A Public Health Response to Pathogen X: Safeguarding Communities through Frameworks for Emerging Epidemics and Pandemics

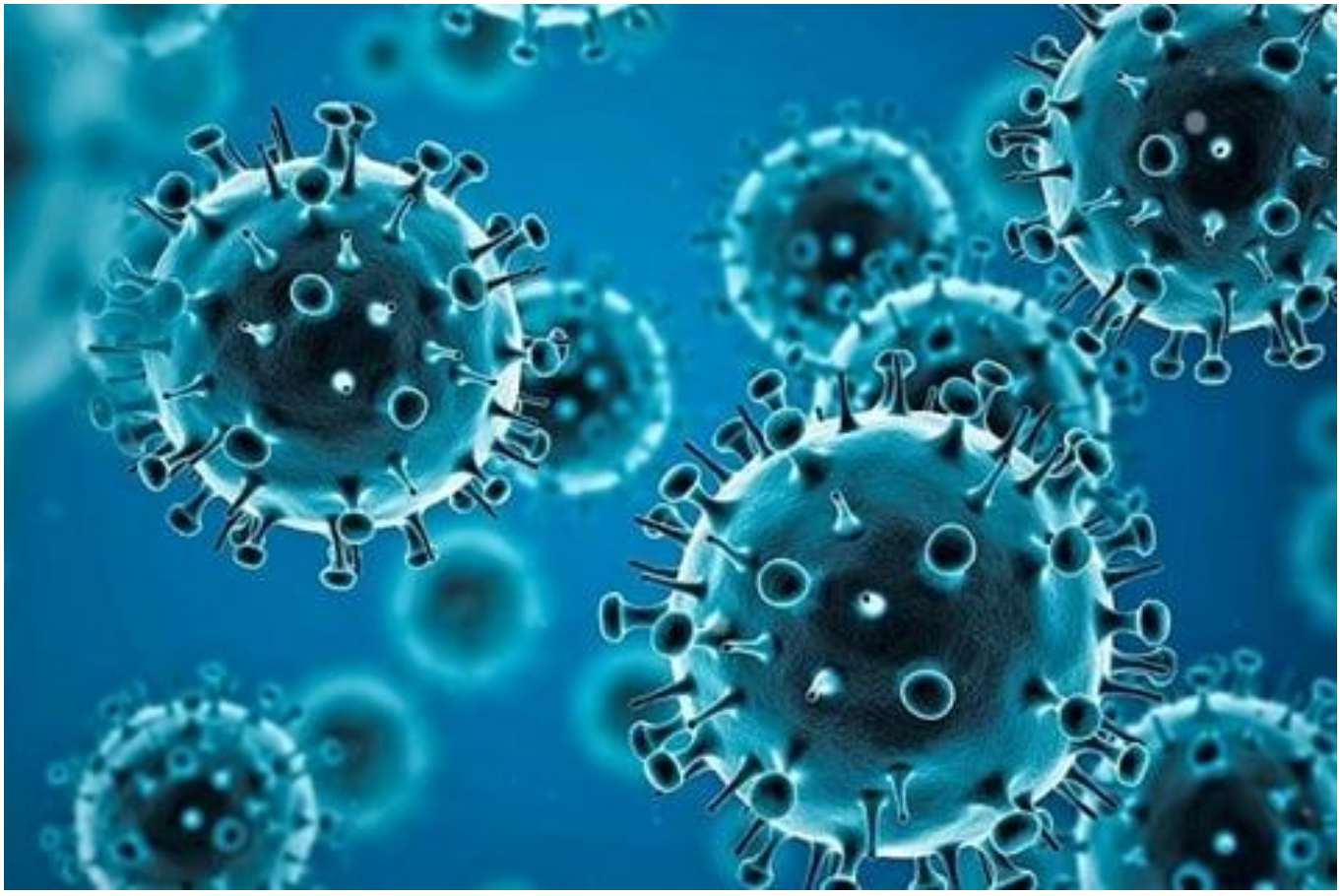

Image: World Health Organization (WHO)

