Fully-integrated, real-time detection, diagnosis and control of community diarrhoeal disease clusters and outbreaks (the Integrate Project)

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Abstract

Background: Diarrhoeal disease, which affects 1 in 4 people in the UK annually, is the most common cause of outbreaks in community and healthcare settings. Traditional surveillance tends to detect point-source outbreaks of diarrhoea and vomiting; it is less effective at identifying low-level and intermittent food supply contamination. Further, it can take up to nine weeks for infections to be confirmed, reducing 'slow-burn' outbreak recognition, potentially impacting hundreds or thousands of people over wide geographical areas. There is a need to address fundamental problems in traditional diarrhoeal disease surveillance due to: under-reporting and subsequent unconfirmed infection by patients and general practitioners (GPs); varying submission practices and selective testing of samples in laboratories; limitations in traditional microbiological diagnostics meaning that the timeliness of sample testing and aetiology of most cases remains unknown; and poorly integrated human and animal surveillance systems meaning that identification of zoonoses is delayed or missed.

Objectives: These are to: detect anomalous patterns in gastrointestinal disease incidence in the (human) community; target sampling; test traditional diagnostics against rapid modern sensitive molecular and genomic microbiology methods, identifying and characterising responsible pathogens rapidly and more completely; determine the cost-effectiveness of rapid modern sensitive molecular and genomic microbiology methods.

Methods: Syndromic surveillance will be used to aid identification of anomalous patterns in microbiological events based upon temporal associations, demographic similarities amongst patients/animals, and changes in trends in acute gastroenteritis cases, using a pointprocess statistical model. Stool samples will be obtained from patients consulting GPs, to improve upon timeliness of cluster-detection and characterise the pathogens responsible, allowing health protection professionals to investigate and control outbreaks quickly, limiting their size

and impact. The cost-effectiveness of the proposed system will be examined using formal cost-utility analysis to inform decisions on national implementation.

Results: The project was funded, starting 1st April 2013. Favourable opinion was obtained from the Research Ethics Committee on 15th June 2015, and the first patient was recruited on 13th October 2015, with 1407 patients recruited and samples processed using traditional laboratory techniques as of March 2017.

Conclusions: The overall aim is to create a new, 'One Health' paradigm for detecting and investigating diarrhoea and vomiting in the community in near-real-time, shifting from passive human surveillance and management of laboratory-confirmed infection towards an integrated, interdisciplinary enhanced surveillance system including management of people with symptoms.

Main Article Body:

Introduction

Diarrhoeal disease, affecting 1 in 4 people in the UK annually [1], is the most common cause of infectious disease outbreaks in community and healthcare settings. Traditional surveillance methods tend to detect point source outbreaks of diarrhoea and vomiting, however, they are less effective at identifying low-level and intermittent contamination of the food supply, unless the organism is very rare. Further, it may take up to nine weeks for infections to be confirmed by a reference laboratory, reducing recognition of ‘slow-burn’ outbreaks that can affect hundreds or thousands of people over a wide geographical area.

There is a need to address fundamental problems inherent in traditional surveillance for diarrhoeal disease. First, surveillance depends upon examination of stool samples obtained

from symptomatic patients attending their general practitioner (GP). The submission practices and selective testing of samples in laboratories can vary and potentially fragment current laboratory-based surveillance systems. Furthermore, as fewer people present in person to their GP, laboratory-based systems have become less sensitive; the 'hidden' burden of disease has increased [1]. Second, limitations of traditional microbiological diagnostic methods mean that the aetiology of diarrhoea in most cases remains unknown. Third, diagnostics are conducted in a hierarchical manner (local detection, confirmation, then typing centrally at national reference laboratories), which can take several days and be delayed during busy periods such as when an outbreak investigation is underway. Finally, although many diarrhoeal diseases are zoonotic, human and animal surveillance systems are poorly integrated meaning that identification of zoonotic events, including emergence of new or antibiotic-resistant strains, is delayed or missed altogether.

