MRC Review of Vaccines Research 2014

Background
Vaccines are hailed as one of the safest and most effective health care interventions of all time, saving millions of lives a year and are among the most cost-effective health practices ever developed. The science behind vaccination has historically been to ‘isolate, inactivate and inject’. Recent scientific advances are enabling a paradigm shift from this model, to ‘sequence, select and synthesise’ yet despite these advances, it remains challenging to produce effective vaccines for many diseases that pose a significant, often global, burden.

MRC last reviewed its vaccine strategy in 2007. The review led to a call in ‘Translational Vaccine Research’ (2008) which successfully funded four proposals. In recent years, translational vaccinology has continued to be funded through the IIB and also the Biomedical Catalyst ‘Developmental Pathway Funding Scheme’ (DPFS). Innovation in vaccines research remains a key priority area for MRC and to ensure we take advantage of new advances and opportunities, the Infection & Immunity Board (IIB) and MRC Strategy Board instigated the current review.

The 2014 review group was chaired by the IIB Deputy Chair Professor Sharon Peacock, and comprised members of the IIB, representatives of from pharma and biotech, and academic specialists from a range of vaccine-related disciplines. A number of themes emerged from expert opinion pieces and during review group discussions, and based on these a number of recommendations were made to the MRC to develop and support vaccines research in the future.

Key Themes / Issues
During the course of the MRC vaccines review day a number of themes emerged, within which there are key strengths, weaknesses, gaps and opportunities. There was a clear need for continued investment in basic science, and for further development of novel tools and technologies to innovate the predominantly disease-led approaches. The review group highlighted the existence of many strengths in existing UK and EU infrastructure, but noted limited access and high costs can be prohibitive (e.g. for GMP manufacture). Multidisciplinary partnerships between funders, academia, clinicians and industry are essential to accelerate vaccine research across the piece. To meet the unmet demand for new vaccines, translation of basic discoveries to products practicable for industry to manufacture should be the aim of vaccinologists. Finally, public health needs for vaccines have changed over time, and with an aging population the review group discussed the opportunities for therapeutic, as well as prophylactic vaccines to lessen the burden of diseases such as Alzheimer’s, cancer and allergies.
**Basic Science**

Many opportunities for innovating human and veterinary vaccines research and production originate in basic science. The review group agreed on the importance of maintaining funding for basic research, and highlighted the following areas as important for underpinning vaccines research.

**Immune correlates of protection** – Advancing research and development (R&D) of novel vaccines that elicit a protective immune response will require identification of the differences between general immune responses to a pathogen or vaccine, and the response that confers protective immunity for the long-term. Studying individuals who show naturally acquired immunity to disease (e.g. sex workers in Kenya with immunity to HIV) would provide insights into true correlates of protection and identify potential candidate antigens.

**Antigen discovery** – Studies of immune correlates of protection as described above will be pivotal in identifying novel antigens that induce protective immunity. This may involve:

- Accessing relevant cohorts and obtaining quality datasets
- Systems-level interrogation of data – MRC is capacity-building in systems medicine and there may be synergies with existing projects, such as the MRC/BBSRC systems immunology consortium modelling B cell expansion in the elderly in response to vaccination
- Identifying ‘universal antigens’ that stimulate T-helper cell responses, boosting the overall immune response so that single, or lower doses are required
- New antigen-screening strategies, such as phage-display cDNA screening, where pathogen cDNA libraries expressed on a phage are screened against sera samples from diseased patients

**Adjuvants** – Our current understanding of adjuvants is relatively poor and the number of useful adjuvants limited. Future priority areas include developing adjuvants that will induce local rather than systemic immune responses, and increasing understanding of how adjuvants target the receptors of the innate immune system, for example adjuvants that comprise immunostimulatory DNA sequences recognised by these receptors. Adjuvant research should also comprise studies into correlates of safety.

