by the audience and Dr. Masopust, pointing out the critical importance of the choice and order of the priming and boosting vectors for successful heterologous prime-boost strategies.

“If you have a “wimpy-to-strong” vector panoply, I think you want to start “wimpy” but good enough to get a good quality of memory, and then build on that with your strong vector.”

David Masopust

Although some of these vectors are available at large-scale GMP, Dr. Kroll mentioned that the manufacturing of live vectors remains a multi-step complex process, with often challenging QC testing. Furthermore, questions remain regarding the reactogenicity profile of vectors and the impact of the insert thereof, as well as the impact of pre-existing immunity against used vectors.

“The increased cost of heterologous prime-boost can be a drawback in certain settings. After all, heterologous prime-boost entails two different processes for two different products.”

Mathias Kroll

Dr. Kroll concludes that heterologous prime-boost approaches are nonetheless first choice to address pandemic and zoonotic outbreaks based on the flexibility of the system and the fast availability of finished product.
Implementing heterologous prime-boost vaccination in paediatric settings

Katie Ewer, associate professor and senior immunologist at the Jenner Institute, addressed the audience about the Institute’s experience with viral vectors in paedriatic settings, knowing that their experience is exclusively limited to malaria vaccines. Interestingly, Dr. Ewer stated that, while most vaccines that are administered during infancy protect primarily through the induction of antibodies, there are a number of diseases affecting infants where a CD8+ T cell inducing vaccine would likely be very useful, like RSV, HIV, tuberculosis and liver-stage malaria.

The Jenner Institute has been working on the ME-TRAP construction for some 15 years now, which is actually the most advanced liver-stage malaria vaccine candidate in development. In this programme, a heterologous prime-boost approach is taken, with the adenovirus (ChAd63) encoding ME-TRAP used as the priming vector and an MVA expressing the same antigen used as a booster 8 weeks later. In adults, this regimen elicits very potent T cell immunogenicity.

Dr. Ewer: “Because we have been developing this ME-TRAP for so many years now, we have comparative data from lots of different constructs. We started with fowl pox administered in homologous prime-boost, with very limited response. Then we moved to three doses of MVA, which also proved to be very weakly immunogenic. And similarly three doses of DNA. But if we give three doses of DNA and then boost with MVA, we get an increased response. However, with ChAd63 we really see a big leap in the T cell response. And if we boost that with MVA we get a massive expansion.”

This heterologous prime-boost regimen was very well-tolerated in children, babies, infants and neonates in both countries. It induced extremely potent T cell responses, much stronger than expected. Also, high titre, high avidity anti-TRAP IgG responses were seen in response to prime-boost immunization. Interestingly, plenty of new liver-stage candidates are in the pipeline using the same heterologous prime-boost platform.

The ME-TRAP construct’s efficacy against malaria was first tested in UK adults in Oxford, revealing that around 50% of the participants receiving the vaccine regimen have some efficacy against malaria. In Kenya, where people also have pre-existing natural immunity, the efficacy increases further. Dr. Ewer: “We moved on from this phase II trial in Oxford to safety trials in the Gambia and Kenya, both of which showed good safety and immunogenicity. Then we moved to phase I age de-escalation trials in The Gambia and Burkina Faso.”

“COMBINING A LIVER-STAGE PRIME-BOOST WITH A SPOROZOITE-STAGE VLP WOULD LIKELY BE THE WAY FORWARD.”