Overall study aim

The overall aim is to create a new, "one-health" paradigm for detecting and investigating diarrhoea and vomiting in the community in near-real-time, shifting from passive human surveillance for GI illness and management of laboratory-confirmed infection towards an integrated, interdisciplinary enhanced surveillance system including management of people with symptoms.

Contribution to the field

The use of syndromic surveillance for cluster detection and targeted sampling within the community compared with using traditional surveillance will provide a series of improvements to the surveillance of GI disease. We hypothesise that enhanced GI surveillance will:

- Allow faster identification of outbreaks of GI disease;
- Lead to more accurate characterization of the 'hidden' burden of disease (under-reporting of episodes of illness in which patients do not visit GPs in person). This will result in an observed increase in the incidence of outbreaks;
- Lead to the identification of a greater number of routes for transmission of pathogens that cause GI illness.

The integration of human and animal syndromic surveillance systems and the use of modern microbiological methods within this project is hypothesised to facilitate:

- Faster detection of zoonotic transmission events;
- Earlier identification of a greater spectrum of disease-transmitting pathogens, reducing the diagnostic gap for GI disease;
- A reduction in the numbers of false positive and false negative stool samples.

There will be differences in the costs and benefits of using improved surveillance techniques to detect outbreaks of GI disease earlier, compared with using traditional surveillance methods. Potentially these differences could be in: parameters relating to host-pathogen interactions; rate parameters that define the transition of patients amongst relevant states (e.g. susceptible, diseased and symptomatic and/or infectious); test characteristics, defined by sensitivity, specificity, positive and negative predictive values; costs (associated with screening, patients' use of NHS community, primary and secondary care services, treatments and other investigations); health outcomes (defined by health state utilities); personal social services; days absent from work or education; and other potential cost impacts.

Overall objectives of the research programme

1) Develop and implement new sampling and microbiological testing algorithms, including strategies for pathogen discovery and evolutionary biology;

2) Run the new system alongside the existing system to assess its performance against a set of outcome-based indicators including time to detection of event, compliance with sampling amongst people with symptoms, numbers of false positive and false negative stool samples, diagnostic yield;
3) Determine the costs and benefits of the new system.

Methods

Setting

The North West area of England (population 7.1 million).

Case recruitment and informed consent

Four data streams will feed in real-time into the new surveillance programme. These are NHS 111 telephone triage data on symptoms of vomiting and diarrhoea (a real-time syndromic surveillance system operated by PHE), data from the Small Animal Surveillance Network (SAVSNET) [2] and *Salmonella* data from the Animal and Plant Health Agency (APHA).

The fourth data stream will be derived from general practices in the Royal College of General Practitioners' Research and Surveillance Centre National Monitoring Network (RCGP RSC NMN) [3]. Members of the public with symptoms of acute gastroenteritis including a Case Definition of vomiting and diarrhoea, who seek health advice from general practices in the RCGP RSC NMN will be invited to submit a stool sample for microbiological examination. Their consent for this procedure will be sought, since normal care would not necessarily entail stool sampling for the majority of patients unless their symptoms were severe or they had persisted for a long time. It is possible that the majority of patients will be recruited as part of a telephone consultation with a member of their primary healthcare team (Physician Assessment by Telephone (PhAT)). The primary healthcare team will arrange for the patient

to receive through the post an invitation letter, an information sheet about the study, a consent form, a stool sampling kit with a reply paid envelope and a short Public Health Acute Gastroenteritis (AGE) questionnaire (which is part of routine public health practice) with a reply paid envelope. Patients who present at a general practice in the RCGP RSC NMN will receive these items in person. Patients who consent to take part and provide a stool sample will be recruited into the study. Consent statements agreed to on the study Consent Form include acknowledgement that taking part in the study is voluntary and consenting patients can leave at any time. Figures 1 and 2 describe the study recruitment procedure, processes and data flows using flow diagrams.

