OUTLINE PROPOSAL: Medical Academic Clinical Fellowship (ACF) for the Health Protection Research Unit in Emerging and Zoonotic Infections (HPRU-EZI)

Title: The impact of inequalities on access to health care services for patients with possible emerging and zoonotic infections

Some emerging and zoonotic infections can arise unexpectedly and rapidly in the UK or across the globe, whilst others cause small numbers of sporadic cases. One of the critical aspects in controlling these diseases is for patients with suspected infections to access appropriate health care support in a timely manner. This requires rapid recognition of potentially important febrile, respiratory, and neurological syndromes, by patients, their relatives and health care workers. Additionally health care systems need to support, rather than hinder the quick diagnosis and appropriate management, including public health interventions. The ongoing threat of Ebola to the UK, previous swine flu epidemics, and sporadic cases of encephalitis demonstrate the challenges in this area. At times of heightened awareness, systems can be overburdened by inappropriate referrals. Additionally there may be erroneous focus on the emergent problems so that other important diagnoses are missed.

This ACF will use patient cohorts and databases acquired through our previous and current NIHR funding, and link this HPRU with the NIHR Collaboration for Leadership in Applied Health Research and Care (CLAHRC) North West Coast on Reducing Health Inequalities. The ACF will explore the patient journey from symptom onset, through primary into secondary care, using a mixed methods approach. The project will look for inequalities in access to health care, for example because of gender, age, ethnicity, education, travel and occupation. This will include interviews of patients, carers, and health care workers, and assessment of research and general practise data.

Outcomes
Linking these approaches will provide a better understanding of the health inequalities which impact on access to care for those with suspected emerging infections, and powerful preliminary data for full NIHR fellowship application.

The project will also strengthen links to NIHR CLAHRC and the NIHR HPRU in Emergency Preparedness (under discussion at the moment), and further develop health protection work in primary care, identified recently as a priority by NIHR.

HPRU Themes to be involved
Clinical Theme
Epidemiology Theme

Other NIHR Infrastructure
*NIHR HPRU in Emergency Preparedness
~NIHR Collaboration for Leadership in Applied Health Research and Care (CLAHRC) North West Coast on Reducing Health Inequalities

Suggested PIs:
Professor Tom Solomon, Dr Mike Griffiths, Dr Roberto Vivancos, *Professor Simon Wessel , ~Professor Mark Gabbay

OUTLINE PROPOSAL: Medical Academic Clinical Fellowship (ACF) for the Health Protection Research Unit in Emerging and Zoonotic Infections (HPRU EZI)

Title: Developing novel approaches to treat severe enterovirus 71 infection

Over the last 20 years, enterovirus 71 (EV71) has become one of the most important emerging infections across Asia, with sporadic cases in the UK. This picornavirus, which is closely related to poliovirus, mostly affects children, manifesting as hand, foot, and mouth disease, aseptic meningitis, poliomyelitis-like acute flaccid paralysis, brainstem encephalitis, and other severe systemic disorders, including especially pulmonary oedema and cardiorespiratory collapse. Work by the Liverpool team, in collaboration with colleagues in Southeast Asia, has identified clinical predictors of severe disease including high temperature lethargy, and Pleocytosis on lumbar puncture.

The pathogenesis of the severe cardiopulmonary manifestations and the relative contributions of neurogenic pulmonary oedema, cardiac dysfunction, increased vascular permeability, and cytokine storm are controversial. Work from the Liverpool and Asian collaborators has shown specific host mediator profiles in the CSF and serum are associated with cardiorespiratory complications. Serum concentrations of interleukin 1β (IL-1β), interleukin 1 receptor antagonist (IL-1Ra), and granulocyte colony-stimulating factor (G-CSF) were raised significantly in patients who developed cardio-respiratory compromise ($P = .013$, $P = .004$, and $P < .001$, respectively). Serum IL-1Ra and G-CSF levels were also significantly elevated in patients who died, with a serum G-CSF to interleukin 5 ratio of >100 at admission being the most accurate prognostic marker for death ($P < .001$; accuracy, 85.5%; sensitivity, 100%; specificity, 84.7%). Given that IL-1β has a negative inotropic action on the heart, and that both its natural antagonist, IL-1Ra, and G-CSF are being assessed as treatments for acute cardiac impairment, the findings suggest we have identified functional markers of EV71-related cardiac dysfunction and potential treatment options.

In the planned fellowship these observations will be taken forward into a physiological model of the heart developed using cardiomyocytes. To date we have shown in the model that cardiac contractility (in terms of beats per minute) was increased by G-CSF, and decreased by IL-1 β, with IL-1RA having no effect. Building on these findings, the fellow will examine the effect of different ratios of these host mediators, which will be chosen to represent the ratios found in patients; the effects of specific inhibitors which are available therapeutically and used in conditions like rheumatoid arthritis will also be examined.

Outcomes
These studies will allow a better understanding of severe cardiac compromise in EV71, and the role of possible treatments. Ultimately these studies will lead to clinical trials of novel therapies in severe EV71 infection. They will also provide preliminary data for an MRC or Wellcome Trust application, to join the many such fellows already funded through the Liverpool group.

HPRU Themes to be involved
Clinical Theme
Pathogen Theme

Other NIHR Infrastructure

Suggested PIs:
Professor Tom Solomon, Dr Mike Griffiths, Professor Julian Hiscox, Professor Lisa Ng, Dr Mong How Ooi