Evolving pharmacovigilance requirements with novel vaccines and vaccine products

Situation paper

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Executive summary

This situation paper explores the vaccines and vaccine technologies pipeline with a 10-year horizon. Whilst older vaccines included live attenuated organisms or inactive products (such as inactivated organisms, sub-units, modified toxins or recombinant proteins), it is now also possible to apply newer technologies. Several products that include such technologies are either already licensed or at an advanced stage of clinical development. Those include use of viral vectors, genetically attenuated live organisms, nucleic acid vaccines, novel adjuvants, increase in the number of antigens present in a single vaccine, novel mode of vaccine administration and thermo-stabilization.

For each of those groups of products, a mini-review presents the experience already available and expected future developments. The Global Advisory Committee on Vaccine Safety (GACVS) monitors novel vaccines, from the time they reach marketing authorization. GACVS role is characterize their safety profile and update this profile as evidence emerges from post-licensure surveillance and observational studies. Vaccines and vaccine formulations that will be produced with novel technologies will have different safety profile, sometimes milder but new challenges will also have to be considered with genetically modified organisms and nucleic acid products. The Global Advisory Committee on Vaccine Safety has started considering viral vector templates developed on the model proposed by Brighton Collaboration and will probably want such tools to be developed and maintained for each viral vector recommended by WHO. The challenges of monitoring genetic modifications will possibly require adding expertise on this area to the committee.

The characteristics of those novel products will also have implications for the risk management plans (RMPs). RMPs of the next decade will include novel methods to characterize products. Questions related to the duration of active monitoring for genetic material, presence of adventitious agents as has been observed with several viral vaccines more easily detected with enhanced biological screening, or

physiological mechanisms of novel adjuvants are all considerations that will belong to the preparation of RMPs.

In addition to assessing those novel products and advising experts, GACVS will also consider how to more broadly communicate about risk assessment, so vaccine users can also benefit from the Committee's advice.

Introduction

As compared to the 20th century, many recent vaccine products and others currently under development present several novel features that will also impact their safety profile. Those will require additional monitoring approaches as compared to the standard safety monitoring of current vaccine products. Whilst older vaccines included live attenuated organisms or inactive products (such as inactivated organisms, sub-units, modified toxins or recombinant proteins), it is now also possible to apply newer technologies. Several products that include such technologies are either already licensed or at an advanced stage of clinical development. Those include use of viral vectors, genetically attenuated live organisms, nucleic acid vaccines, novel adjuvants, increase in the number of antigens present in a single vaccine, novel mode of vaccine administration and thermo-stabilization.

The Global Advisory Committee on Vaccine Safety (GACVS) has monitored numerous novel vaccines, from the time they were reaching market authorization, to characterize their safety profile and update this profile as evidence emerges from post-licensure surveillance and observational studies. Here we review new vaccines and new vaccine formulations that will be produced with novel technologies, with a perspective on the next 10 years, and examine their implications for the risk management plans of novel vaccine products.

Vaccines and vaccine technologies pipeline

Driven by its mission to support all countries in the delivery of quality immunization services, WHO's strategic goals for vaccines include: promoting the development of new vaccines and vaccine delivery technologies to meet public health priorities, establishing norms and standards for vaccines and delivery technologies and ensuring vaccines and delivery technologies are of assured quality [1]. As such, WHO supports vaccines and novel technologies from early product development through to the publication of

global policy recommendations [2]. WHO's Product Development for Vaccines Advisory Committee (PDVAC) facilitates early assessment of pipeline products, typically in clinical phase I or II, for which there is the greatest unmet public health need [3]. Since its inception in 2014, PDVAC has reviewed 36 pathogen areas and prioritized ten (Figure 1) urgently required vaccines. It is anticipated that WHO's engagement will likely expedite their development, availability and access. A key component of PDVAC's remit is horizon scanning of novel candidates, and an increasing number of these are based on innovative manufacturing, presentation or delivery technologies. These assessments provide a landscape analysis of products that are the most advanced and of novel platforms are the most significant in terms of applicability. Since these candidates are typically 5-10 years from licensure, they present a forward-looking perspective on innovations to come, and where WHO should be proactively preparing guidance.

As the number of WHO recommended vaccines increases [4], there is a critical need for cheaper, more effective vaccines that are easier to deliver, with the ability to rapidly manufacture and scale up in response to disease outbreaks. These requirements prioritize technologies that offer one or more of the following advantages: i) an increase vaccine efficacy through induction of both humoral and cellular immunity, thereby enabling dose sparing or a reduction in the number of doses per regimen, such as with genetic attenuation of live organisms, novel adjuvants and potentially novel delivery routes; ii) the ability to combine multiple antigens, either from the same pathogen or different pathogens within the same formulation, possibly with the inclusion of genetic adjuvants to reduce the number of vaccinations, such through the use of viral vectors and nucleic acid vaccines, or combinations of individual antigens; iii) the ability to rapidly manufacture low-cost vaccines with new antigen sequences in a matter of weeks rather than months, such as with nucleic acid based platforms; and iv) the improved safety and acceptability of vaccines at the point of delivery, such as through the use of needle-free and integrated reconstitution technologies.