**‘Reverse vaccinology’ (RV)** – Initiating vaccine production starting from the bioinformatic sequence data, it is possible to determine the entire antigenic repertoire of a pathogen and go on to refine candidates for testing. Centralised bioinformatic resources to support researchers using this approach are becoming available, e.g. the ‘Vaxign’ programme, which allows users to identify *in silico* candidates for >350 pathogen genomes. The Novartis Meningococcal B vaccine was developed using this approach where 600 *in silico* candidates were narrowed to 350 recombinant proteins. These were reduced to 91 surface antigens and then to 28 proteins that induce

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3 Vaxign has been created by Professor Yongqun He and is maintained at University of Michigan Medical School, Ann Arbor, MI, USA. [http://www.virolinet.org/vaxign/](http://www.virolinet.org/vaxign/)
bactericidal antibodies, and finally 4 that were selected for vaccine production\textsuperscript{4}. The vaccine was approved for use in the EU in 2012, 15 years after this work began.

Whilst RV has innovated vaccines research and continues to have great potential, it has limitations due to the inability to identify non-protein antigens such as polysaccharides and lack of elucidation of 3D antigen structure. Also, poor understanding of vaccine-induced and pathogen-induced correlates of immunity is rate-limiting in screening for protective immunity (see next section).

‘Structural vaccinology’ – Where vaccines may not have worked in the past due to loss of structural integrity of the antigen, structural approaches can now be taken to ensure that potential antigen structure is preserved, thus retaining its immunogenic properties. Structural vaccinology is complementary to, and builds on the advances of reverse vaccinology and has the potential to help develop vaccines to pathogens such as respiratory syncytial virus (RSV)\textsuperscript{5}.

Conjugate vaccines – Some polysaccharide-conjugate vaccines have succeeded in inducing immune responses that prevent or eliminate colonisation in the host (e.g. pneumococcal), but a better understanding of the long-term implication of eliminating well understood pathogens that may permit colonisation (and infection) with less-understood pathogens is needed. We also need a better understanding of how polysaccharide conjugation activates the adaptive immune system to induce T cell responses (e.g. meningococcal C).

Mucosal vaccines – The portal of entry for many systemic infections is a mucosal surface. Because of the compartmentalization of the mucosal and systemic immune systems, effective protection of mucosal surfaces requires a mucosal route of vaccination. There is scope for further research to elucidate mechanisms of mucosal-induced immunity and better characterise innate lymphoid cells in the mucosa.

**Novel Tools and Technologies**

There have been recent advances in vaccine biomanufacturing that have enabled vaccines to be produced that could not have been envisaged a decade ago. The review group agreed there is huge scope for new tools and technologies to innovate further human and veterinary vaccinology and strongly supported investment in these areas.

Antigen delivery – When embarking on antigen discovery studies, investigators need to consider how this could be formulated and delivered. Multidisciplinary vaccine research networks or consortia should include bioprocess engineering expertise to ensure that manufacture and scale-up of promising antigens is feasible. Novel approaches to antigen delivery include nanoparticle-encapsulated \alpha-galactose-modified antigen\textsuperscript{6}.


\textsuperscript{5} Data presented at the review by Dr Rino Rappuoli, Novartis

Vaccine delivery – There is a potentially huge market for alternative vaccine delivery mechanisms that circumvent the need for injection and refrigeration of vaccine. One such alternative is the recently developed microneedle dermal patches which can deliver small molecules, biological compounds and vaccines\(^7\).

Systems biology – Interdisciplinary systems biology approaches have great potential to innovate vaccinology, such as:

- pathology of infectious diseases – integrating transcriptomic and proteomic immune signatures of the host-response to pathogens (identification of correlates of protection)
- integrating transcriptomic and proteomic immune signatures of the host-response to vaccination (termed ‘systems vaccinology’\(^8\)) over the lifecourse
- identification of early innate signatures that predict vaccine immunogenicity
- identification of potentially novel mechanisms of immune regulation
- antigen prediction and design
- rational vaccine adjuvant design
- rigorous systems analysis of potential outcomes (e.g. host pathogen data, immunogenicity data, predictive modelling) to mitigate against late-stage failures in industry

The potential for bioinformatics to innovate vaccine development is inextricably linked to the quality of bioinformatic tools and capabilities that are currently available. Moreover, new computational methods and programmes along with better immune-informatic tools can be used to predict immune responses. The difficulty in integration of vaccine-related data into common or accessible platforms is a barrier to progress, however, as is the available server capacity to boost storage and integration.

