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Simpson, C.R., Thomas, B.D., Challen, K. et al. (8 more authors) (2020) The UK hibernated pandemic influenza research portfolio : triggered for COVID-19. *The Lancet Infectious Diseases*, 20 (7). pp. 767-769. ISSN 1473-3099

[https://doi.org/10.1016/s1473-3099\(20\)30398-4](https://doi.org/10.1016/s1473-3099(20)30398-4)

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The United Kingdom hibernated pandemic influenza research portfolio – triggered for COVID-19

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In 2012, the UK funder, the National Institute for Health Research (NIHR), in response to delays in research for 2009 influenza A/H1N, funded a portfolio of nine projects, described in a Personal View [1]. They were put on standby mode in a maintenance-only state awaiting activation in the event of new pandemic influenza. The portfolio covered key pathways of healthcare, including surveillance, primary prevention, triage and clinical management. In 2018 we were requested to adapt projects for new and emerging infectious diseases. Eight of nine projects have been repurposed and activated in response to the COVID-19 pandemic.

Flu Telephone Survey Template study (FluTEST), the first study to be activated is a survey of public knowledge, attitudes and behaviour and has been evaluating the impact of official communications on behaviour change in the community (table 1). The Early estimation of pandemic influenza Antiviral and Vaccine Effectiveness (EAVE) study has been expanded with data from 1.5m patients and the addition of new datasets including hospital ePrescribing. Potential therapies and the natural history of COVID-19 are to be explored. FLU-CATS, a real-time refinement and validation of criteria in primary care to aid hospital referral has been adapted to gather data from possible COVID-19 cases including gathering data from telephone consultations. The ISARIC WHO Clinical Characterisation Protocol for emerging infections UK (CCP-UK) study facilitates the collection of standardised clinical data and samples on patients hospitalised with suspected or confirmed infection with COVID-19. Funded by MRC, recruitment to CCP-UK has exceed 3,250 cases and samples are being distributed [2]. Data from CCP-UK is supporting Scientific Pandemic Influenza Modelling Committee (SPI-M) and the Scientific Advisory Group for Emergencies (SAGE). PAINTED has become the PRIEST Study: Pandemic Respiratory Infection Emergency System Triage, reflecting expansion to include all pandemic respiratory infections and the involvement of the ambulance service, alongside the emergency department, in deciding who needs hospital

admission. The UKOSS pregnancy study has been activated, no alterations to the study, other than the change to collection of data on COVID-19 infection have been needed. The Dexamethasone arm of RECOVERY (www.recoverytrial.net) is effectively an adaptation of The Multi-centre Adjuvant Steroids in Adults with Pandemic Influenza (ASAP) Trial. The first patient was recruited to the Trial within two weeks of the declaration of a pandemic by WHO (on 11 March 2020). The RTM Trial had been activated prior to COVID-19 pandemic, creating real time models to predict the impact of seasonal influenza [3]. More recently, our model has been adapted to COVID-19 and has been assisting SAGE through SPI-M. Decisions were guided through simulation of possible scenarios (in February) and now estimating epidemic evolution from initial data on confirmed cases and deaths. These estimates are being used to predict ICU demand, both nationally and at regional level. The PIPS study has not been activated as The Health Survey for England has cancelled field work due to social distancing measures. This has made the timely collection of specimens for serology not possible.

This national portfolio of hibernated pandemic studies is illustrating the value of the UK's clinical research system and the potential for rapid research, as well as clinical and public health response, to this pandemic. That most studies have been activated, and are performing well, exemplifies this model as an optimal way of using hibernating research studies to prepare for pandemic and emerging infections.

Contributors: CS led the writing of this personal view. All authors made contributions to the writing and discussions on scope and critically reviewed revisions.

Conflicts of interest: SG is Chair of the NIHR Health Technology Assessment

Commissioning Committee and chaired the NIHR Pandemic Influenza Themed Call Board.