KATIE EWER

* Reference: Katie Ewer, Sarah Sebastian, Alexandra J. Spencer, Sarah Gilbert, Adrian V. S. Hill & Teresa Lambe (2017): Chimpanzee adenoviral vectors as vaccines for outbreak pathogens, Human Vaccines & Immunotherapeutics, DOI: 10.1080/21645515.2017.1381575
implementing heterologous prime-boost vaccination in resource limited settings

At the start of his talk, Prof. Adrian Hill, director of the Jenner Institute, reminded the audience that many vaccines are already used in prime-boost-like regimens today: DNA-protein, poxvirus-protein, heterologous flu strains, DNA-MVA or NYVAC, fowl pox-MVA, DNA-Ad / ChAd, ChAd-MVA, Ad-MVA, Ad- heterologous Ad and Ad-protein. Dr. Hill: “We focus on ChAd-MVA because we need extraordinarily strong T cell responses to get protection at the liver stage of malaria. You can’t get very high level of protection even with these excellent vectors, so we’re not going to consider any of the weaker approaches.”

Dr. Hill: “IN CONTRAST TO WHAT TEXTBOOKS SAY, INFANTS CAN MAKE VERY GOOD T CELL RESPONSES, EVEN IF YOU VACCINATE THEM AT ONE WEEK OF AGE.”

Adrian Hill

A simple randomized control trial of ME-TRAP was performed in 120 healthy adults in Kilifi, Kenya, not a high endemic area for malaria. With a very high T cell response, the researchers saw a 67% efficacy over a two months period. Along with the challenge study data, this trial in East Africa is the best example of CD8 T cell mediated protection in any disease with a vaccine in humans. Dr. Hill: “As in Oxford, the T cells, across individuals, correlated with efficacy.”

The Kenyan study was conducted in adults, but the target population for malaria are young children and infants. The ChAd63 and MVA vectors were therefore taken into a phase II efficacy trial in the 5 – 17 months age group. The study showed a 13,5% efficacy against clinical malaria, which is statistically not significant. Dr. Hill: “The reason why the vaccine works in adults in Kenya and doesn’t work in infants in Burkina Faso is most likely to do with malaria endemicity.”

Immunosuppression in malaria-endemic areas is an under-recognized problem that impacts on RTSS. Dr. Hill: “You can’t get RTSS to work in adults because they are immunosuppressed by malaria almost certainly. It impacts on malaria vectors and sporozoite vaccines as well. Possible solutions include early vaccination (at 2 – 4 months of age) using viral vector vaccines, or with VLPs (at 5 – 7 months of age).”

Matrix-M is an adjuvant that can be mixed in with viral vectors and does not impair their immunogenicity. Most adjuvants do, Matrix-M does not.

Dr. Hill: “MVA DOES NOT INDUCE ANTIBODIES IN NON-PRIMED HUMAN INDIVIDUALS. IT IS A FANTASTIC BOOSTING VECTOR AND A PRETTY AwFUL PRIMING VECTOR.”

Adrian Hill

A promising variant of prime-boost immunization is what is now called prime-target immunization. It is a new means of targeting CD8 T cells to the liver, which requires a priming intramuscular immunization, preferably with an adenovirus. This is followed by an intravenous booster using the same vector. This vaccination regimen induces high levels of resident memory T cells in the liver, dramatically improving malaria vaccine efficacy. On the bright side, prime-target immunization against liver infections not only shows promising results for malaria infection, but is also applicable to hepatitis B and C immunotherapy.
Heterologous prime-boost vaccination acceptance - Insights from a multi-country assessment and on-line survey

The Swiss Tropical and Public Health Institute (Swiss TPH) is carrying out an assessment among several stakeholders to understand perception and acceptance of an heterologous prime-boost regimen. This assessment entails a literature review, in-depth interviews in six countries and an ongoing online survey. Xavier Bosch-Capblanch, Group Leader at the Swiss TPH, opened his presentation with the remark that the presented work is still in progress. As a full analysis has not been completed yet, the outcomes described in this article are preliminary.

An important starting point that arose from the literature review was that prime boost strategies will have to compete with existing vaccination delivery models and therefore will need to show superiority over existing vaccines in terms of efficacy, safety and ease of administration.

“Remarkably, almost half of the vaccination experts we interviewed were not familiar with the concept of heterologous prime-boost.”