We aim to recruit 6,000 participants. This will allow us to detect period (annual) prevalence of symptomatic GI infection in the community of 20% +/- 1%.

Sample processing

On receipt at one of three diagnostic laboratories taking part (Royal Liverpool and Broadgreen University Hospitals NHS Trust, Central Manchester University Hospitals NHS Foundation Trust or Lancashire Teaching Hospitals NHS Foundation Trust) the stool sample will be divided into two. Half the sample will be processed according to routine clinical practice at each of the three laboratories. The other half will be processed with a rapid first line diagnostic screen, using a molecular multiplex RT-PCR assay (a commercially available CE marked kit (Luminex xTAG® Gastrointestinal Pathogen Panel - xTAG GPP) [4]), which incorporates most of the major community GI pathogens relevant to the UK. This will be complemented by tests for Enteroaggregative *Escherichia coli* and Sapovirus, which have been incorporated into the xTAG GPP assay, using assays already developed for PHE's Olympics Response [5]. Downstream from the rapid xTAG GPP diagnosis, an algorithm for testing stool samples from presumed outbreaks using Next-Generation Sequencing technologies will allow for molecular characterisation of known pathogens. Where a

pathogen has not been identified (likely in 60% of samples), samples from clinically severe outbreaks will be fast-tracked and characterised using a relatively low-throughput platform for combined RNA/DNA viromes and bacterial metagenomes. If they are from less clinically urgent cases they will be sequenced at reduced cost on a high-throughput platform.

If a patient does not wish to take part in the study but does submit a stool sample this will be processed according to routine clinical practice.

All results will be reported to the patient's General Practitioner. Results from the Luminex assays will be issued as an interim report via "Telepath," which is the routine electronic reporting system between diagnostic laboratories and General Practice, and the results of the routine clinical practice assays will be issued as a final report via "Telepath." In each laboratory an experienced Consultant Medical Microbiologist, who is a co-investigator on the grant with research time costed into it, will be available to discuss any discrepant results with the patient's GP. The most likely scenario is that a stool sample negative using traditional methods will be positive using the xTAG GPP. This is to be expected since the xTAG GPP, which is a multiplexed PCR, will detect the presence of pathogen DNA/RNA in stool even if an organism has died off in the sample during transit to the laboratory.

Public Health Acute Gastroenteritis (AGE) questionnaires

Public Health questionnaires will be returned to PHE's Health Protection Teams via reply paid envelopes. These questionnaires contain the routine follow-up information that is collected and collated by PHE to assist outbreak detection or investigation. Additionally these questionnaires will contain questions on quality of life during the acute illness. Quality of life will be measured using the EuroQol-5D-3L [6], which is the gold standard tool. This gives

snapshots of quality of life at points in time. At this time point (Time point 1) we will capture quality of life during the acute illness.

Resource use and costs

Resource use and costs will be assessed from several different perspectives, described below, including the public sector and patients.

Public sector, including NHS and social services

Consistent with National Institute for Health and Care Excellence's (NICE) methods for the development of public health guidance, we will adopt a public sector costing perspective. While productivity costs are not routinely included in analyses, we will collect the data for consideration in sensitivity analysis. Unit costs will be derived from standard sources such as the Personal Social Services Research Unit Costs of Health and Social Care, the British National Formulary for drug costs, and NHS reference costs. The costs of laboratory and public health services will be obtained from Public Health England.

Patients

Patients who indicate on their consent form that they are willing to be contacted about a Patient Experience Survey will receive a questionnaire that seeks information about resource use two weeks after returning their stool sample pot. The majority of patients will have recovered fully two weeks later and so a complete picture of the costs to them associated with their illness should be available. The short resource use questionnaires will capture details about use of health care services, personal social services, days absent from work or school, and other potential costs. Quality of life, using EuroQol-5D-3L, will be assessed during the acute episode (Time point 1) and at two weeks post recovery (Time point 2). It will be used to calculate Quality-Adjusted Life-Years (QALYs).

