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Vaccines against Ebola virus

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ABSTRACT

We have just witnessed the largest and most devastating outbreak of Ebola virus disease, which highlighted the urgent need for development of an efficacious vaccine that could be used to curtail future outbreaks. Prior to 2014, there had been limited impetus worldwide to develop a vaccine since the virus was first discovered in 1976. Though too many lives were lost during this outbreak, it resulted in the significantly accelerated clinical development of a number of candidate vaccines through an extraordinary collaborative global effort coordinated by the World Health Organisation (WHO) and involving a number of companies, trial centres, funders, global stakeholders and agencies. We have acquired substantial safety and immunogenicity data on a number of vaccines in Caucasian and African populations. The rapid pace of events led to the initiation of the landmark efficacy trial testing the rVSV-vectored vaccine, which showed high level efficacy in an outbreak setting when deployed using an innovative ring vaccination strategy. Though the Public Health Emergency of International Concern (PHEIC) declared by the WHO has now been lifted, the global scientific community faces numerous challenges ahead to ensure that there is a licensed, deployable vaccine available for use in future outbreaks for at least the Zaire and Sudan strains of Ebola virus. There remain several unanswered questions on the durability of protection, mechanistic immunological correlates and preferred deployment strategies. This review outlines a brief history of the development of Ebola vaccines, the significant progress made since the scale of the outbreak became apparent, some lessons learnt and how they could shape future development of vaccines and the management of similar outbreaks.

1. Introduction

On 26 December 2013, when an 18-month-old boy in Meliandou, Guinea developed a fatal illness characterized by fever, black stools, and vomiting, the global scientific community were unaware of the significance of what this heralded. The responsible pathogen was later identified as the Zaire species of the Ebola virus and the World Health Organisation (WHO) issued a public announcement on the 23 March 2014, where 49 cases and 29 deaths were officially reported [1]. Subsequently, we have witnessed the largest and most devastating outbreak of Ebola virus disease (EVD) resulting in more cases and deaths than all previous outbreaks combined. Ebola first appeared in 1976 in simultaneous outbreaks in Sudan and Democratic Republic of Congo (DRC) and takes its name from the Ebola River in DRC [2,3]. It is a large, negative-strand RNA virus composed of 7 non-segmented genes encoding viral proteins, including a single glycoprotein (GP) [4,5]. The GP comprises two subunits, which appear as trimeric spikes on the virus surface [6]. It plays a pivotal role in cell attachment, fusion and cell entry and its broad cellular tropism results in multisystem involvement and associated high mortality [6]. Therefore, the GP has become the key antigenic target for the development of vaccines against EVD.

2. Setting the stage – Ebola vaccine development prior to the 2014 West African outbreak

Commencing soon after the initial identification of the virus, the first attempts at vaccine development used an inactivated whole virus. This approach never progressed to clinical trials due to potential safety concerns, and failure to demonstrate efficacy in the more predictive non-human primate (NHP) model [7] despite some earlier efficacy in guinea pigs [8]. Recognition of the potential of DNA and viral-vectored vaccines during the 1990s resulted in the first pre-clinical studies expressing the envelope GP or nucleocapsid protein (NP) genes of Ebola virus [9,10]. Efficacy against lethal challenge was demonstrated in the 'gold standard' model of cynomolgus macaques when administered singly or in combination prime-boost regimes [10–12].

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The first ever human clinical trial to administer an Ebola vaccine in 2003 used a three-plasmid DNA vaccine encoding the transmembrane-deleted (ΔTM) GP from the Zaire and Sudan species as well as NP, which showed that a 3 dose-schedule was safe and immunogenic [13]. Second was a replication-defective, recombinant human adenovirus serotype 5 vaccine (rAd5), which encoded GP genes with a point-mutation (PM). A single vaccination successfully induced T cell and humoral responses against the insert though the latter was partially blunted by pre-existing immunity to Ad5 [14]. Non-human primate (NHP) studies, ongoing in a similar timeframe to these human clinical trials, showed that ΔTM GP and PM GP antigens conferred inferior protection to wild-type (WT) GP, which subsequently became the focus of vaccine development [11].

The second clinical trial of a DNA Ebola vaccine assessed safety and immunogenicity of constructs encoding WT GP from Ebola virus Zaire (EBOV) and Sudan (SUDV) species and the Marburgvirus Angola strain [15]. Though these trials demonstrated acceptable safety profiles, multiple doses were required and immune responses waned without the administration of a homologous booster dose at 32 weeks [13,15], and similar findings were shown in a Phase Ib study in Uganda [16].