XAVIER BOSCH-CAPBLANCH

In-depth interviews (n=20) revealed that vaccination specialists expect prime-boost regimens to be of added value especially in fields where no vaccines are currently available, or as a replacement of an existing vaccine that does not offer life-long protection. It was also stated that the first large scale implementation of heterologous prime-boost vaccination must be a flawless one in order to pave the way for future successes. As to the challenges, the vaccination experts assume that prime-boost will be more expensive than single dose vaccination strategies, and certainly more complex in terms of logistics and communication.

The interim output of the online survey (n=19) showed that the major expected benefits of heterologous prime-boost vaccination regimen included efficacy/immune response and duration of protection. While the main expected challenges are adherence to the guidelines by healthcare workers and practical, logistical hurdles. Respondents would required prime-boost vaccines to be substantially better than regular vaccines in terms of efficacy and duration of protection as a condition for acceptance. In terms of safety and costs, however, any improvement seemed to suffice for prime-boost vaccines to be preferred over regular vaccines.

The outcomes of the assessment and online survey will be published in a scientific journal.
Glenda Gray, President of the South African Medical Research Council, introduced her presentation reminding the audience that as yet, 35 million people have died from AIDS and 36.7 million people are currently living with HIV. She briefly summarized the evolution of HIV vaccine since the 1990s.

"THE DEVELOPMENT OF VACCINES AGAINST HIV HAS RELIED ON 80% CHANCE AND 20% STRATEGY."

GLENDA GRAY

Dr. Gray provided an overview of past and ongoing large-scale HIV vaccine efficacy trials, of which so far only one (RV144 trial) showed modest efficacy results.

Dr. Gray informed the participants that the MRKAd5 trivalent clade B HIV vaccine yielded good and long-lived immune response in gag, pol and nef. Trials in South Africa, however, were futile and revealed increased susceptibility in men. The HVTN 505 DNA/rAd5 prime-boost trial demonstrated that the DNA priming substantially improved the quality of the response to the recombinant Ad5 vaccination. This vaccine trial too was futile, even though the vaccine was extremely immunogenic, both in terms of humoral and cell-mediated immunity.

So why then did these vaccines fail? For the MRKAd5 vaccine, both the lack of envelope inserts and the anti-vector immunity against adenovirus and diminishing the CD8 T cell responses were likely the cause of the enhanced infection seen in this trial. However, despite the addition of a large amount of envelope antigenic mass to the HVTN 505 vaccine, there was no improvement in the efficacy signal in this trial. To Dr. Gray, this prompts the question whether the envelope insert choice was wrong... Comparison of the immune response in HVTN 505 with other trials, including RV144, indicates that this may be the case. Strikingly, the dominant response in HVTN 505 was against gp41, a distractor or decoy antibody. Dr. Gray concluded that the insert does matter and that not all HIV envelopes are created equal.

The important question to answer now is: “Can non-neutralizing antibodies be potent enough to achieve desirable vaccine efficacy (>50%) for at least 2 years?” Can this be achieved by designing better recombinant proteins and adjuvants, or by eliciting better T helper responses to drive higher and more durable antibody production?

The RV144 using ALVAC/gp120 in Thailand showed that a wimpy vector can produce modest efficacy. This was met with great surprise and scepticism. By 12 months, the efficacy was around 60%, although the durability waned, indicating a need for a boost in this regimen. The RV144 resulted in a massive effort to understand the correlates of protection. It also demonstrated that the insert and structure of the envelope antigen that one puts in the vector may be as critical to the vaccine design than the vector itself.

The P5 Clade C study built on the RV144 data. A clade C based ALVAC was constructed, as well as a new bivalent subtype C gp120/MF59 construct, and a booster was planned at month 12 and 18 to
optimize the regimen for increased potency and durability. RV144 was replicated and performed well in South Africa (HVTN 097), and a phase I study established and passed the go no go criteria for HVTN 702. The latter started in 2016 to assess potency and durability.