Synthetic biology
Intrinsically linked to advances in bioinformatics and integrated systems approaches, synthetic biology (synbio) combines \textit{in silico} analysis to design and construct \textit{de novo} new biological systems, or improve existing ones to produce chemicals or biomolecules of interest. In vaccinology, synbio has been used to

- improve vaccine safety
- improve vaccine immunogenicity
- improve vaccine vector design and generation
- generate live attenuated vaccines and viral/bacterial vectored vaccines

Working in partnership to integrate novel tools and technologies into vaccine research – The development and processing of vaccines should be considered at all stages of the pipeline, with bioscientists and engineers working in partnership. However, while there may be common ground in approaches to produce vaccines, there is no single platform process due to pathogen specific differences. Rapid identification of areas of convergence (of human, and animal vaccinology areas, especially in the early stages) and identifying areas where proven methods can be applied to speed up

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\(^8\) Quote one of Oliver He's papers.
processes would maximise success. There is scope for cross-Research Council working with BBSRC and EPSRC to provide routes to fund both human and veterinary vaccinology, for example, in synbio and vaccine bioprocess engineering.

Infrastructure
Despite the pathogen-specific differences in vaccine production, the infrastructure needs are often the same and the underpinning technologies for vaccines development can be shared, if appropriate, for both human and animal vaccines. The review group agreed that there were a number of strengths (detailed below), but also some clear needs. Greater networking and partnership would enable the vaccinology community to capitalise on existing infrastructure.

In vivo and in vitro models – There is a critical need for predictive, humanised, in vivo models to ensure that only the most promising candidates proceed to clinical trials, since there are numerous candidates that have been shown to be effective in models that then become late-stage failures. Access to a range of animal species and the potential to exploit existing models to greater mimic the human and animal response is needed. It is vital that the UK retains the capacity and skills-base to conduct this work e.g. Porton Down has unrivalled resources in the UK for vaccines research using non-human primates and can provide these at highly competitive rates. The review group agreed the importance of models that take into account a challenge regimen and dosage levels that reflect the natural disease state; under- or over-estimation of this will skew analysis of prophylactic or therapeutic interventions, possibly hiding true efficacy effects. The review group acknowledged the importance of iteration between animal modellers and clinicians to provide access to most recent clinical isolates.

In vitro models are also highly relevant for their application in rapid screening and analysis of vaccines, and the Group recommended some effort be focussed on developing better in vitro models.

GMP and biomanufacturing – Biomanufacturing and GMP-grade materials are fundamental to vaccinology research, and while resources to make GMP material in the UK do exist, greater access as well as reduced costs are needed. Economically viable production of small, lab-scale sample lots would represent a step-change.

Infrastructure hosted by the National Biologics Manufacturing Centre (Darlington, UK) may prove to be beneficial for the vaccinology community, providing open access facilities to prove and scale up process and support for the development of new innovative process technologies and manufacturing routes up to the pre-GMP stage.

Computational Power – Funding will be critical to enable data storage on computer servers, provide resource for algorithms and development of software programmes, and provide access to up-to-date bioinformatic tools. There is a strong case to establish an integrative platform for sharing and mining data and information, and also to support a vaccine safety and monitoring system.

Networking - Creating a national network to share resources (for e.g. vectors and adjuvants) would support researchers across the whole vaccines research sector. The
review group suggested that consolidation and cohesion of resources could create an EATRIS\(^9\)-style network due to the capabilities that already exist.

**Translation and Industry**

The review group stressed the importance of translating basic research in vaccines to immunization products, and highlighted the role of funders in brokering partnerships between industry and academia, especially in the early stages of product development. Industry has identified the vaccines market - estimated to be worth €21bn in 2015 - as a key area for further growth. Some current interests for vaccine development include HIV, HBV (in China), HSV / CMV / EBV, TB, acne and periodontal disease caused by *Porphyromonas gingivalis*. But pharma are also pursuing vaccines for non-infectious diseases, most notably cancer but potentially neurodegenerative disorders and inflammatory diseases.

**Early clinical studies** - Costs for early translational work are high, and so any partnership or networking activities that lead to shared resources could be very beneficial – not only in the UK, but EU-wide - engaging with infrastructure such as EATRIS and the European Vaccine Initiative (EVI)\(^10\). Access to patients and volunteers is essential for translation but no one institute in the UK has the resource to conduct clinical trials alone, therefore networks and partnerships are required between HEIs, NHS Trusts, contract research organisations (CROs) and funders.