All authors reports grants from NIHR, during the conduct of (and related to) the studies. CS reports grants MRC, National Environment Research Council and The Ministry of Business, Innovation and Employment. DA reports grants from Public Health England, outside the submitted works. MGS reports grants from NIHR and MRC related to this work and is a member of NERVTAG. WSL's institution has received unrestricted investigator-initiated research funding from Pfizer for an unrelated research study in pneumonia where WSL is the chief investigator.

Acknowledgements: The authors would like to thank all the collaborators of this work. These studies were funded by grants from the National Institute for Health Research Health under its Pandemic Preparedness call. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the HS&DR, HTA and Public Health programmes, NIHR, NHS or the Department of Health.

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Table 1 National Institute of Health Research Pandemic Preparedness Portfolio – COVID-19 pivot

Project	Lead Applicant and Institute	Purpose of study	Pivot to COVID-19 and status	Link
Flu Telephone Survey Template study (FluTEST)	Dr James Rubin, King's College London	Survey to identify public knowledge, attitudes and behaviour. During a pandemic we will support the UK Department of Health and Social Care in deploying these items and interpreting the results.	The first study to be activated. No substantial changes and findings being used to inform public health strategies. Study in progress.	https://www.ncbi.nlm.nih.gov/books/NBK263566
Early estimation of pandemic influenza Antiviral and Vaccine Effectiveness (EAVE): use of a unique community and laboratory national linked dataset	Professor Colin Simpson, The University of Edinburgh	Sentinel system linking primary care data to RT-PCR swabs, serology and hospital and mortality outcome data. Rapid evaluation of vaccination, antivirals and therapies. Intelligence on groups considered to be at increased risk of serious illness or death from infection.	Increase in country-wide population coverage and new datasets (including A&E, ambulance, ICU and ePrescribing). COVID-19 related morbidity and therapy data added. Therapeutic effectiveness and natural history of COVID-19 to be explored. Undergoing ethical and privacy permissions via substantial amendment of EAVE permissions.	https://www.ncbi.nlm.nih.gov/books/NBK321438
Real time refinement and validation of criteria and tools used in primary care to aid hospital referral decisions for patients of all ages in the event of surge during an influenza pandemic - FLU-CATs (Influenza Community Assessment Tools)	Professor Calum Semple, University of Liverpool	FLU-CATs is a study that checks if decision tools can be used by GPs and other Health Care Professionals to help them choose who can be cared for safely in the community and who needs urgent referral to hospital. FLU-CATs runs each winter influenza season in a small number of GP practices to keep the study processes running smoothly and ready to react should there be a 'new influenza' outbreak. In the event of a 'new influenza' outbreak FLU-CATs will quickly identify which problems that patients have best predict the level of care that they need.	Adapted to gather data from possible COVID-19 cases. Gathering data from telephone consultations. Study underway.	https://www.nottingham.ac.uk/research/groups/healthprotection/projects/flu-cats.aspx

<p>International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) WHO Clinical Characterisation Protocol for emerging infections UK (CCP-UK)</p>	<p>Professor Calum Semple, University of Liverpool</p>	<p>Provides an ethically approved framework for enrolling patients to a clinical study which offers new insights into this emerging global threat. It facilitates the collection of standardised clinical data and samples on patients hospitalised with suspected or confirmed infection with COVID-19. This informs the outbreak response and patient care. COVID-19 patients now identified in the UK, the UK health research community is well-prepared to advance our understanding of this disease.</p>	<p>Over 3250 COVID-19 cases recruited (as of 31/03/2020). Data and samples are being distributed. Reporting automated analysis in real-time to Scientific Pandemic Influenza Modelling group (SPI-M), the New Emerging Respiratory Virus Threats Advisory Group (NERVTAG) and Scientific Advisory Group for Emergencies (SAGE)</p>	
<p>PAndemic INfluenza Triage in the Emergency Department (The PAINTED study)</p>	<p>Professor Steve Goodacre, University of Sheffield</p>	<p>PAINTED aims to identify the most accurate triage method for predicting severe illness among patients attending the emergency department with suspected pandemic influenza.</p>	<p>Changed to PRIEST (Pandemic Respiratory Infection Emergency System Triage) to include all pandemic respiratory infections and include ambulance services. Status – study in progress following expedited ethics and regulatory review of amended protocol.</p>	<p>https://www.sheffield.ac.uk/scharr/sections/hsr/cure/priestpages/priest</p>