The multi-clade approach using rAd26/MVA/gp140 is a large ongoing collaboration and is based on a study in NHP suggesting non-neutralizing antibodies and T cell responses may be important correlates of protection. The trial is a double prime double boost regimen using a mosaic of Ad26 constructs and gp140 Clade C boost, with a proof-of-concept trial in women in Southern Africa starting enrolment in November 2017.

To Dr. Gray, it is time to reflect on the non-neutralizing strategies now undertaken in the field of HIV vaccination.

Glenda Gray: “We will see whether the presumed correlates of protection are shown consistent in human efficacy trials and whether any NHP challenge studies are predictive of vaccine efficacy. For the first time in 16 years, a reasoned vaccine design approach is proposed, using human trials with intense evaluation of correlates of protection as the basis for a true rational vaccine design.”

“FOR THE FIRST TIME, THE BASIC SCIENCE AGENDA IN HIV VACCINE DEVELOPMENT WILL BE BASED ON HUMAN CLINICAL TRIALS.”

GLENDA GRAY
Prime-boost strategies for bacterial vaccines

Dr. Camille Locht, head of the Center for Infection and Immunity of Lille (CIIL), France, acknowledged that heterologous prime-boost strategies for bacterial vaccines is too large a topic to be covered in the limited timeframe of his presentation. He therefore decided to focus on two bacterial diseases which both are still very important public health problems: pertussis and tuberculosis. Vaccines exist that are quite effective against these diseases, and they are widely used, with coverage rates up to 85%. Yet, the diseases are still there. Prime-boost strategies may be called for to help reduce their impact.

Dr. Locht compared the epidemiology of both diseases to show that TB claims 1.8 million lives/year, whereas ‘only’ 200,000 people die per year from pertussis. “However, in terms of disease frequency, we see a totally different picture. 2014 saw about 10 million new cases of TB as compared to up to 40 million cases of pertussis. It is also interesting to note that mortality rates of TB are highest in adolescents and adults, whereas most people dying from pertussis are very small children, less than six months of age.”

To improve protection against both diseases, Dr. Locht suggested implementing a prime-boost strategy where individuals receive a live attenuated vaccine as a primer and an acellular vaccine as a booster. However, while live attenuated vaccines are available for TB and acellular vaccines exist for pertussis, there is no acellular vaccine for TB and no live attenuated vaccine for pertussis.

95% of TB infections in adults are latent infections, not associated with disease. But a small percentage of these latent infections evolve into reactivation tuberculosis, a pulmonary disease with a high bacterial load and hence highly contagious. Dr. Locht: “If we could develop a vaccine that prevents reactivation, I believe we would be able to eradicate tuberculosis in the timeframe of a few generations. After all, Mycobacterium tuberculosis is a strictly human pathogen.”

To prevent TB reactivation, Dr. Locht’s team examined the possibilities of using heparin-binding haemagglutinin (HBHA) as a boosting antigen in BCG primed individuals. Studies in mice indeed confirmed the protective impact of HBHA as a boosting antigen.

Switching from tuberculosis to pertussis, Dr. Locht explained that acellular pertussis vaccines protect very well against pertussis disease, but they do not protect against the infection by B. pertussis, the
agent of whooping cough. In fact, the introduction of an acellular pertussis vaccine in the nineties in the US, Australia, England and other countries had actually led to an increase of pertussis cases. Studies in a baboon model indeed showed that baboons who received an acellular pertussis vaccine were not protected against infection, they even carried the infection longer than the non-vaccinated subjects. Camille Locht: "There are two main reasons why after introduction of the acellular vaccines, pertussis incidences have increased: the protective immunity mediated by these vaccines are strong in the beginning but wane very quickly and the acellular pertussis vaccines do not prevent infection and transmission of the organism."

The older, whole cell vaccines do provide some protection, but the best way to protect baboons against infection is prior infection. This inspired Dr. Locht’s team to develop a live attenuated pertussis vaccine for intranasal administration: BPZE1. Studies in baboons have shown that BPZE1 reduces bacterial load with 99.99%. In the meantime, the vaccine candidate has successfully passed phase I trial and will now go into phase II.