Figure 1 presents an overview of the vaccine candidates for the PDVAC priority pathogens by phase of clinical development. It also highlights those that are based on novel technologies, i.e. that have either not been licensed previously, or for which there is currently limited human safety data available. The most clinically advanced candidates are for respiratory syncytial virus (RSV), tuberculosis (TB) and human immunodeficiency virus (HIV) vaccines. Of these, only the HIV candidate is based on a novel technology, namely a viral vector, and is being administered through heterologous prime boost which is itself a novel delivery approach [5]. However, approximately half of the candidates in phase II clinical development for priority pathogens are based on novel technologies, including three based on nucleic acids (DNA, mRNA), eight based on viral vectors (modified vaccinia Ankara and chimpanzee adenovirus), and several on live attenuated and on novel adjuvants (Matrix M, etc.). The tuberculosis [6], RSV and Shigella pipelines are predominantly based on novel technologies.

Recommendations from WHO's Strategic Advisory Group of Experts (SAGE) on immunization are based on evidence that goes beyond the safety, quality and efficacy data requirements for licensure. They include factors related to the vaccine's potential impact on disease epidemiology, the perceived benefits and harms; equity considerations; economic considerations; social values and interaction with other existing interventions and control strategies. Whilst the pipeline of novel vaccines and technologies offers potential game-changing product attributes and every effort should be made to expedite their development, we must ensure there is a concomitant assessment of their potential risk and adequate provision for timely collection of data that will facilitate policy recommendation and country introduction decisions.

Safety considerations

Viral vectors

Recombinant viral vectors are attractive platforms for developing novel vaccines. They provide an efficient means for heterologous antigen expression in vivo and induce robust cellular and humoral immunity, both without need for exogenous adjuvant [7]. Targeted deletion of specific genes allows dampened or complete elimination of viral replication thereby increasing safety. The ideal viral vaccine vector: has a good safety profile; is not associated with any disease in humans; has no or low pre-existing immunity in the target population; can easily be produced at low costs; can easily accommodate foreign vaccine antigens; is genetically stable; and can easily be stored, transported, and administered [8]. Viral vectors are the most popular approach among the many new approaches emerging from the biotechnology revolution. About half (N=11) of the 20 awards for vaccine development awarded by the Coalition for Epidemic Preparedness and Innovation (CEPI) to date support use viral vectors and several of the others support use recombinant nucleic acids (Table 1). Several veterinary and two human viral vector vaccines (Japanese encephalitis and dengue vaccines based on yellow fever 17D vaccine platform) have been licensed with many others in the pipeline, including vaccine candidates against Ebola virus [7;9]. There is an increasing but still limited clinical experience about the efficacy and safety of such vectors in humans, however.

Much has been learned about viral vectors since the first studies with Vaccinia in 1984 [10]. Several issues of critical importance about this platform remained unknown and warranted investigation per a 2003 World Health Organization (WHO) informal consultation [11]. These included issues such as recombination with wild-type pathogenic strains and public acceptance (Table 2). With increasing

numbers of viral vector vaccines entering human clinical trials, new regulatory measures to ensure their quality, safety and efficacy have been established [12;13].

On occasion, vector-based vaccines have been associated with unexpected higher rates of the disease they are designed to prevent. This has been the case with HIV infection acquisition among participants of the STEP and Phambili [14] trials who had received a replication-defective Ad5 vector vaccine candidate. The reason for higher HIV acquisition in the vaccine recipients remains unclear. More recently, a tetravalent dengue vaccine could not overcome the problem of disease enhancement among vaccine recipients who are naïve to wild-type dengue virus infection [15].

Despite these setbacks, the overall advantages of viral vector vaccines seem to outweigh the disadvantages [16]. There have been promising results. The first HIV vaccine candidate to show (modest) protection in large human trials consisted of a recombinant canary pox virus vector vaccine (ALVAC-HIV [vCP1521]) and a recombinant glycoprotein 120 subunit vaccine. Follow-on trials using multiple updated viral vector vaccines are underway in Southern Africa. A recombinant rhesus cytomegalovirus (CMV) vaccine vector engineered to express simian immunodeficiency virus (SIV) proteins has resulted in progressive clearance of a pathogenic SIV infection in rhesus macaques in Africa [17]. An Ebola vaccine based on the vesicular stomatitis virus (VSV) vector has proven to be highly efficacious [18].

The Brighton Collaboration Viral Vector Vaccines Safety Working Group (V3SWG) was launched in 2008 to improve our ability to anticipate safety issues and meaningfully assess and interpret safety data from clinical trials of new viral vector vaccines, thereby enhancing public confidence in their safety and efficacy, and in turn the vaccines' acceptance and uptake [18]. The V3SWG has provided guidance on several issues of critical importance needing further investigation, many initially identified by the 2003 WHO consultation. These include to date: a) archiving samples of biological materials for retrospective

analysis [20]; b) potential for and theoretical consequences of recombination with wild type virus strains [21]; and c) defining the interval for monitoring potential adverse events following immunization (AEFIs) after receipt of live viral vectored vaccines [22].

