**PROJECT PROTOCOL**

**1. PROJECT TITLE**

EArly pandemic evaluation and enhanced surVeillancE (EAVE) - use of a unique national community linked dataset.

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**2. PLANNED INVESTIGATION**   
**2.1 Research objectives**

Building on prior work [1-3], we aim to enhance an approach used to determine effectiveness of the 2009 H1N1 influenza pandemic vaccine [2]. By linking primary care clinical, prescribing and vaccination data from 250 (and potentially all) general practices to laboratory serology and swab information using a unique patient identifier the Community Health Index (CHI) number [HTA refs: 09/84/90] we will be able to determine once a new pandemic is underway:

* The uptake and effectiveness of any new pandemic (including COVID-19) vaccine once available;

and using already collected serological information and swab data:

* The existence of any protective effect provided by previous exposure to and vaccination from A/H1N1 pandemic or seasonal influenza/identification of susceptible groups or other virus/vaccine exposures.
* The attack rate of pandemic influenza/COVID-19.
* The analysis of any protective effect conferred by antivirals and other therapies
* Other epidemiological questions required as and when required during a rapidly moving situation

**2.2 Existing research**

During the 20th and 21st centuries, there have been four pandemics (global epidemics) of influenza (1918-1919, 1957-58, 1968-1969, 2009) producing very large numbers of clinical cases and in the case of the first three, large numbers of deaths (with an estimated 20-40 million, 1 million and 1 million deaths respectively). This was due to the population having little immunity to the novel influenza viruses involved (H1N1, H2N2, H3N2 respectively) [2]. The lack of herd immunity to the novel influenza viruses implicated (i.e. H1N1, H2N2 and H3N2) is believed to have been a key factor contributing to these very high numbers of deaths in the 20th century [1]. The influenza A subtype: H1N1 virus, which emerged in Mexico in March 2009, [2] also produced a very large number of clinical cases with a third of the population being found to be infected by early 2010 [4]. Previous vaccination to seasonal influenza vaccine conferred little or no cross-reactivity antibody responses [5]. Furthermore, persons under the age of 30 years were found to have little evidence of cross-reactivity to the pandemic virus, with a proportion of older adults having pre-existing antibodies.

After the introduction of any new pandemic influenza, as well as frontline healthcare workers, any new vaccination will be targeted at those who are considered to be at increased risk of serious illness or death from influenza like illness i.e. those with any underlying medical conditions: e.g chronic renal disease; immunosuppression resulting from disease or treatment; chronic heart disease etc. and also those that may lack herd immunity (cross-reactivity) from exposure to previous pandemics or vaccinations. These national vaccination strategies have been shown to represent a potentially important approach to reduce both influenza-related illness and death, hence the considerable investment in this approach in many parts of the world. However, in the 2009 H1N1 pandemic the earliest estimate of Vaccine Effectiveness (VE) in the UK was published in July 2010 [2] four months after the last case of influenza in that season (March 18th 2010 in Scotland) [6]. Further VE estimates were published in 2011 [7-8]. Serology and data gathered in Scotland during 2009/10 also found that rates of immunisation for those most susceptible to serious influenza like illness were less than optimal. For instance, just one in four patients aged five to 50 years with serious underlying illnesses received monovalent H1N1/A vaccine and an estimated 10,000 patients aged >75 years with no underlying disease were issued the H1N1/A vaccine in Scotland. Furthermore, the most socioeconomically deprived patients in Scotland were also found, after the first round of vaccinations, to be more susceptible and were no more likely to receive the vaccine than the most affluent people [4].

**2.3 Research methods**

**2.3.1 Design**

Once the study commences, during a twenty-three month preparatory period, we will instigate a data and serology collection linkage system whereby, once a new pandemic occurs, we will be able to undertake a timely analysis of a large national retrospective observational cohort of patients using a unique community, hospital and laboratory linked dataset.