Hospital Episode Statistics

Patients' use of secondary care services will be assessed by accessing Hospital Episode Statistics data sourced from the NHS Digital. This will require a bespoke download, matching patients who have consented according to their NHS number, name, and date of birth, following a standard operating procedure to ensure patient anonymity and data protection.

Costs of technology

These will include set-up costs, including capital costs, the marginal costs of delivering the service and the cost implications for patients using the NHS services. These costs will be obtained from Luminex and from time and motion studies conducted at participating microbiology laboratories.

Patient Experience Survey (PES)

The purpose of this survey is to explore service-users' and, where relevant, their caregivers' perceptions and experiences of accessing the 'Integrate' service. Questions contained within the patient experience survey were developed from themes identified from the extant literature and include:

- Motivations for accessing health care in relation to diarrhoea;
- Predisposing or enabling motivations for accessing a given health care service;
- Experience and perceptions including the acceptability of self-stool sampling;
- Dimensions of patient satisfaction, including for example communication and clarity of information.

Members of the public eligible to participate in the survey will be either:

- A patient (aged 16 years and over) who has recently suffered diarrhoea and provided a stool sample;
- A person who has parental, guardian or caregiver responsibility for, and who will act as a proxy on behalf of a patient who has recently suffered diarrhoea and provided a stool sample.

No upper age limit for sampling patients applies. However, where the patient is a minor (under 16 years of age), the parent, guardian or caregiver will be invited to respond on their behalf (as a proxy). We estimate approximately 5,000 members of the public will be eligible to take part in the survey within a timeframe of 15 months. During this period all eligible participants will be consecutively recruited to participate in the survey as a means to achieving maximum variation in clinical and socio-demographic characteristics and to facilitate comparison across key purposive sampling criteria [7]. Participants will be invited to complete the questionnaire two weeks after returning their stool self-sample pot, allowing a three week recall period from date of contact with the NHS.

Survey distribution

When a member of the public contacts a collaborating GP practice they will receive information in their study pack about the Patient Experience Survey. If they express an interest in finding out more about this survey, they will be asked to identify a preferred contact route, by either:

a) Receiving a self-completion questionnaire via the post;

b) Accessing a self-completion questionnaire on-line.

If prospective participants choose to receive this information via the post (option a) they will be sent a public survey information pack containing an introductory letter, an information sheet explaining the aims of the study and the processes involved in participating in the survey, a copy of the self-completion questionnaire and a pre-paid, return envelope addressed to the Project Office at the University of Liverpool. If prospective participants prefer to access these details on-line (option b) they will receive an e-mail. The e-mail will include an electronic link to a secure, web-enabled system containing a study introduction page. If interested, prospective participants can then access two further links. The first link will open an information page which will outline the aims of the study and processes involved in participating in the on-line survey. The second link will enable prospective participants to access and complete the electronic version of the self-completion questionnaire (via the PHE Select Survey facility, [[8]).

Participants will be given two weeks in which to complete and return/submit their questionnaire. Non-responders will be prompted (via their preferred route) with one follow-up reminder. These will include, as appropriate, a follow-up letter containing a further copy of the questionnaire and a prepaid return envelope, or, alternatively, a follow-up email with an electronic link to the on-line questionnaire. The use of reminders is generally endorsed in texts on survey methods [9].

Summary of outcome measures

The outcome measures to be quantified within the research project are summarised in tables 1, 2, and 3.