In addition to extending the paradigm of standardized case definitions to this realm, the other major V3SWG activity has been to adapt and use a standardized template describing the key characteristics of a novel vaccine vector. Since this domain of vaccine development is highly technical with many acronyms and since key stakeholders (e.g. regulators, institutional review boards (IRBs), public health practitioners, public at large) lack technical training, the risk for misunderstanding is high. By organizing the key questions in understandable language, the standardized template will hopefully facilitate scientific discourse among key stakeholders and increase the transparency and comparability of vital information (Table 2). The V3SWG templates published to date include the yellow fever 17D vaccine vector, the recombinant vesicular stomatitis virus (rVSV) and its application to the Ebola virus [18]. At the June 6, 2019 meeting of the WHO Global Advisory Committee on Vaccine Safety (GACVS), the GACVS recognized the value of the structured information conveyed in the completed V3SWG template to policy makers and urged other new vaccine developers to also complete the V3SWG template, starting with the most advanced Ebola vaccine candidates [23].

Genetic attenuation of live organisms

Most licensed viral vaccines and those in development are live, attenuated viruses derived from virulent clinical isolates through multiple passage in culture (e.g., measles, mumps, yellow fever, polio). Attenuated viral vaccine strains have the potential to mutate and regain virulence during growth in cell substrates resulting in an unacceptable safety profile of the vaccine, potential reduction in potency and efficacy. State of the art technology allows genetic modification of wild-type viruses, bacteria and other

micro-organisms to generate attenuated vaccine strains that can replicate the pattern of natural infection without causing disease or other untoward side effects. Examples include reassortant influenza vaccines combining RNA segments from different strains [24], chimeric flaviviruses [25], including a recently licensed dengue vaccine [26], as well as genetically modified enteric bacteria [27]. New strains for oral polio vaccine (OPV) represent another prominent example of the use of targeted systematic genetic modifications to improve vaccine safety as described below.

Genetic mutations occurring in Sabin poliovirus from conventional OPV strains result in regaining of virulent properties and can cause cases of vaccine associated paralytic polio (VAPP) [28]. Following eradication of wild-type 2 polioviruses paralytic cases were caused by virulent circulating type 2 vaccine derived polioviruses (cVDPV) that are indistinguishable from wild-type polioviruses [29]. Even though trivalent OPV was withdrawn and replaced with bivalent vaccine that no longer contained the type 2 polio component, outbreaks of type 2 cVDPV that occurred prior to the switch cannot be controlled by inactivated polio virus vaccine nor type 2 OPV. It was thought that development of genetically stable attenuated strains of OPV will be critical to ensure the success of the entire polio eradication campaign. State of the art technology combined with knowledge of poliovirus biology and genetics were used to rationally design and generate genetically modified strains of poliovirus predicted to be safe and immunogenic, but with increased stability compared to conventional Sabin strains. To maximize genetic stability two candidate Sabin polio strains with different combinations of targeted modifications were prepared and evaluated. The modifications included re-coding the RNA element in the 5'-untranslated region that is a critical determinant of attenuation and virulence, to decrease the potential for mutations to occur [30]. Second, a critically important cis-acting replicative element (cre) [31] was transplanted from the centre of the molecule into the 5'-UTR to prevent elimination of this stabilized element due to recombination. Third, mutations were introduced to the viral RNA-replicase to increase its fidelity to prevent the emergence of mutations and to limit the ability of these genetically engineered

viruses to recombine with other enteroviruses [32]. Finally, RNA sequences coding for the viral capsid proteins were recoded using different combination of codons, while preserving the same amino acid sequence [33]. Phase 1 clinical trials [34] that evaluated shed polioviruses using deep sequencing and the transgenic mouse neurovirulence test have demonstrated that these strains are indeed more genetically stable than the original Sabin virus. It is expected that after the Phase 2 clinical immunogenicity evaluations are complete, these new OPV constructs will be used in final polio eradication efforts. This project represents the first example of targeted rational design of vaccine virus genomes, which may serve as a future paradigm for the development of viral vaccines against other diseases. It also illustrates that use of new technologies, such as de novo chemical synthesis of vaccine genomes and next-generation (deep) sequencing (NGS) to evaluate the genetic composition of the entire genome of vaccines viruses are important tools for monitoring the molecular consistency and genetic stability of polio vaccines and vaccine products in general [35]. The use of vaccines derived by genetic engineering will require safety surveillance and monitoring to confirm that these modifications increase product safety in large-scale public immunization campaigns.

Adjuvants and novel formulations

Adjuvants have been added to vaccines for nearly a hundred years, initially with aluminium salts, and more recently oil emulsions (notably squalene-containing oil-in-water emulsions such as MF59™ and AS03), bacterial membrane extracts such as monophosphoryl lipid A (MPL) or synthetic derivatives, plant extracts such as the Quillaia saponins used in AS01 and MatrixM adjuvants, and synthetic oligonucleotides such as CpG. These adjuvants enhance the antibody titres to the antigen (such as aluminium in most childhood vaccines), and some also enhance the breadth of the response (such as the MPL in HPV vaccines), permitting antigen-dose reduction (such as oil-in-water emulsions in pandemic influenza vaccines), enabling immunization in older adults (such as the oil-in-water adjuvant in Fluad™),

and inducing cell-mediated immunity (such as the AS01 adjuvant in the Herpes Zoster vaccine Shingrix™).