**2.3.2 Setting**

The Practice Team Information (PTI) network of 40 general practices currently covers a six per-cent representative sample of the Scottish population (n=300,000). These primary care practices are given financial incentives by NHS National Services Scotland to record and code additional data electronically, over and above that routinely recorded for clinical care or as part of the PTI project (e.g. age, co-morbidity, out of hours contacts and socioeconomic status), including influenza vaccination status [9]. Data from general practices within Scotland have shown to be of high quality and useful for epidemiological research [10]. The completeness of capture of contacts and accuracy of clinical event coding in primary care (using Read codes) has been found to be above 91% [11]. The NHS in Scotland is free at the point of care. Access to secondary and tertiary care is usually provided through primary care with almost all of the population being registered with a general practitioner. We aim to recruit further practices (n = 250-1000).

Once the pandemic is underway and using the unique Community Health Index (CHI) number, general practice patient level data will be extracted and linked to the Scottish Morbidity Record (SMR) catalogue which has information on all in**-**patient hospitalisations within Scotland (as well as information on death certification linked from the General Register Office for Scotland [GROS now known as NRS] [12]) from 1981. Hospital data are reliable, with completeness and accuracy rates exceeding 90% [11]. Other new datasets will be included e.g. SICSAG, HEPMA, A&E, GP out of hours calls etc.

In a sub-study, data on vaccination and other patient characteristics will be linked to serological information collected from patients with influenza-like-illness by practices. Scottish laboratories (West of Scotland Specialist Virology Laboratory & Regional Virus Laboratory Specialist Virology Centre [Edinburgh]) will collect and store up to a potential 2,000 biochemistry samples from a subset of participating practices. Once 2,000 specimens have been collected we will explore the replacement of patients’ samples who have died or deregistered from participating practices using deterministic data linkage between the laboratory and primary care. Using this technique we will also explore whether patient descriptions can be elucidated (e.g. ageband, sex, comorbidity, socioeconomic status) and stored in readiness for a pandemic. Once the pandemic begins, we will undertake a data linkage to determine other fields such as vaccination status (and other data including e.g. antiviral and other prescribing and influenza/influenza like illness) of these patients. Their serum will then be tested to determine exposure to previous influenza viruses/vaccine (by the presence of antibodies) once a suitable validated test has been developed. Swabs submitted to test for new pandemic e.g. influenza/COVID-19 will be compared to determine if previous vaccine or exposure confers protection. Other epidemiological questions will require study data as and when required.

**2.3.3 Target population**

1.5-5 million people of all ages registered with participating practices throughout Scotland.

**2.3.4 Recruitment**

The two hundred and fifty/all general practices/HEPMA hospitals and two laboratories will be recruited by the University of Edinburgh and Health Protection Scotland (HPS) through the Trusted Third Party (broker) Albasoft Ltd.

**2.4 Planned inclusion/exclusion criteria**

All registered patients will be studied so there are no exclusion criteria.

**2.5 Planned interventions**

This study will involve a quantitative evaluation of aspects of any future vaccination programme (implemented through general practice) to prevent pandemic influenza/ COVID-19. Vaccine effectiveness will be estimated by linking serology information generated from patients presenting with influenza-like-/ COVID-19 illness (via swabs on a convenience sampling basis 10 per week per practice) to clinical information generated from primary care and hospitalisation and mortality data. Similar information on antivirals (if a well matched antiviral is available) will also be extracted.

In a sub-study, stored residual biochemistry samples from practices will be used to elucidate important serological information on antibody cross-reactivity. This information will be used to inform policy makers, clinicians and the public of the relative benefits of the vaccination programme and help target any vaccine at groups susceptible to infection.

**2.6 Ethical and privacy arrangements**

Permission to link the primary care, SMR, and laboratory databases for research purposes will be obtained from the Privacy Advisory Group. Further permissions will be sought from the appropriate Research Ethics Committee. Permissions from the general practices/Health boards with appropriate data sharing agreements that contribute data to this project will be required.

**2.7 Risks and anticipated benefits for trial participants and society, including how benefits justify risks**

As this study will assess VE using routinely collected and de-identified data, this work will not add any known additional risks or benefits for the individual patients present in the databases. Informing patients as to the potential risks and benefits of vaccination will remain at the discretion of the appropriate primary care clinician. There are however potentially large societal benefits from targeting vaccination programmes to groups vulnerable to infection and assessing the effectiveness and impact of any vaccine for Scotland and the UK as a whole, but also for the international scientific community.