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Abbreviations

Abbreviation	Name
ARI	Acute Respiratory Infection
CHI	Community Health Index (Scottish NHS number equivalent)
CMR	Computerised Medical Record
COG-UK	COVID-19 Genomics UK Consortium
COPI	Control of Patient Information
COVID-19	Coronavirus 2019 disease
CPRD	Clinical Practice Research Datalink
Cq	Cycle of quantification
CVST	Cerebral Venous Sinus Thrombosis
DaC-VaP	Data and Connectivity: COVID-19 Vaccines Pharmacovigilance
ECDS	Emergency Care Dataset
EDAP	Enterprise Data Analytics Platform
EAVE	Early estimation of pandemic influenza Antiviral and Vaccine Effectiveness
EAVE II	Early Pandemic Evaluation and Enhanced Surveillance of COVID-19
GDPR	General Data Protection Regulation
GPDPR	General Practice Data for Planning and Research
GISAID	Global Initiative on Sharing All Influenza Data
HARISS	Hospital-Based Acute Respiratory Infection Sentinel Surveillance
HES	Hospital Episode Statistics
H1N1	H1N1 influenza is a subtype of influenza A virus

H1N2v	A novel swine influenza A virus variant
hMPV	Human Metapneumovirus
ICU	Intensive Care Unit
IG	Information governance
ILI	Influenza-like Illness
ISARIC	International Severe Acute Respiratory and Emerging Infection Consortium
JCVI	Joint Committee on Vaccination and Immunisation
LFD	Lateral Flow Device
MSDS	Maternity Services Data Set
NDRS	National Disease Registration Service
NHS	National Health Service
NIHR	National Institute for Health Research
NIMS	National Immunisation Management System
NIRP	National Incident Response Plan
NPI	Non-pharmacological Intervention
ONS	Office of National statistics, mortality registry
PCR	Polymerase Chain Reaction
POCT	Point of Care Tests
PPE	Personal Protective Equipment
QCovid	Living risk prediction algorithm for risk of hospital admission and mortality from coronavirus 19 in adults
RCGP	Royal College of General Practitioners
REACT	REal-time Assessment of Community Transmission
RECAP	Remote COVID-19 Assessment in Primary Care, study

RSC	Research and Surveillance Centre
RSV	Respiratory Syncytial Virus
RWE	Real World Evidence
SAGE	Scientific Advisory Group for Emergencies
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAIL	Secure Anonymised Information Linkage Databank
SDE	Secure Data Environment
SGSS	Second Generation Surveillance System
SIREN	SARS-CoV-2 Immunity and Reinfection Evaluation
sKIDs	COVID-19 surveillance in school KIDs
SNOMED CT	Systematised nomenclature of Medicine Clinical Terms
SUS	Secondary Uses Service
TTS	Thrombosis with thrombocytopenia syndrome
UK	United Kingdom
UKHSA	UK Health Security Agency
VIVALDI	Understanding SARS-Cov-2 infection, immunity and its duration in care home residents and staff in England
WHO	World Health Organization

Executive Summary

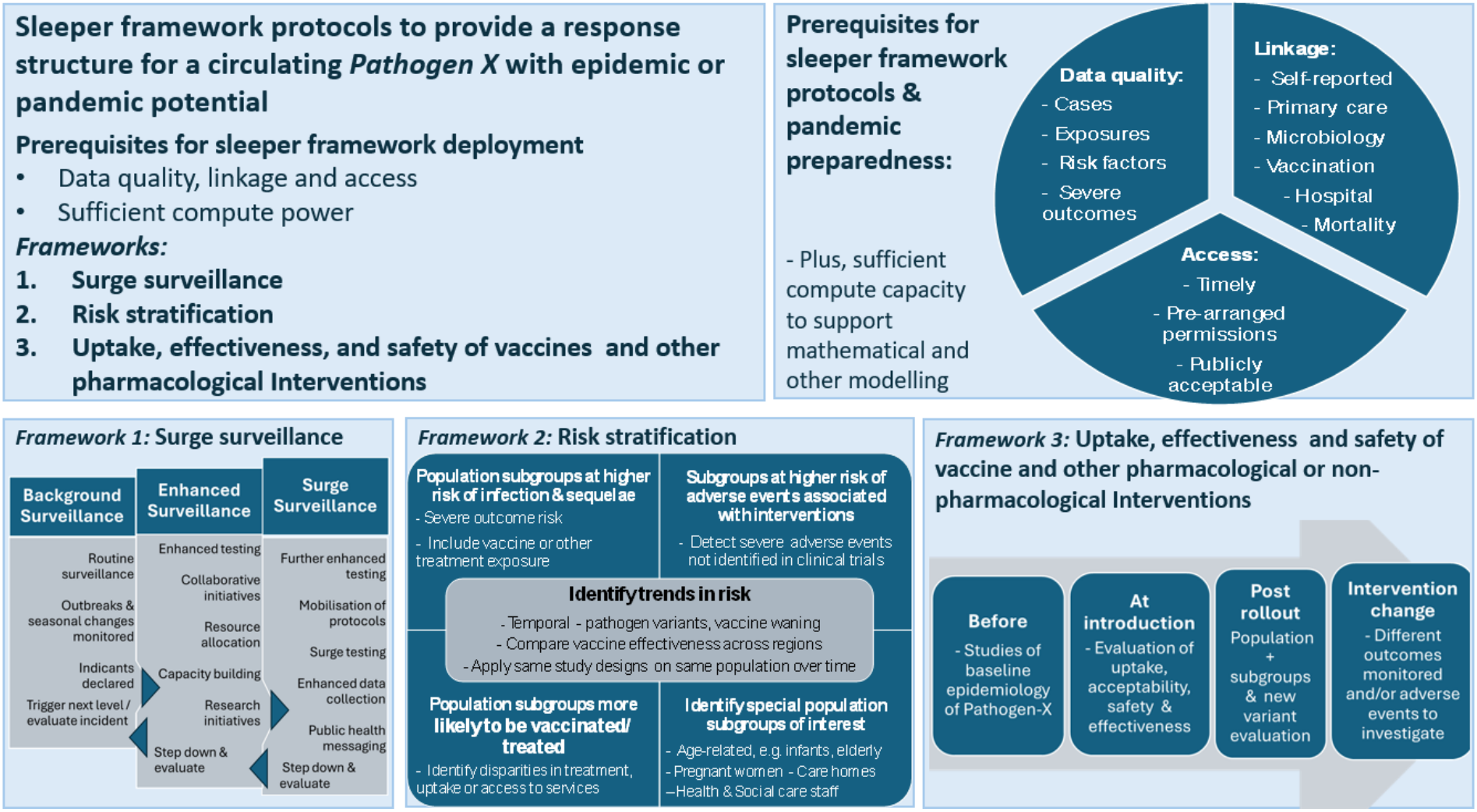
This report was commissioned by the UK Health Security Agency (UKHSA). It provides generic frameworks to support surge surveillance, risk stratification and assessments of the uptake, effectiveness and safety of vaccines and other pharmacological interventions that could be deployed by UKHSA in response to the emergence of Pathogen X with epidemic or pandemic potential.