Areas of need in increasing the UK’s capacity for translational work will require:

- more research-active clinicians
- excellent administrative support to streamline processes and ensure trials run effectively
- a mechanism for fast-tracking through small trials designed to test new ideas and generate preliminary data

MRC has played a role in supporting early clinical work through the Developmental Clinical Studies (DCS) and Developmental Pathway Funding Scheme (DPFS). These schemes were implemented to support the translation of fundamental discoveries toward benefits to human health, funding the pre-clinical development and early clinical testing of novel therapeutics, devices and diagnostics, including “repurposing” of existing therapies. A case study demonstrating the impact of DCS/DPFS funding in accelerating vaccines research can be seen in Box 1.

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\(^9\)EATRIS comprises over 70 leading academic institutions across Europe (NB. the UK is not a partner) and provides a development pathway for researchers and companies for advancing biomedical innovations. The EATRIS Vaccines Product Platform ([http://www.eatris.eu/platforms/vaccines.html](http://www.eatris.eu/platforms/vaccines.html)) is one of five platforms, and provides expertise and infrastructure in translational vaccinology to advance candidates up to phase IIa trials. EATRIS Vaccine institutions have a broad range of scientific, technological, clinical and regulatory expertise as well as infrastructure for production and testing, and operate high-quality and standardized services.

\(^10\) The European Vaccine Initiative (EVI) seeks to align all major stakeholders with a view to developing vaccines for diseases of poverty for low income populations. EVI funds research into major diseases of poverty such as malaria, tuberculosis, leishmaniasis, meningitis and dengue ([http://www.euvaccine.eu/about-us/mission-and-aims](http://www.euvaccine.eu/about-us/mission-and-aims)).
**Cost-Benefit Analyses** - Unless there is a strong commercial case supported by cost-benefit analyses, industry is highly unlikely to commit to develop and produce a vaccine. Diseases that present low medical need but high feasibility (e.g. anthrax) may be as unlikely to be produced by industry as those where there is a high medical need but low production feasibility (e.g. *Klebsiella*). While industry recognises that some diseases may pose an urgent public or global health need, the costs to develop such treatment may be prohibitively high in the early phases. The review group emphasised the role of funders in brokering partnerships between academia and industry to de-risk areas of research that industry may not otherwise pursue, and in particular, de-risking costly work in the early pre-clinical stages of vaccine development that can allow pharma to pursue stronger candidates. Challenges for industry also include global distribution and meeting the supply needs for different countries. When a vaccine is produced, industry must consider the biological production system and scale-up processes that will enable them to reach ‘last dose’ sooner; i.e. efficiently producing in the shortest time sufficient doses of vaccines for a given population.

There have been changes in the UK pharma R&D and manufacturing presence in recent years, and some perceptions that the UK is losing primacy in pharma R&D have arisen. However, the pharma sector remains one of the UK’s key industries, generating a trade surplus of over £5.5 billion in 2012. Whilst there are no vaccines produced in the UK, there are opportunities to capitalise on the infrastructure that exists and promote UK-based vaccine development through partnership.

**Partnerships**
The review group recognised the excellent work MRC has done to facilitate partnerships between different stakeholders.

**Cross-disciplinary partnerships** – There are several internationally recognised centres of excellence in the UK undertaking vaccines research. The review group agreed the sector would benefit from better networking and support to bring activities and centres

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11 Presented by Professor Jeff Almond, Sanofi Pasteur  
12 HM Revenue and Customs, UK Trade Info.
of excellence together, but agreed that MRC Centre funding may not be the right model. The BSSRC ‘Veterinary Vaccinology Network’ is in the early stages of establishing better cohesion among veterinary and some human vaccinologists, and the review group agreed that this is an important activity.

The review group agreed that to maximise quality/potential of cross-disciplinary partnerships to integrate novel tools and technologies with vaccines research, partnerships should be established early on in the R&D process. Best-practice was shared with the review group from the UCL/EPSRC manufacturing centre, in that the most innovative and productive partnerships are those that are established early on in the R&D process.