Numerous allegations of safety issues have been directed at vaccine adjuvants. Aluminium salts have the longest and largest safety track record of all vaccine adjuvants, with an attractive risk and benefit ratio. There have been a few cases of macrophagic myofasciitis (MMF) in which aluminium was found within intracytoplasmic inclusions, leading some researchers to suggest that alum in vaccines was the cause [36]. To date however, no relationship between the presence of aluminium and clinical MMF has been established. GACVS found that there was no basis for recommending a change in vaccination practices [37].

Oil-in-water emulsions were added to two monovalent pandemic influenza vaccines that were used during the 2009 H1N1 pandemic (Pandemrix and Focetria). These emulsions contained squalene, an oil purified from sharks, and the emulsion in Pandemrix further contained alpha-tocopherol (vitamin E). The public acceptance and uptake of these vaccines was hampered by media claims of the dangers of squalene, a concern that derived from a 2002 claim that soldiers returning from the Gulf War with the so-called 'gulf war syndrome' had anti-squalene antibodies which had been induced through receiving vaccines allegedly containing squalene [38]. Although the vaccines used in the Gulf War did not apparently contain squalene, the GACVS reviewed all available data including data from clinical trials with the approved squalene-containing influenza vaccine Fluad™ and concluded that there was no evidence that squalene could induce pathological anti-squalene antibodies [39].

During the 2009 influenza “pandemic”, one of the adjuvant-containing pandemic influenza vaccines (Pandemrix, containing AS03) was associated with an observed increase in narcolepsy rates in several European countries. While the association bewtween Pandemrix administration and narcolepsy was clear, no mechanism of action has been demonstrated. Proposed hypothetical mechanisms whereby

the adjuvant heightened and broadened the immune response to include induction of pathological mimicry responses [40] are difficult to reconcile with the uneventful use of the same adjuvant in another H1N1 pandemic influenza vaccine (Arepanrix) [41].

Other adjuvant-associated concerns include the observed increase in solicited local symptoms with AS01 adjuvant [42]. A nasally-delivered inactivated influenza vaccine, containing a mutated heat-labile toxin from E. coli as an adjuvant, was found to be associated with increased rates of Bell's palsy resulting in the vaccine being withdrawn [43]. Subsequent studies [44] showed that the adjuvant can induce transient facial nerve paralysis.

Vaccine development is likely to involve increased research on and use of novel adjuvants. Demonstrating the safety of the vaccines containing these adjuvants and ensuring it will be critical.

Combination vaccines and increasing valency

Adding antigens to an existing vaccine formulation simplifies vaccine administration, reduces the risk of immunization errors and increases the protection against additional germs. The modification also may present challenges related to product stability and need of titration of each antigen for maximum effect. The number of antigens in individual vaccines has increased for several combinations including measles, mumps, and rubella vaccines in various bi- to tetravalent combinations and combined products with diphtheria, tetanus and pertussis (whole cell or acellular) vaccines with other non-live vaccines. The diphtheria-tetanus-acellular-pertussis-inactivated polio-hepatitis B-*Haemophilus influenzae* type b (DTaP-IPV-HepB-Hib) vaccine referred to as a hexavalent vaccine currently protects against the largest number of diseases (six different micro-organisms). One available presentation contains 5 different antigens against pertussis and 3 types of poliomyelitis vaccines and is therefore composed of twelve antigens in total [45].

Multivalent vaccines are more complex to produce than monovalent ones. Each component must be manufactured, and quality tested separately and then in combination. Clinical development requires demonstrating non-inferiority of the combination for each component of the vaccine [46]. In most of cases, multivalent vaccines have been found to be equally immunogenic as the same components administered separately. This was, for example, essentially the case with measles, mumps and rubella [47]. A quadrivalent live influenza vaccine was, however, found to have lower efficacy than non-live preparations [48].

Greater amounts of antigen per dose administered are sometimes related with increased vaccine reactogenicity. For example, the measles-mumps-rubella-varicella (MMRV) vaccine causes more febrile seizures than measles-mumps-rubella (MMR) and varicella vaccines administered separately at the same time [49]. When compared to similar products with fewer antigens, DTaP5-IPV-HepB-Hib safety profile has a slightly higher risk of pyrexia [50].

Multivalent vaccines are composed of different types of the same micro-organism. Trivalent live and inactivated poliovirus vaccines were the first example of such products. Today, pneumococcal conjugate vaccines (PCV) and those against human papilloma virus (HPV) have large valences. There can be up to 13 components for PCV, and a 20-valent product is under clinical development [51]. HPV vaccines can have up to 9 for HPV.