Table 1. Resource use and costs outcome measures to be quantified within the research programme

Outcome measures	How to measure
Use of health care services	Resource use questionnaire (PES) to patients
Use of personal social services	Resource use questionnaire (PES) to patients
Days absent from work or education	Resource use questionnaire (PES) to patients
Other potential cost impacts	Resource use questionnaire (PES) to patients
Use of Secondary Care Services	Hospital Episode Statistics from NHS Digital
Costs of Technology	Interviews with Luminex (new technology) and Time and Motion studies at microbiology laboratories (existing technology)

Table 2. Health outcome measures to be quantified within the research programme

Outcome measure	How to measure
Health outcomes	EQ-5D-3L questionnaire administered at two time-points: Time point 1, during the acute illness Time point 2, two weeks after submission of a stool sample to the laboratory

Table 3. System outcome measures to be quantified within the research programme

Outcome measures[1]	How to measure
Time to detection of event	Laboratory records, date of AEGISS anomaly detection, date that Consultants in Communicable Disease Control initiate an investigation

Compliance with sampling amongst people with symptoms	Laboratory records (number of samples requested) and GP records (number of samples submitted)
Time to detection of a positive result	Laboratory records
Numbers of false positive and false negative stool samples	Laboratory records
Positive predictive value	Calculated from laboratory records using the formula: Σ True positives / Σ Test outcome positives (i.e. true positives + false positives)
Diagnostic gap	Laboratory records - % of negative samples using either system
Size of outbreaks detected	Outbreak investigation reports - range, mean and median numbers of cases

[1] (These will be captured for traditional methods and for the new diagnostic technology)

Plan of analyses

Anomaly detection

The underlying statistical model for human case incidence will be a spatio-temporal Cox process [10] in which the rate of calls at location x and time t is modelled as

$$\rho(x,t) = \lambda(x)\mu(t)R(x,t). \qquad [1]$$

In [1], the terms $\lambda(x)$ and $\mu(t)$ describe the normal patterns of variation in the spatial and temporal dimensions, respectively, of the call rate, thereby taking account of the geographical distribution of the user-population, seasonal variation in disease risk and reporting artefacts such as day-of-week effects. The term $R(x,t)$ is a stochastic process with expected value 1, and represents unforeseen, spatially and temporally localised variations in the underlying disease risk.

Model parameters will be estimated by likelihood-based methods and fed into algorithms that update the predictive distribution of the "unexpected" component $R(x,t)$ automatically on receipt of each day's incident call data. Results will be posted overnight in the form of maps

showing localities, if any, where the data indicate a high probability that the current value of *R(x,t)* exceeds a specified threshold.

System performance

The performance of the new surveillance system compared with routine sampling will be assessed by analysing the outcome-based indicators and comparing time to detection, decision to act, and the size of outbreaks described using both traditional and new diagnostic systems (range, mean and median number of cases), outbreak settings, modes of transmission identified and vehicles identified. Each critical time-point along the diagnostic and detection pathway from symptom onset to diagnosis and detection of a cluster or outbreak will be examined.

Economic modelling

The model structure will be based on a decision analysis in which the alternative options will be specified according to treatment pathways and strategies for public health intervention. The impact and scale of outbreaks will be modelled using agent-based models in which hypothetical cohorts are subject to an instantaneous rate of infection, which varies depending on the proportion of the population who are infected. This approach has several advantages over traditional health economic models which are restrictive in their predictive capabilities, and scenario testing. The model will be parameterised with point estimates and associated variances, derived from a purposive review of the published literature, from routinely collected data from Public Health England (both historical and contemporary), and from data generated during the research. These will include: parameters relating to host-pathogen interactions; rate parameters that define the transition of patients among relevant states (e.g. susceptible, diseased and symptomatic and/or infectious); test characteristics, defined by sensitivity, specificity, positive and negative predictive values; costs (associated with screening, patients' use of NHS community, primary and secondary care services, treatments

and other investigations); and health outcomes (defined by health state utilities based on UK tariff scores assigned to each model state, and mortality estimates).