**Academic-Industry Partnerships** – The importance of funders in committing to academic-industrial partnerships is especially acute where cost-benefit analysis makes industry reluctant to invest in a particular disease or vaccine. Product development partnerships (PDPs) and partnerships with organisations such as the Gates Foundation have proved instrumental in developing new vaccines for a global market such as AERAS for TB vaccine production. Although there are limited opportunities for partnering with vaccine-producing companies in the UK, the Research Councils can support partnerships with international companies. There are also opportunities to work with SMEs and biotechs (such as Absynth Biologics) who are developing vaccine candidates, for example, through vaccine-related work in the Technology Strategy Board (TSB) Catapults supporting innovative bioscience in the UK and through the Biomedical Catalyst Fund. The Group highlighted the importance of Research Councils keeping application processes as straightforward as possible.

**Government Departments and Research Councils** - ‘Ownership’ of vaccines research is spread between a number of different public-funded bodies in the UK. Partnerships between Research Councils (MRC, BBSRC, EPSRC) and government departments (PHE, DoH, DfID, DSTL, DEFRA) are essential to ensure integration of vaccines research and vaccine use in public health, global health, animal health and agriculture across government.

**Future Health challenges and vaccines research**

**Vaccinations across the life course** - With an increased aging population, it is important that vaccinologists and policy makers consider target groups for vaccination across the whole of the life course. The most widespread adult vaccine is for seasonal influenza, but there are emerging needs for vaccines against diseases that prevail in later life, to pathogens such as *Clostridium difficile* and MRSA. Better understanding of the aging immune system is needed, as well as better understanding of the optimal timing throughout the life course to vaccinate against pathogens that may prevail during immunosenescence.

There is also an opportunity for research on maternal vaccination, to better understand the role this intervention could play to benefit the expectant mother, the unborn child, or both.

**Therapeutic vaccines** - There is huge potential for development of therapeutic vaccines for Alzheimer’s disease, allergies, asthma and cancer. Diagnoses of asthma and allergies have increased, and with a growing aging population the burden of Alzheimer’s and cancer on the NHS is predicted to increase, In addition to the scientific
opportunities in developing new vaccines for these areas, there are public health drivers for the UK to shift focus away from infectious communicable disease.

There have been some notable advances in cancer vaccines in recent years (e.g. licensure of a therapeutic vaccine for prostate cancer and mass vaccination against HPV that can cause cervical cancer), but there is very little knowledge on what constitutes a successful candidate vaccine antigen for cancer or on the correlates of anti-tumour immunity and what constitutes a protective immune response. While the majority of vaccinology research funded by MRC supports infectious disease, there may be a greater role for MRC in cancer vaccine research, possibly in partnership with CRUK.

Take up by public health providers - Whilst there is a clear need for new and improved prophylactic and therapeutic vaccines to prevent disease, the review group raised the importance of the ‘Joint Committee on Vaccination and Immunisation’ (JCVI) which advises UK health departments on immunisation and influences decisions on which vaccines are taken up as public health interventions. Working in partnership and learning from case studies of best-practise will be invaluable, such as the recent case of the Bexsero vaccine for meningococcal B. The JCVI produced a model which showed that the vaccine wasn’t cost-effective therefore initially advised the UK government a mass vaccination programme would be uneconomical. Following this, a period of stakeholder consultation to improve the model parameters ensued and a refined, final model showed that the vaccine could be cost-effective for the NHS at a low price. Bexsero will now be used in the routine immunisation of babies in the UK13.

Concluding remarks
The review group agreed that there is huge potential to innovate vaccines research in the UK, and that the UK research base has expertise to develop and deliver in this area. Their discussions covered many topics, but they prioritised two areas of research that could have short-term impact for longer-term gain:

- The importance of identifying true correlates of protection through studying immune responses to vaccination, responses to pathogen infection and in cohorts who have acquired natural immunity
- Novel tools and technologies that will transform both animal and human vaccinology, such as synthetic biology or innovative processes for industrial scale-up for cost-effective production of vaccines

Key recommendations for the MRC
1. To stimulate more research in basic science, in the areas of understanding protective immune responses to vaccines and pathogens across the life course
   a. Raise the profile of key areas of need through a Highlight Notice on the MRC website
2. To stimulate more research in novel tools and technologies for vaccines that cut across Research Council remit
   a. Hold a workshop event to define areas of key need
   b. Conduct a mapping exercise of existing research in this area
3. To facilitate networking and partnership building, in recognition of existing centres of excellence and the need to develop academia/industry partnerships