A larger antigen charge, the impact of higher carrier protein levels, and occasionally the need for higher adjuvant titres, can increase the frequency and intensity of non-specific local and systemic reactions. With HPV vaccines, a recent 9-valent product induces a higher frequency of adverse events than its 4-valent predecessor. Higher amounts of antigen and adjuvant are a likely explanation for this observation. On the other hand, polyvalent vaccines can replace older components with less reactogenic ones. The prime example being use of acellular pertussis instead of whole cell. This,

however, appears to come at the expense of actual protective efficacy. Finally, immune overload is not a real concern and had already been reviewed by GACVS in 2006 as the increasing number of vaccines offered and administered did require assisting [52].

Innovative vaccine delivery technologies

At present, most human vaccines are presented as liquid or lyophilized formulations, in single or multi-dose vials, the latter of which often contain preservatives for non-live products. The doses are typically administered via the intramuscular (IM) or subcutaneous (SC) routes. These conventional presentations constitute potential safety hazards: vaccine reconstitution introduces the possibility of using the incorrect diluent, the use of multi-dose vials raises the potential for contamination [53] and the use of needles for reconstitution, withdrawal and administration could result in needle-stick injury and consequent disease transmission [54]. These risks, as well as the need to improve ease of administration and ensure vaccine potency at the point of delivery, are driving the product development of innovative vaccine delivery technologies with a potential to improve vaccine and vaccination safety.

One of the most compelling innovations in the development pipeline is the microarray patch (MAP). A MAP consists of hundreds or thousands of projections, coated with or composed of dry vaccine formulation, on a 'patch' backing. The most clinically advanced vaccine MAPs either have no applicator [55], or an integrated applicator [56] and when pressed on the skin, deliver the vaccine to the dermis or epidermis over seconds or a few minutes. MAPs are 'pre-filled', needle-free, single use presentations that remove the need for reconstitution and the associated risk of contamination, use of the incorrect diluent or needle stick injuries. In addition, the novel antigen formulation that will need to be developed for the MAP presentation presents an opportunity to improve the thermostability of the

vaccine so that it can be used outside of the regular cold chain [57]. This could reduce the risk of administering a vaccine that has lost potency during delivery.

Since the intradermal compartment is rich in antigen-presenting cells, it is conceivable that MAPs may offer the opportunity for dose sparing. This has been demonstrated in animal models for several antigens [58] and in the clinic with a monovalent influenza antigen [57]. However, this increase in immunogenicity may be associated with high and unacceptable levels of reactogenicity. Minor local reactions lasting several days following application have been observed in clinical studies [55; 59; 60] and may be more pronounced with adjuvanted vaccines. To date there have only been clinical studies with influenza vaccine and data with additional antigens are needed.

Integrated reconstitution delivery technologies package the dry vaccine and diluent in separate compartments that can be easily mixed, removing the risk associated with needle and vial constitution. Dual chamber delivery devices are fully integrated with the delivery component, further reducing the risk of needle stick injury. Most dual chamber devices are in early stage development and do not yet incorporate an auto-disable feature.

For liquid vaccines, next generation compact prefilled auto-disable devices (CPADs) are in the pipeline. These are similar in presentation to the commercially available Uniject [61], however can be manufactured by an automated, continuous, aseptic process known as Blow-Fill-Seal (BFS). This reduces the potential for contamination during manufacturing. The BFS CPAD presentation is envisaged to be composed of a blister package containing a single dose of vaccine, a pre-assembled needle hub with an auto disable feature and a removeable vaccine shield. If all these elements are included in the final presentation, they offer the potential to reduce vaccine contamination, needle stick injuries and disease transmission.

Whilst these innovations, and others in the pipeline, offer the potential of significant safety benefits, they are likely to incrementally increase the procurement cost per dose of the vaccine. Efforts are needed to evaluate these trade-offs, and to further rationalize the programmatic and public health benefit that these innovations offer.

Nucleic acid vaccines

In 1990, direct gene transfer into mouse muscle in vivo demonstrated that plasmid DNA (pDNA) containing a gene of interest when directly inoculated into host tissue resulted in in situ production of the corresponding protein [62]. In the context of vaccination, this observation suggested that nucleic acids could be used as a platform for delivery and expression of target immunogen(s) and genetic adjuvants and heralded the age of nucleic acid technology (NAT) as a simple and versatile platform for vaccination. A promising feature of NAT vaccines was the potential to induce both humoral and cellular immunity to the target immunogen and the apparent absence of an adaptive immune response (albeit not the absence of certain innate immune responses) against the vector that could limit repeated use either for the same or different immunogen(s) of interest. For a variety of technical reasons (e.g., stability and ease of manufacturing), the focus of early NAT vaccine efforts was directed to pDNA rather than other DNA or RNA approaches and hundreds of clinical trials with pDNA ensued [63]. Although no NAT vaccines have been licensed for use in humans, three have been licensed for veterinary use to prevent infectious diseases to date.