Calculating and judging cost-effectiveness

Expected costs and benefits will be estimated to calculate incremental cost utility ratios (costs per QALY gained) for a range of scenarios, specified by infection type, clinical course and public health response. Estimates of the incremental cost-effectiveness ratios (ICERs) will be compared with the £20,000 to £30,000 per QALY threshold of cost-effectiveness set by NICE, and a range of one-way sensitivity analyses will be conducted to assess the robustness of the analysis. These will be presented as a Tornado plot. Multivariate sensitivity analyses will be applied where interaction effects are suspected. The joint uncertainty in all parameter estimates will be propagated through the model by use of probabilistic sensitivity analysis and construction of cost-effectiveness acceptability curves that present the probability of clinical strategies being cost effective, conditional on the chosen threshold for cost-effectiveness (representing the marginal value of health). Scenario analyses representing, for example, changes in service configuration, will be conducted to estimate a range of ICERs for different circumstances.

Ethics

For the human case data ethics permissions and approvals have been obtained from:

- National Research Ethics Service (NRES) REC reference: 15/NW/0233
- NHS Health Research Authority (HRA) Confidential Advisory Group (CAG) CAG reference: 15/CAG/0131
- The Information Governance Toolkit (IGT), Department of Health and Social Care hosted by the Health and Social Care Information Centre (HSCIC) (now NHS Digital) UoL reference: 8HN20, Lancaster University reference: EE133831-HAM-EAOPOCR

- NHS Research Management and Governance Committees IRAS number: 173789
- University of Liverpool Ethics Sub-Committees reference: UoL001111
- Honorary NHS contracts, research passports and letters of access have been obtained for research staff working on the project as necessary.

Results

The project was funded, starting 1st April 2013. Favourable opinion was obtained from the Research Ethics Committee on 15th June 2015, and the first patient was recruited on 13th October 2015, with 1407 patients recruited and samples processed using traditional laboratory techniques as of March 2017.

Discussion

This study investigates whether modern microbiological methods can be used to improve surveillance for GI disease, whilst also examining the costs and limitations associated with the enhanced system. It compares the results of traditional laboratory testing with the results identified using modern sensitive molecular and genomic microbiology techniques. The strength of the study is the collaboration between lead public health partners and researchers in this field. However, there are a number of challenges in this study. For example, the plans for work are based on the assumption that the way surveillance streams are implemented, and their providers, will continue in their current form for a least the period of study recruitment. Ethical permissions are granted under this proviso, but as with the provision of all health services, changes can occur rapidly. If there are changes to the study protocol then these must be reflected in amendments to the ethics agreements, and the research governance including confidentiality agreements required for this to happen can take a significant amount of time to

go through the review process, delaying the progression of data collection. Another challenge is that of recruiting a sufficiently large number of patients for analysis, including for reasonable comparison of the results of the traditional and modern microbiological testing. This is particularly true given that GPs often do not encourage patients to provide a stool sample unless they have had clinical GI symptoms for an extended time-period, or unless they are in a high risk group such as those young, old or immune compromised.

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Conflicts of Interest

The authors declare that they have no competing personal financial interests related to the subject matter discussed in this manuscript. Simon de Lusignan has subsequently received funding through University of Surrey to explore household transmission of acute gastroenteritis.

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Abbreviations

Animal and Plant Health (APHA)

Confidential Advisory Group (CAG)

Department of Health and Social Care hosted by the Health and Social Care Information Centre (HSCIC)

Gastrointestinal (GI)

General Practitioners (GPs)

Incremental Cost-Effectiveness Ratios (ICERs)

Luminex xTAG® Gastrointestinal Pathogen Panel (xTAG GPP)

National Health Service (NHS)

National Institute for Health and Care Excellence (NICE)

National Research Ethics Service (NRES)

NHS Health Research Authority (HRA)

Physician Assessment by Telephone (PhAT)

Public Health Acute Gastroenteritis (AGE) questionnaire

Public Health England (PHE)

Quality-Adjusted Life Years (QALYs)

Royal College of General Practitioners' Research and Surveillance Centre National Monitoring Network (RCGP RSC NMN)

Small Animal Veterinary Surveillance Network (SAVSNET)

Information Governance Toolkit (IGT)

Availability of data and material

The datasets generated during the current study are not publicly available due to issues of data confidentiality and patient identifiable information. Data are however available from the authors upon reasonable request and with appropriate ethical permissions.