Priming with whole cell vaccines against pertussis and boosting with acellular vaccines may also be an interesting pathway that deserves further investigation. Whole cell vaccines, however, have been associated with frequent minor adverse reactions such as redness and swelling at the site of injection, along with fever and agitation. While they are still widely used, whole cell vaccines are unlikely to be licensed for sale in most European countries or the US, according to Dr. Locht.

“THE BENEFITS OF A LIVE ATTENUATED PERTUSSIS VACCINE INCLUDE EASE OF ADMINISTRATION AND LONG LIVED IMMUNE RESPONSE.”

CAMILLE LOCHT
Valérie Oriol-Mathieu, Global Medical Affairs Lead at Janssen Vaccines, addressed the heterologous prime-boost issue from a different angle as she focused on concrete technologies that can facilitate the implementation of heterologous prime-boost vaccination campaigns. Her talk accounted of the practical knowledge and experience acquired by the EBODAC consortium in Sierra Leone.

Dr. Oriol-Mathieu envisaged that the first comprehensive heterologous prime-boost campaign will be rolled out in the very near future, based on the fact that an impressive number of scientists, companies and funding partners are currently developing heterologous prime-boost programs. She also noted that heterologous prime-boost strategies may be a tool to answer unmet medical needs, such as vaccination of the elderly (answering the issue of immunosenescence) and pandemic preparedness (influenza for instance).

"Now is the right time to discuss heterologous prime-boost. Our knowledge is advancing fast and the first real prime-boost vaccines will be available in the very near future."

Valérie Oriol-Mathieu

Vaccination regimens that are similar to heterologous prime-boost have been implemented in recent years. A good example is the vaccination strategy for pneumococcal pneumonia, where conjugated and polysaccharide vaccines are combined in Europe and the United States. These vaccines, however, have been licensed separately with each component having demonstrated its benefits and no strict interval has been set between the vaccinations.

Many of the diseases that research is targeting with heterologous prime-boost regimens occur in resource-poor settings, which leads to specific implementation challenges: transportation and storage, but also acceptance and compliance by the population. Monitoring vaccine uptake on an individual level is hence necessary, and to that end technological solutions have been developed and tested: iris scans and fingerprints instead of ID cards, and mobile phone reminders.

The EBODAC project (EBOla vaccine Deployment, Acceptance and Compliance) was established to support Janssen’s Ebola vaccine clinical trial in Sierra Leone. EBODAC focused on community engagement, biometric identification and mobile technology to build a platform for the successful deployment of Ebola vaccines, maximizing the impact of the vaccination campaign.

Biometric identification tools had to be culturally acceptable, low cost and easy to scale, and should not require physical contact. Iris scans were hence implemented, rather than identification by finger prints. This biometric technology was used in combination with mobile technology, where individuals received automatically generated voice messages to remind them of medical visits.
EBODAC yielded some positive results as 100% of participants accepted to receive phone messages, all participants had been successfully identified through iris scans, and they all complied with receiving the booster vaccine. Qualitative surveys revealed that participants found the technology acceptable and easy to use. It should be noted, however, that EBODAC was carried out in a very specific, resource-deprived context, and that the cost effectiveness of using these technologies has yet to be evaluated.
Johan Vekemans is a Medical Officer at the Initiative for Vaccine Research (IVR) of the World Health Organisation (WHO). WHO IVR provides guidance on vaccine research and development pathways to ensure that adequate evidence is being generated to support appropriate WHO policy decision. SAGE (Strategic Advisory Group of Experts on Immunization) is the principal WHO advisory group for vaccines and immunization, and through their evidence review, considers whether candidate vaccines are fit to address the true societal and medical needs for candidate vaccines.