Not unexpectedly for a novel immunogen and vaccine delivery system, early on there was uncertainty about both efficacy and safety of pDNA in humans, the latter of which included somatic chromosomal integration, germline alterations, autoimmunity, and immunopathology. The initial guidance documents called for extensive nonclinical studies, including biodistribution, chromosomal integration, germline

evaluation, in addition to typically vaccine toxicology studies. Now, with an abundance of nonclinical evidence that pDNA do not biodistribute or persist throughout the host when delivered parenterally into muscle, subcutaneous tissue, or various dermal layers, the typical nonclinical evaluation of pDNA prior to clinical study has been significantly streamlined. Likewise, published data from those hundreds of clinical trials indicate that pDNA vaccine candidates have been generally safe, with acceptable reactogenicity profiles. The reactogenicity that has been observed clinically relates more to the delivery method than the pDNA, with electroporation and particle-mediated bombardment being examples. As such, both the nonclinical and clinical sections of the *WHO Guidelines for assuring the quality, safety, and efficacy of DNA vaccines* are being revised in light of existing nonclinical and clinical data that, when taken as a whole, support the conclusion that prior concerns about integration, autoimmunity, and immunopathology have not been realized.

Although robust desired immune responses using pDNA alone have been observed in humans in a few instances, much of the data suggest that pDNA alone does not induce a sufficient immune response in humans to warrant late-stage clinical development. A variety of approaches have been tested and are being evaluated to enhance the immune response in humans, including optimization of the primary and secondary structure of the pDNA, addition of excipients that enhance delivery or have an adjuvant effect, and changes in the mode or route of administration. Beyond evaluation of pDNA alone, more effective immunogenicity seems to be induced when pDNA is used to prime immune responses that are subsequently boosted by delivery of a heterologous vaccine candidate, be it protein antigen or gene-based viral vectors. Of note and likely driven by the insufficient immunogenicity in humans of pDNA vaccine candidates alone and the complexity of heterologous prime-boost approaches, there has been a decline in publications on pDNA and a recent increase in publications and clinical evaluation of a variety of RNA-based NAT vaccine approaches (Figure 2).

RNA vaccines now being clinical tested incorporate the use of modified nucleosides and novel delivery excipients that appear to have overcome previous limitations of instability, transient production of encoded protein, and undesired innate immune responses [63]. Like pDNA, the current uncertainty of both efficacy and safety of RNA-based vaccine candidates in humans will likely yield to more streamlined evaluations once sufficient databases are established.

Evolving risk-management plans

Modern regulatory review of health products includes examination and continued monitoring of risk management plans (RMP). RMPs typically include information on a product's safety profile, based on data from clinical evaluation, possible safety signals and any other theoretical considerations and have a product life-cycle perspective. If by the time of marketing authorization, no significant issues are identified, risks are primarily monitored using passive safety surveillance systems after products have reached the market. For products with identified safety issues or when safety data are limited, RMPs will include the conduct of pharmacoepidemiologic studies and other activities to gain more knowledge about the safety and efficacy of the product [64]. Those are referred to as active safety surveillance and CIOMS recently published a guide specifically dedicated to active vaccines safety surveillance [65]. RMPs also discuss how risks will be prevented or minimised in patients and measure the effectiveness of risk-minimisation measures.

Novel vaccines, based on genetic modifications, open a whole new field of research. The Brighton Collaboration viral vector templates provide an illustration of the many dimensions related to assessing stability of the new constructs and their potential for recombination and interaction that will have to be factored in and similar issues will have to be considered for nucleic acid vaccines. RMPs of the next decade will also include novel methods to characterize products. Questions related to the duration of

active monitoring for genetic material, presence of adventitious agents as has been observed with several viral vaccines [66] more easily detected with enhanced biological screening, or physiological mechanisms of novel adjuvants are all considerations that will belong to the preparation of RMPs.

Consideration for use in emergency settings and fragile states

The routine evaluation of a new candidate vaccine in low and middle-income country (LMIC) settings with limited resources, infrastructure, regulatory and clinical trial experience is already very challenging (67; 68). To conduct such vaccine trials under emergency settings and in fragile states further compounds these difficulties exponentially. While these challenges may have been most apparent during the recent Ebola outbreaks in West and Central Africa [68; 70], they presumably were present historically with clinical trials of vaccines against any epidemic disease in such settings [71; 72]. The difference is with the advent of modern technologies such as mobile phones, digitization of data, internet, social resource mobilization and "hyper" communication and organization/networking, which have made previously unimaginable activities now possible despite the still high odds against success [68; 73].

Several papers documenting how interlocking challenges for conducting Phase 2b trial from infrastructure, to staffing, participant communication, and technology integration were designed, planned, tackled and solved during the constantly evolving West African Ebola outbreak from various perspectives are now available, including some key lessons learnt [68; 70; 73; 74].

In 2015, two additional emerging infections, Zika and Middle East Respiratory Syndrome (MERS) struck the globe [75; 76]. Plotkin et al argued that a "Global Vaccine Development Fund" was urgently needed to provide the resources and momentum necessary to carry candidate vaccines against such pathogens from their conception through development and licensure — thereby averting future Ebola crisis. These

ideas have gelled into the formation of the Coalition for Epidemic Preparedness and Innovation (CEPI; www.cepi.net), a new initiative targeted at developing candidate vaccines against Lassa fever, Middle East Respiratory Syndrome (MERS), SARS, Nipah virus, Rift Valley fever, chikungunya, and others on list of deadly pathogens without a vaccine [73; 77] (Table 2).