<p>Maternal and perinatal outcomes of pandemic influenza in pregnancy (UKOSS)</p>	<p>Professor Marian Knight, University of Oxford</p>	<p>The UKOSS influenza in pregnancy study will use an existing research platform to collect information on pregnant and postpartum women admitted to hospital with confirmed influenza infection. The management of women will be described, focussing particularly on the role of extracorporeal membrane oxygenation (ECMO), and women will be followed up to pregnancy completion in order to collect information on both maternal and perinatal outcomes.</p>	<p>Collecting information on pregnant/postpartum women with COVID-19. Study has begun – no known issues at this stage.</p>	<p>https://www.npeu.ox.ac.uk/ukoss/current-surveillance/flu</p>
<p>Multi-centre Adjuvant Steroids in Adults with Pandemic Influenza (ASAP) Trial</p>	<p>Professor Wei Shen Lim, Nottingham University Hospitals</p>	<p>The ASAP trial is a multicentre (>40 sites) blinded randomised controlled clinical trial to determine if low dose corticosteroids (dexamethasone 6mg started within 24 hours of admission once a day for 5 days), in addition to standard care, is associated with a lower risk of death or admission to intensive care, compared to placebo.</p>	<p>The ASAP trial has become an arm of RECOVERY. Research sites at hospitals are completing training and once the intervention drugs are available (Kaletra, INFbeta, low-dose Dexamethasone) recruitment will begin.</p>	<p>https://asaptrial.org/www.recoverytrial.net</p>

<p>Real-time Modelling of a Pandemic Influenza Outbreak (RTM)</p>	<p>Professor Daniela De Angelis University of Cambridge</p>	<p>The real time model (RTM) project advances real time pandemic modelling by developing an existing model used to reconstruct the 2009 H1N1 pandemic on the basis of realistic epidemic surveillance data collected. A monitoring tool that allows to: capture spatial variation in influenza transmission; uses efficient computational algorithms for the provision of timely statistical estimates and predictions; and incorporates the above into freely available software. The tool is used by Public Health England, and key staff has been trained in its use, supported by collaborators at the University of Cambridge to deal with workforce shortage during a pandemic. The real time model has been tested in the monitoring of the 2017/2018 seasonal influenza and ready to be used in the current season to estimate infection and clinical attack rates and to predict timing and magnitude of the peak influenza activity.</p>	<p>Adapted to assist the Scientific Pandemic Influenza Advisory Committee (SPIM) and SAGE via simulation and estimation of epidemic evolution to predict ICU demand (National and Regional). Was activated prior to pandemic COVID-19 to create real-time models predicting the impact of seasonal influenza.</p>	<p>https://www.ncbi.nlm.nih.gov/books/NBK458958/pdf/Bookshelf_NBK458958.pdf</p>
<p>The population-level susceptibility, severity and spread of pandemic influenza study (PIPS)</p>	<p>Professor Andrew Hayward, University College London</p>	<p>Rapid assessment of real-time community-level susceptibility and spread of infection and illness in the event of a pandemic. Achieved this by adding additional questions and specimen collection to the Health Survey for England, an annual, nationally-representative survey that recruits participants throughout the year.</p>	<p>Not activated. The Health Survey for England has cancelled field work during the recommended period of social distancing making timely collection of specimens for serology not possible through this period.</p>	<p>https://www.ncbi.nlm.nih.gov/books/NBK299604/pdf/Bookshelf_NBK299604.pdf</p>