Strategies to circumvent pre-existing immunity to Ad5 resulted in exploration of the use of serotypes that seldom circulate in humans (e.g. Ad26 and Ad35) and chimpanzee adenoviruses, which have a low human seroprevalence. Promising efficacy data in NHP models showed that rAd26-GP at a dose of 10^{12} viral particles (vp) when given as a single-shot, resulted in 75% efficacy against EBOV challenge. In the same study, a 4 week heterologous prime-boost regime with rAd26-GP/rAd35-GP resulted in 100% efficacy when macaques were challenged 4 weeks post-boost [17]. Both recombinant chimpanzee adenovirus serotype 3 (ChAd3), a subgroup C adenovirus with properties similar to those of Ad5, and serotype 63 (ChAd63) vectors were also considered for development of a new Ebola virus vaccine. Both vectors were shown to be safe in human studies evaluating candidate vaccines for other infectious diseases [18,19]. An efficacy study in NHP of the ChAd3 in both monovalent and bivalent preparations expressing EBOV and SUDV GPs demonstrated 100% efficacy against EBOV challenge with no detectable viraemia [20]. Furthermore, durable protection to EBOV challenge 10 months after vaccination was observed when a heterologous boosting vaccination of replication deficient modified vaccinia Ankara (MVA) expressing both GPs was administered 8 weeks post ChAd3 prime. This effect was not seen when boosted with either the same vector or ChAd63, which itself had shown limited immunogenicity and protective efficacy. Hence, the ChAd3 vector was favoured for development into an investigational vaccine for human clinical trials. The well recognised ability of MVA vaccines to provide excellent boosting effect in a number of infectious diseases [21,22] and the durable efficacy observed in the NHP studies [20] provided evidence for the inclusion of a MVA boost vaccine in human clinical trials.

In addition to the above replication-deficient viral vectors, a recombinant, replication-competent vesicular stomatitis virus (rVSV)-based vaccine encoding EBOV GP had also progressed through preclinical development with encouraging efficacy data in NHP primates [23,24]. It had also been successfully administered to one patient on a compassionate basis for post-exposure prophylaxis following a needle stick injury [25].

3. Ebola vaccine development since the outbreak

Prior to the 2014 West African outbreak there had only been four completed Phase I vaccine clinical trials in the 38 years following the discovery of the virus [13–16]. As the outbreak spread rapidly from Guinea to neighbouring countries, Sierra Leone and Liberia with unprecedented number of cases and deaths, the WHO declared this a Public Health Emergency of International Concern (PHEIC) on 8th August 2014, by which point over 900 people had succumbed to the disease. In addition to other control measures orchestrated by the WHO and local stakeholders, this announcement heralded extraordinary efforts from the global scientific community to accelerate the development of an Ebola vaccine, ideally one for use in an outbreak setting. National and international efforts to provide funding, coordination, regulatory and ethical review support, expert advice and industrial and manufacturing support were initiated at remarkable speed. Funders included the Wellcome Trust, the European Commission, the US National Institutes of Health (NIH), the UK Medical Research Council, Departments for International Development and Health, and the Bill and Melinda Gates Foundation, many of whom introduced accelerated review mechanisms. Regulatory and ethical reviews of clinical trial protocols were accelerated in Europe, north America and Africa. New vaccines were rapidly designed, developed and manufactured in the US, Europe and Asia with trials rapidly initiated in these continents, Africa and Australia. Coordination activities were led by the WHO with strong input from several major vaccine manufacturers, regulators, public health experts and authorities from the affected countries and regions, academics, funders and relevant non-governmental organisations.

The two leading vaccine candidates that entered Phase I clinical studies in centres in three continents were the monovalent and bivalent ChAd3-vectored vaccine and the rVSV-vectored vaccine, both encoding the GP from the Ebola virus. These immediately accessible vaccines, in addition to a multi-valent MVA-vectored vaccine and an Ad26-vectored vaccine had been manufactured to Good Manufacturing Practice standards earlier, at times some years earlier, supported largely by biodefense funding allocated to develop vaccines that would protect better-off populations from a potential bioterrorist attack.

The numerous Ebola vaccines in clinical development have been reviewed extensively previously [6,26], so we will subsequently focus on lessons learned from this outbreak for vaccine development, its impact on the future of this field and outbreak management. However, a brief summary of all the vaccines in clinical development precedes this perspective.

4. Chimpanzee adenovirus 3 vectored vaccine

ChAd3-vectored vaccines expressing the Ebola glycoprotein, both in monovalent and bivalent forms, were the first vaccines to be administered to humans as part of this new wave of clinical trials, in the UK, Europe and US [27–29], and subsequently in Mali [30]. These trials were based on early positive pre-clinical studies in non-human primates by the Sullivan group at NIH [20] partnered with the Okairos biotechnology company in Italy, subsequently acquired by GSK. Encouraging clinical safety and immunogenicity provided the basis to commence a large Phase III trial in Liberia, eventually amended to a phase II design due to the decline in new cases of EVD (ClinicalTrials.gov NCT02344407). Clinical trials assessing this vaccine in children aged 1–17 years in Nigeria, Mali and Senegal are ongoing (ClinicalTrials.gov NCT02548078). In addition to single shot vaccine assessment, it has been trialed with prime-boost regimes using MVA [30,31] and Ad26 vectors (ClinicalTrials.gov NCT02495246).

5. Vesicular stomatitis virus vectored vaccine

Phase I clinical trials with this replicating vectored vaccine commenced across Europe and Africa shortly following initiation of the