CEPI has funded the Brighton Collaboration' Safety Platform for Emergency vACcines (SPEAC) to help assess the safety of various CEPI-funded vaccine candidates undergoing clinical trials (https://cepi.net/news_cepi/cepi-partners-with-brighton-collaboration-to-support-safety-assessment-of-vaccine-candidates-against-emerging-infectious-diseases/). SPEAC will help provide members with safety expertise to independent data safety monitoring boards (DSMB). It will also constitute a "meta-DSMB" that will help oversee across vaccine platform against the same pathogen, as well as across pathogens using the same vaccine platform. The quality of safety data will be optimised by creating an online vaccine safety resource, which will include technical guidance, tools, a platform for information exchange, and training modules. A V3SWG template will be completed for each CEPI vaccine candidate. [19]. Hopefully more experience will soon be added to how best to organize and obtain useful safety data in hitherto unthinkable situations.

Discussion

There is an exciting evolving pipeline of vaccine products that will display very different characteristics than those of currently available products. There will be changes in vaccine reactogenicity, either with stronger non-specific reactions such as could be the case with more potent adjuvants, or in the direction of milder non-specific reactions if doses can be reduced and the area of administration broader. Use of genetically modified organisms and nucleic acids will require attention to any possibilities of mutation or

recombination, an area for which the current vaccine experience is primarily around the evolution of oral polioviruses.

The Global Advisory Committee on Vaccine Safety has started considering viral vector templates developed on the model proposed by Brighton Collaboration [23] and will probably want such tools to be developed and maintained for each viral vector recommended by WHO. The challenges of monitoring genetic modifications will possibly require adding expertise on this area to the committee. Finally, as new vaccine combinations will likely be proposed, understanding the reactogenicity of each individual component will remain essential before assessing their effects when combined. In addition of assessing those novel products and advising experts, GACVS will also consider how to more broadly communicate about risk assessment, so vaccine users can also benefit from the Committee's advice.

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Tables

Table 1: Awards for vaccine development, Coalition for Epidemic Preparedness and Innovation (CEPI) to Date (www.cepi.net)

Developer	CfP	Pathogen	Date	Construct type	Construct name
Emergent	1	Lassa	2018.08	Viral Vector	VesiculoVax
IAVI	1	Lassa	2018.05	Viral Vector	rVSVΔG-LASV-GPC
Inovio	1	Lassa	2018.04	DNA with Electroporation	INO-4500
Oxford/Janssen	1	Lassa	2018.09	Viral Vector	ChAdOx1
Themis	1	Lassa	2018.03	Viral Vector	Measles vaccine
IDT Biologika	1	MERS	2018.08	Viral Vector	MVA
Inovio	1	MERS	2018.04	DNA with Electroporation	INO-4700
Oxford/Janssen	1	MERS	2018.09	Viral Vector	ChAdOx1
Themis	1	MERS	2018.03	Viral Vector	Measles vaccine
Emergent/Profectus/PATH	1	Nipah	2018.05	Recombinant subunit	HeV-sG
Oxford/Janssen	1	Nipah	2018.09	Viral Vector	ChAdOx1
PHV	1	Nipah	2019.08	Viral Vector	rVSV
University of Tokyo	1	Nipah	2019.02	Viral Vector	Measles vaccine
CureVac	2	Lassa, rabies, YF, Disease X	2019.02	lipid-nanoparticle (LNP)	mRNA
University of Queensland	2	MERS, Disease X	2019.01	molecular clamp	molecular clamp

Imperial College	2	Rabies, Flu, Marburg, Disease X	2018.12	self-amplifying RNA (saRNA)	RAPIDVAC
Themis	3	Chikungunya	2019.06	Viral Vector	Measles vaccine
Valneva	3	Chikungunya	2019.07	Live attenuated	Live attenuated
Colorado State	3	Rift Valley	2019.07	Live reverse genetics	DDVax
Wageningen	3	Rift Valley	2019.07	Live reverse genetics	RVFV-4

Table 2 Table 1 from [19]

Table 1
Issues of critical importance to be investigated by Brighton Collaboration Viral Vector Vaccine Safety Working Group (V3SWG).[a]

1) Potential of recombination of the viral vector vaccine with wild type pathogenic strains.
   a) Vector–circulating virus could create a more pathogenic strain.
   b) This issue should be addressed in vitro or in animal studies.
2) Implications of prior infections on the immunogenicity of vectored vaccines.
   a) Prior infection with related viruses may reduce vaccine immunogenicity (e.g., adenoviruses, poxviruses (smallpox vaccine))
   b) Immunogenicity of subsequent doses, especially with different gene in same vector (e.g., modified poxviruses, adenoviruses): should be addressed if relevant.
3) Genetic stability of replicating *recombinant* viruses in vivo should be studied focusing on:
   a) The sequence insert, and known areas of attenuation
   b) Known epitopes
4) *The impact of the addition of foreign genes on the pathogenicity of the viral vaccine vector when compared to the parent virus.*[b]
5) Tests for absence of reversion to virulence should be performed when an attenuated vector is used.
6) The absence of replication competent virus when replication incompetent vectors are used should be demonstrated.
7) Public acceptance of vectored vaccines with specific safety concerns could be an issue. A need for a forum to discuss concerns, and how best to communicate the risks and benefits of the new approach to general public was identified and WHO was requested to take a lead on it.
8) Assessing vectored vaccine effects on innate immunity and on the possible induction of an immuno- suppressive window or *alternatively* immune activation.
9) Defining the length of time for monitoring AEFIs after receipt of vectored vaccines.
10) Developing guidelines for archiving samples of vectored vaccine samples to enable potential future testing to assess inadvertent contamination by adventitious agents.
11) Assessing possible secondary transmission of vectored vaccine virus.

