MRC/BBSRC GCRF Networks for Vaccine R&D:

Following the outline meeting of the Global Challenge Research Fund Networks for Vaccine Research & Development Expert Panel (membership below) on the 23rd November, we have invited 8 applications to apply to our Full Stage meeting, which will take place on 16th March 2017. The deadline for the Full Stage Applications is the 9th February.

- Professor Calman MacLennan – BactiVac
- Professor Helen McShane - Vaccine development for complex Intracellular neglected pathogens (VALIDATE)
- Professor Sarah Gilbert - Viral vectored vaccines to address global health challenges
- Professor Peter Openshaw - Human infection challenge vaccine (HIC-vac) network
- Professor Beate Kampmann - IMPRINT- Immunising pregnant women and infants network
- Professor Daniel Altmann - Correlates of protection in vaccine development network
- Professor Robert Heyderman - MRC/ BBSRC Systems Vaccinology Network (SYSVACC) - novel solutions for vaccine evaluation
- Dr Tim Connelley - International Veterinary Vaccinology Network

To support groups with aligned interests to these successful proposals potentially join with them, abstracts and contact details for each of these proposals is provide below.

The Expert Panel consists of the following members:

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<th>Name</th>
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<td>Professor Stephen Inglis</td>
<td>Former - NIBSC</td>
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<td>Dr Phillipe Denoel</td>
<td>GSK</td>
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<td>Dr Nathalie Garcon</td>
<td>Bioaster</td>
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<td>Professor Mary Collins</td>
<td>Okinawa Institute of Science and Technology</td>
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<td>Professor Adrian Hill</td>
<td>University of Oxford</td>
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<td>Dr Mike Francis</td>
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<td>Professor Stephen Gordon</td>
<td>Liverpool School of Tropical Medicine</td>
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<td>Dr Joann Prior</td>
<td>Defence Science and Technology Laboratory</td>
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<td>Professor Mike Levine</td>
<td>Maryland – Centre for Vaccine Development</td>
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Network Abstract:

Globally, bacteria cause around six millions deaths/year in humans and many more in animals. As anti-microbial resistance (AMR) increases, this number will rise with devastating personal and economic consequences. Low and middle-income countries (LMICS) are particularly affected. Implementation of vaccines against bacterial infections in LMICS has led to major reductions in disease burden. Nevertheless, bacterial infections remain for which no vaccine is available. Many represent straightforward targets for vaccine development, but have been neglected due to lack of commercial incentive. Many of the required skills for successful research and development for bacterial vaccines are already present in the UK. Also, the UK has strong links with LMIC researchers through the MRC and Wellcome Trust major overseas programmes. A network to harness these skills for bacterial vaccine development is currently lacking. This proposal will establish such a network centred in the UK, but with strong links to LMICs, and to the industrial sector, particularly industry-based global health institutes and developing country manufacturers. The network will serve to interconnect diverse expertise in order to drive forward vaccine innovation, and to advocate strongly for bacterial vaccines among UK, LMIC and global health policy makers. Its work will be facilitated by pump priming of pilot research projects, particularly those directly involving LMICs and industry, and providing support for training of members from LMICs. An annual network meeting will be held alternately in an LMIC setting and an industry setting to connect members who are least likely to meet through existing channels.

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Vaccine development for complex Intracellular neglected pathogens (VALIDATE)

Network Abstract:

For several complex intracellular pathogens, we have an incomplete understanding of protective immunity. This limits our ability to develop effective vaccines. The current linear approaches, which identify a component of the immune response, induce it by vaccination and evaluate efficacy in animal models, are flawed and inefficient. We propose an iterative approach to developing an accurate working model of immunity by repeated integration of data from human experimental studies and animal models. The inclusion of veterinary vaccinologists will facilitate the One Health agenda, and the inclusion of LMIC country partners and industrial partners will ensure relevance and translation. The experimental medicine and larger animal models provide the touchstone for relevance and for translation, the smaller animal models provide the tools with which to easily dissect mechanisms and immune pathways. The integrated approach incorporates in-silico and invitro tools to expand the model and delineate mechanisms. This Network call provides a unique opportunity to bring together individuals and promote free sharing of information within a protected environment. Positive and negative results can be disseminated rapidly and the working models for each of the complex diseases can learn from the success and failures of the others. Key activities and deliverables include annual meetings for knowledge sharing; creation of a virtual network for real-time data sharing; proof-of-concept funding to fill knowledge gaps, provide data to enhance the competitiveness of larger grant applications; and career development by funding, training and mentoring of early post-doctoral and new PI researchers.