**2.8 Statistical analysis**

Odds and risk-ratios (adjusted for age, sex and deprivation) will be calculated for differences in vaccine uptake rates between different groups of patients (sex, age, Scottish Index of Multiple Deprivation categories and at-risk groups) and for investigating trends in vaccine uptake. For VE using information from linked virological swab data and for serology data (both of which are binary events), a logistic regression model will be fitted adjusting for the effects of gender, age, socioeconomic status and being in an at-risk morbidity group. VE will be measured by comparing swabs taken after vaccination with swabs taken before vaccination for all vaccinated individuals, and secondly by comparing swabs taken after vaccination among those vaccinated to swabs taken among those never vaccinated. A delay of fourteen days after vaccination will be used to establish the protective effect of the influenza vaccine. Propensity scores, such as vaccinations, consultations and hospitalisation in the previous flu season, and the effect modifiers will be used to control for the healthy vaccine effect [13]. In addition, using the cohort method the proportion of influenza like illness, acute respiratory disease, and other adverse outcomes between vaccinated and unvaccinated cases will be ascertained. Confidence intervals for the rate ratio and tests of the differences between two rates will be carried out using the ‘midp method’ in the ‘rate ratio’ (RR) function and rate2by2.test function respectively using the ‘epitools’ package in R [14]. For small samples, confidence intervals for the RR will be estimated using the Excel workbook [15].

Illness RRs, i.e. the ratio of the rate of first admission to hospital or general practice (GP) consultation in the vaccinated compared to the rate of first admission to hospital or GP consultation among those who did not receive the vaccine will be calculated in both the ‘at-risk’ populations and the general population. This is a direct measure of VE. The unadjusted estimate of VE = (1-RR)\*100. Adjusted RRsof VE for prevention of first hospitalisation/GP consultation will be derived from Poisson regression models, adjusting for gender, age, deprivation and clinical risk group.

**2.10 Proposed outcome measures**

With the emergence of any new pandemic influenza, we will calculate:

* The vaccination uptake in the relevant ‘at risk’ populations (patients <65 with ‘at-risk’ co-morbidities and those >65 years) and the general population recorded by general practices;
* Influenza positivity from virological swab data in vaccinated and unvaccinated patients stratified by ‘at-risk’ populations, age, sex and socioeconomic status.
* Influenza positivity from serology data in vaccinated and unvaccinated patients stratified by ‘at-risk’ populations, age, sex and socioeconomic status, which will permit the estimation of incidence of influenza.
* Consultation for e.g. influenza/COVID-19-related morbidity (e.g. influenza, pneumonia, COPD and cardiac related consultations) and issue of antiviral therapy from general practice data in vaccinated and unvaccinated patients stratified by ‘at-risk’ populations, age, sex and socio-economic status;
* Mortality and e.g. influenza/COVID-19-related serious morbidity (e.g. influenza, pneumonia, COPD and cardiac related death and hospitalisation from SMR01 records) in vaccinated and unvaccinated patients stratified by ‘at-risk’ populations, age, sex and socioeconomic status; and
* For patients with stored serology (and prior to the introduction of any vaccination) whether cross-reactivity occurs due to previous exposure to A/H1N1 or A/H1N1 vaccination, other pandemic influenza or other seasonal influenza vaccination or other exposure.

**4. Project timetable and key milestones**

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| **Time point** | **Milestones** |
| 1st September 2012 | Study commencement |
| 1st September - 1st July 2013 | Practice recruitment, regulatory approvals (Research Ethics and Privacy and Advisory Committees) and setting up of laboratory collection and storage and automated practice data collection operating procedures. |
| 1st July 2013 – 30th June 2014 | Begin collection and storage of serology samples.  Test pilot data extraction and linkage. Development of statistical script. |
| 1st July 2014 (and every year hence until pandemic) | Assessment of serology samples to determine numbers collected. Pilot data practice data extraction and linkage (using CHI). |
| 1st August 2014 | Submission of analysis plan for publication. |
| ***Pandemic commencement*** |  |
| Month 1-2 | Serology samples tested for A/H1N1 pandemic/seasonal influenza sero-positivity. Practice data extraction and linkage to virology SMR01 data |
| Month 2 | Processed statistical dataset undergoes statistical analysis by Statistics and Modelling Group (Strathclyde University) |
| Month 3 | Initial results published online (once validated) |
| Month 6 | Final report |

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