Public health perspective of heterologous prime-boost vaccination

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<td>Considering poverty, household impact of disease, budget impact. Principle of rights, fairness, and autonomy.</td>
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SAGE considers a wide array of evidence for their recommendations on policy for new vaccines
Dr. Vekemans stated that, while continued efforts are needed for the implementation of current vaccine recommendations, it is acknowledged that the global immunization approaches need to evolve as we will surely see more complex regimens and partially effective vaccines that reach the whole life course. Dr. Vekemans: “There is also an urgent need to evolve in terms of vaccine presentation and delivery approaches. I believe this is one of the main challenges when it comes to technologies, as vaccine delivery strategies will largely determine the success of future vaccination programmes.”

Dr. Vekemans emphasized that heterologous prime-boost is at the heart of vaccine innovation. It indeed provides opportunities, but it is also associated with specific non-scientific challenges that need to be addressed: complexity of implementation, policy regulation, and logistics. “The HVTN 702 trial in South Africa, for instance, involves 5 injections with two different vaccines at specific time intervals over a period of 12 months, for evaluation of prevention of HIV infection.”

“SOME COUNTRIES IN THE WORLD STRUGGLE TO REACH CURRENT TARGETS OF IMMUNIZATION COVERAGE WITH THE THIRD DOSE OF DTP VACCINES, FOR INSTANCE. SUCCESSFUL IMPLEMENTATION OF MORE COMPLEX VACCINATION REGIMEN WILL HENCE BE CHALLENGING IN SOME RESOURCE CONSTRAINED SETTINGS.”

JOHAN VEKEMANS

Dr. Vekemans pointed at the importance of the WHO R&D Blueprint for action to prevent epidemics. The R&D Blueprint was developed in the aftermath of the Ebola epidemic in West Africa and it is a global strategy and preparedness plan that allows the rapid activation of R&D activities during epidemics. Its aim is to fast-track the availability of effective tests, vaccines and medicines that can be used to save lives and avert large scale crisis. Dr. Vekemans added that prime-boost vaccination is certainly considered in this programme, although there is an obvious preference for a one dose schedule that provides rapid protection, especially in an epidemic context.

In his concluding remarks, Dr. Vekemans emphasized the need to carefully evaluate the value proposition of new vaccines with an end-to-end vision. While there is always a preference for a minimal number of doses, products and visits required, it is acknowledged that complexity may need to increase in order to reach hard-to-get targets. The potential risk associated to delivery of an incomplete schedule needs to be considered. The added value of increased complexity needs to be demonstrated.

“IN 2018, WHO WILL ORGANIZE FURTHER DISCUSSIONS ON VACCINE INNOVATION INCLUDING ON THE ROLE OF PRIME-BOOST VACCINATION STRATEGIES.”

JOHAN VEKEMANS

Funders, researchers, manufacturers, regulators, policy makers, health programs: the public health community as a whole need to embrace the idea that the scientific challenge drives complexity in vaccine research and development.
**Heterologous prime-boost strategies may be the answer to unmet medical needs**, such as HIV, vaccination of the elderly (answering the issue of immunosenescence) and emerging infectious diseases.

**The first comprehensive heterologous prime-boost campaign may be rolled out in the very near future.** There is already considerable experience in different resource settings of delivering sequenced vaccines (incl. stock management, training of health-care workers, tracking of vaccinated subjects, management of administration errors, and ensuring compliance with the required doses in the right order).

**Abundant memory CD8 T cell quantity can be achieved through heterologous prime-boost vaccination strategies**, with the efficiency of memory generation increased with boosting, and without proliferative or functional senescence.

**Heterologous prime-boost induces T cell responses that retain qualities of proliferation and differentiation potential.**

**Heterologous prime-boost is most probably the best strategy for T cell vaccines to achieve rapid recognition and rapid control of pathogens.**

**Heterologous prime-boost strategies can combine live vectors, DNA/RNA and recombinant adjuvanted proteins in any combination and order**, and can be applied for infectious disease and cancer therapy.