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Viral vectored vaccines to address global health challenges

Network Abstract:

Viral vectored vaccines offer the opportunity for rapid development of novel vaccines, inducing potent humoral and cellular immune responses often with a single dose. For widely used adenoviral and poxviral vectors there is also substantial evidence of large-scale lowcost biomanufacturing feasibility, safety in humans and many other species, and product thermostability. Replication-deficient viral vectors have been safe in many thousands of vaccinees including infants and elderly, and in HIV-infected subjects. The UK has a leading position in the development of such vaccines, but this expertise is focal and access to vectors and know-how needs to be widened to fulfil the exciting potential of this technology for a range of globally important diseases. We propose here to bring together diverse expertise spanning virology and initial vector design and improvement, through immunogenicity and efficacy testing, all the way to largescale field trials. This will provide multiple new opportunities: i) to compare directly the potential of a range of different viral vectors derived from adenovirus, poxvirus and herpes viruses; ii) to produce higher level and more sustained immunogenicity through novel rapid synthesis and engineering of novel vectors; iii) to unblock the bottleneck in evaluation of such vectors by generating recombinants in a dedicated high-throughput high-quality facility; iv) to facilitate translation of promising pre-clinical constructs by sharing the knowhow of those with extensive clinical development experience; and v) to interface productively with companies developing such vectors commercially, and also with product development partnerships, to help prioritise candidates for translation to larger-scale trials.

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Network Abstract:

Since the time of Edward Jenner, the UK has distinguished itself in volunteer challenge to prove vaccine efficacy. Challenge studies streamline vaccinology (PMID: 21179119), elucidate disease pathogenesis and allow true mechanisms of protection to be discovered. They are particularly important for sporadic or unpredictable diseases, when animal models are inadequate and when events early after exposure need to be studied (rarely possible in observational human studies). The UK provides an excellent legal and ethical environment for experimental infections and is a global leader in this field.

Pathogens used in volunteer challenge include *E. coli*, *H. pylori*, *Shigella*, *Salmonella* (para)typhoid (PMID: 24519873), pneumococcus, meningococcus, worms, *Francisella* and gonococcus, malaria, cholera, dengue, rhinovirus, influenza and RSV (PMID: 23174372; PMID: 27199398); and there is interest in Zika and coronaviruses. These agents are all important in low and middle income countries (i.e. OECD DAC list) and are priorities for research in the UK. National coordination, collaboration and mutual support would greatly accelerate these studies, reducing commercial risks and facilitating vaccine and antimicrobial development.

This network will link researchers across the UK and elsewhere to provide shared frameworks and reagents, assisting with safe working, ethics and in developing and enhancing public understanding of these vital studies. The network will focus on defining those responses that are protective and those that are pathogenic and on early events occurring in the prodromal phase of infection that predict outcome. We will encourage new investigators to enter the field, accelerating vaccine development for diseases in resource-poor settings.

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Network Abstract:

Over 40% of deaths in young children now occur in the neonatal period and further progress in decreasing child mortality depends on reducing the 2·9 million neonatal deaths that occur each year, around a quarter of which are directly due to infections. The principle that vaccination in pregnancy can prevent infant infections is now strongly established for tetanus, pertussis and influenza. New pregnancy vaccines (Group B streptococcus and RSV) are in phase II/III trials and other vaccines designed to prevent congenital and neonatal infections are in development (CMV, Zika virus). Strategies for prevention of other infections can additionally be strengthened by the addition of neonatal vaccines, as exemplified by Hepatitis B.

A number of scientific and programmatic challenges must be overcome before the full potential of this approach can be achieved. These can be met through a better understanding of:
1. maternal immune responses and transplacental antibody transfer in the context of different vaccines and different co-factors such as nutrition;
2. neonatal immune ontogeny and the impact of vaccines on subsequent immune responses;
3. optimal assessments of the efficacy, safety and acceptability of vaccination in pregnancy.

Our network investigators have a proven track record in this field, will address these challenges and provide access to relevant technical and policy platforms. They will share existing data and expertise, conduct fundamental experimental science, leverage additional funding and offer mentorship and training to developing vaccinologists from LMIC settings.