[a] Items 1–7 identified by WHO informal consultation on characterization and quality aspect of vaccines based on live viral vectors, December 2003 [27]; items 8–11 added by V3SWG.
[b] originally: Potential changes of tropism may lead to know properties of replicating viruses and should be carefully evaluated.
Italicized = modifications/updates by the V3SWG.

Figures

Figure 1 **Overview of the PDVAC pipeline by novel antigen presentation platform.** Regimens involving heterologous prime boost approaches, or candidates incorporating more than one platform are shown as stripped bars.

Note: Ebola virus vaccines are overseen by the R&D Blueprint, but are included in this PDVAC overview to reflect the pipeline status of novel platforms for this antigen

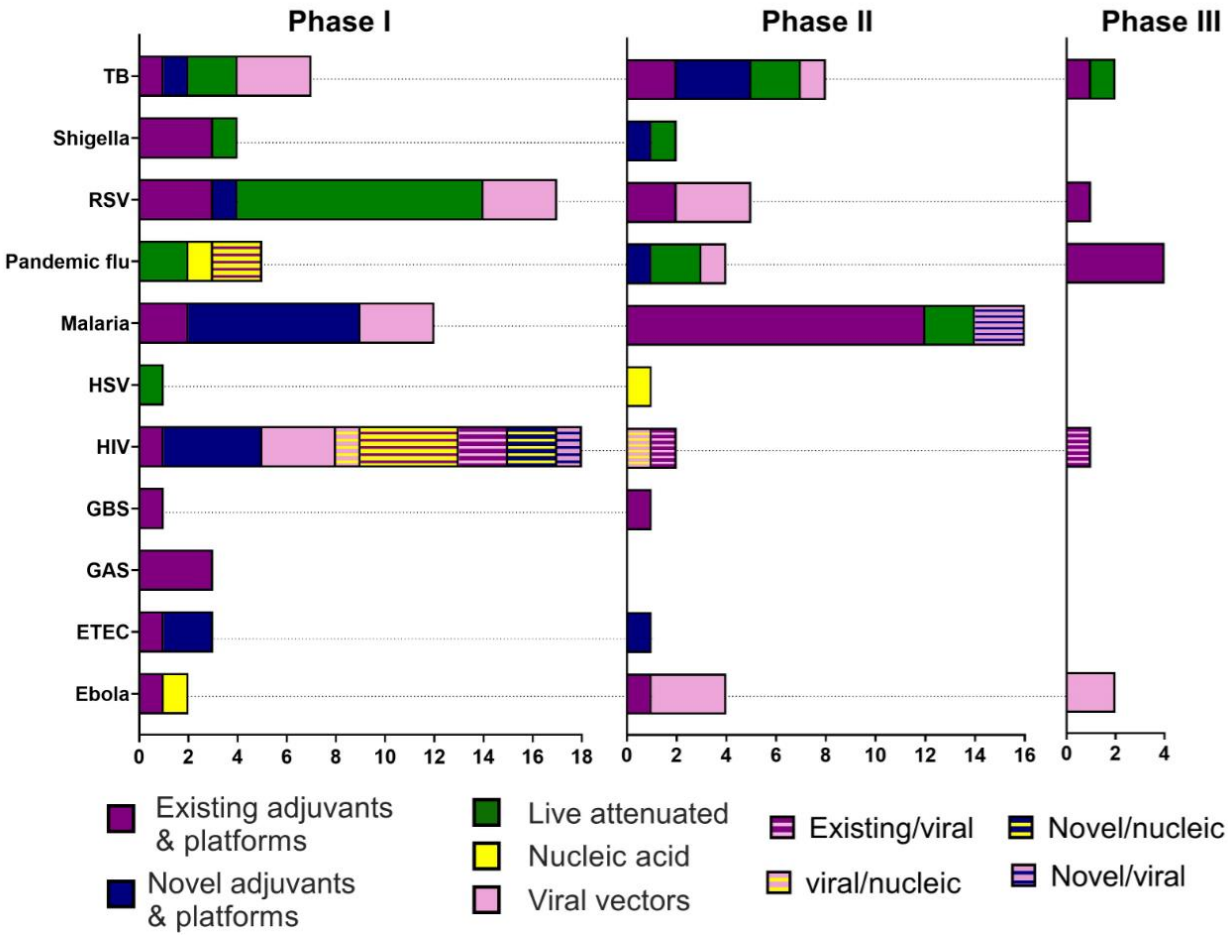

Figure 2 Publications on DNA and RNA vaccines 1990-2019