**Vaccinia virus, adenovirus and measles virus vectors offer attractive platforms for the development of heterologous prime-boost-based vaccines** due to their relative ease of manipulation and propagation, large insertion capabilities, excellent safety profiles, and induction of good humoral and T cell immune responses.

**The Jenner Institute’s ME-TRAP construction follows a heterologous prime-boost approach**, with the adenovirus (ChAd63) encoding ME-TRAP used as the priming vector and an MVA expressing the same antigen used as a booster 8 weeks later. Trials in Oxford, Kenya, Gambia and Burkina Faso showed good safety and immunogenicity.

**Plenty of new liver-stage candidates are in the pipeline** using a heterologous prime-boost platform.

**Immunosuppression in malaria-endemic areas is an under-recognized problem** that impacts on RTSS.
MVA is an excellent boosting vector, but does not induce antibodies in non-primed human individuals.

Prime-target immunization is a new means of targeting CD8 T cells to the liver. It requires a priming intramuscular immunization, followed by an intravenous booster using the same vector.

It is time to reflect on the non-neutralizing strategies now undertaken in the field of HIV vaccination.

Effective vaccines against bacterial infections like pertussis and tuberculosis do exist. Yet, both diseases remain a public health issue. Prime-boost strategies may be called for to help reduce their impact.

Research at the Center for Infection and Immunity of Lille confirms the protective impact of heparin-binding haemagglutinin (HBHA) as a boosting antigen in BCG primed individuals. The ultimate aim is to develop a vaccine that prevents TB reactivation.

In order to get accepted as a public health strategy, heterologous prime-boost vaccines need to show superiority over existing vaccines in terms of efficacy, safety and ease of administration.

Real or perceived non-scientific challenges need to be addressed: complexity of implementation, policy regulation, and logistics.

The potential risk associated to delivery of an incomplete schedule needs to be understood and possibly addressed. The added value of increased complexity needs to be demonstrated.

Vaccination specialists expect heterologous prime-boost regimens to be of added value especially in fields where no vaccines are currently available, or as a replacement of an existing vaccine that does not offer life-long protection.

Many of the diseases that research is targeting with heterologous prime-boost regimens occur in resource-poor settings, which leads to specific implementation questions: transportation and storage, but also acceptance and compliance by the population.

Monitoring vaccine uptake on an individual level is necessary. Technological solutions have been developed and tested: iris scans and mobile phone reminders. In the meantime, technology advances rapidly and new solutions could just be around the corner.
The EBODAC project (EBOla vaccine Deployment, Acceptance and Compliance) focused on community engagement, biometric identification and mobile technology to build a platform for the successful deployment of Ebola vaccines.

New vaccine strategies, presentation and delivery approaches are urgently needed, as vaccine delivery strategies will largely determine the success of future vaccination programmes.

Some countries in the world struggle to reach current targets of immunization coverage already. Successful implementation of more complex vaccination regimens will hence be challenging in these settings.

As evidence is building on heterologous prime-boost vaccines regarding their efficacy in terms of improved immune responses, their potential application in a range of situations including public health emergencies, and use in special populations, such as the elderly and infants, experts must continue to come together to align and discuss approaches to make implementations of the first heterologous vaccine a success for the global community.
The One Health Platform wishes to thank the colloquium speakers for their inspiring contributions. We are extremely grateful for the time and effort they took to share their knowledge and experiences with the colloquium participants.

ABOUT THE ORGANIZER
The One Health Platform is a strategic forum of stakeholders and a One Health reference network that aims to enhance understanding of and preparedness for the current and future outbreaks of zoonoses, emerging infectious diseases in humans and animals, and antimicrobial resistance, including the ecological and environmental factors which impact on these diseases.
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The following partners have provided unrestricted grants to support the Heterologous Prime Boost Vaccination colloquium. Unrestricted grants imply that the partners financially supported the colloquium, but have not been involved in the preparation of the event in any way.