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Correlates of protection in vaccine development network

Network Abstract:

The ‘MRC Review of Vaccines Research’ highlighted immune correlates of protection (COP) as a key bottleneck in vaccine development. Investigators, producers, regulators and policy-makers developing new vaccine programmes have attached considerable importance to COP in trial evaluation. These have often been neutralizing antibody titres, deduced to offer a correlate of in vivo protection. The ability of an immunization regimen to attain the required value may have profound impact on trial evaluation and ‘stop–go’ decisions. For many vaccines in development, the criteria may be more complex and we urgently need creative approaches to assessing endpoints and protection. For many pathogens that impose a high disease burden and for which no effective vaccines are available, we lack pertinent mechanistic insights (and thus, validated, relevant assays) into those biological parameters that best correlate with efficacy. Relevant approaches may include T cell analysis, transcriptomics/systems biology, mathematical modeling and in vitro neutralization/bactericidal models. Development, exchange and validation of reagents for international agreement on COPs will be paramount in enhancing pathways to licensure. We propose a highly inclusive network, initial membership spanning expertise in >18 viral, bacterial and parasite pathogens, including TB, Zika, Ebola, malaria and MERS. Initial membership covers investigators across many LMICs; an early goal will be to further broaden membership and outreach internationally across researchers, vaccine producers, regulators and other stakeholders. We seek funds for build-up and establishment of the network and for a series of catalyst activities to enhance communication, training, expertise, data and reagent sharing, leading to actual impact, easing the COP bottleneck.

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Network Abstract:

Prevention of high burden infectious diseases is critical to public health, yet knowledge of how to assess novel and existing vaccines, optimise vaccine doses and schedules, and measure protection remains incomplete. SYSVACC will build cutting-edge interdisciplinary partnerships in UK and LMICs, generating new insights into the optimisation of vaccine protection for evaluation in large-scale trials, transforming vaccine development and implementation to improve human and animal health. SYSVACC will prioritise high disease burden “Vaccine Challenges” relevant to LMICs. The “Challenges” initially focus on the pneumococcal, influenza, salmonella, rotavirus and TB vaccine strengths of the membership, establishing data curation and computational tools to integrate vaccine-related data for data sharing and mining. “Vaccine Challenge” pump-priming catalyst grants for early-career researchers and collaborative groups will generate the experimental data necessary to inform large scale clinical trials in LMICs. Projects will include the identification of the best time points to measure immunity in human challenge models; optimisation of vaccine route, dosage and scheduling; identification of readouts following maternal immunisation; and putative correlates of protection. Annual meetings will encourage information sharing, networking, collaborative projects and joint grant applications. We will raise awareness of SYSVACC and the “Challenges” through a website, social media, and a Blog, facilitating communication with other Networks, academic institutions, industry, policymakers, and the public. Training workshops and conference scholarships will enhance the capabilities of UK and LMIC early career researchers. SYSVACC will therefore move vaccine evaluation research towards a more integrative systems approach applicable across multiple target diseases.

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Network Abstract:

Vaccines are required for many diseases that adversely impact animal production in LMICs. Vaccinology is a multi-disciplinary field and success is dependent on effective integration of skills and resources from a range of basic and applied scientific disciplines. Here we propose the formation of an International Veterinary Vaccinology Network (IVVN) that provides a forum for the integration of inputs from research scientists, other specialists (e.g. economists), industry, policymakers and regulatory bodies to focus specifically on development of vaccines for livestock, poultry, aquaculture and comparative vaccinology to support human vaccine development in LMICs. The IVVN will focus on diseases that contribute to rural poverty in LMICs and also limit global food production, threaten food security and/or have serious zoonotic potential. By establishing an accessible integrated community and facilitating and promoting the coordination of research, the IVVN will make the range of skills required to effectively develop vaccines accessible to many researchers, both in the UK and in LMICs, who would otherwise find it difficult to engage such a broad assembly of expertise. This new Network will work alongside the UK Veterinary Vaccinology Network (UVVN); overlap of the steering groups and membership of the two networks will ensure they function collaboratively and bring mutual benefits. To achieve its aim it will be essential that the IVVN considers vaccinology within the context of the agricultural sectors of LMICs; this knowledge will be provided by LMIC vaccinologists whose representation and leadership will be fundamental to the success of the IVVN.

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