Our approach emphasises the importance of primary care data in an integrated epidemic or pandemic response. This is based on the authors' experiential learning from the Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC), the Early Pandemic Evaluation and Enhanced Surveillance of COVID-19 (EAVE) and their international collaborations. There have been many calls internationally for changes to enhancing preparedness, but also recognition of the time and resources for implementing such an approach.

Our proposed approach identifies and creates frameworks, and flags how a more dynamic approach to readiness might improve the underpinning data resources and promote greater integration of surveillance assets. Such developments including of infrastructure may help to improve the quality and timeliness of any response. We also highlight how creating a seamless process of progressively increased surveillance might best support responses to future epidemics and pandemics. Any implementation of framework protocols will need to take account of World Health Organization (WHO) and national recommendations. The latter may include those from the UK's Scientific Advisory Group for Emergencies (SAGE), and government directions.

This report brings together the resources and protocols required to underpin the response to a future national incident that might transition into an epidemic or pandemic threat. After providing context for the rationale for this work (Section 1), we describe in Section 2 the need for improved data quality, linkage and access, which will be foundational to effective data informed public health responses. Our goal has been to identify resources and provide insights into what is likely to be needed to support surge surveillance (Section 3), risk stratification (Section 4) and assess the uptake, effectiveness and safety of vaccines and other pharmacological interventions (Section 5). We flag below where pandemic planning might be strengthened and include in our appendices an index of current protocols that might be drawn upon (Appendix A) and more information about surveillance resources (Appendix B). An overview of the report, the data infrastructure prerequisites, and its three framework protocols are summarised in an infographic (Figure 1).

Figure 1: Infographic summarising the data and information system prerequisites and the three frameworks included in this report



Our framework protocols can be summarised as follows:

Section 3: Surge testing optimisation: A r*esponsive surveillance team* could underpin surge capabilities:

- Those currently or soon to be involved in surveillance could have their collaborative responsive surveillance role developed further. Common hosting of their data within UKHSA's Enterprise Data Analytics Platform (EDAP), or similar high-performance environment, would improve accessibility in any future incident, epidemic or pandemic.
- Responsive surveillance could create a seamless transition from national incident where its director wanted more support through responsive surveillance and be escalated further in any epidemic or pandemic.

Section 4: Risk stratification operationalisation: High quality, linked and rapidly available data could enhance effective risk stratification:

- Rapidly available high-quality data are required for risk stratification. These need to include sociodemographic features including risk groups and multioccupancy residences of different types, clinical risk groups, and links to key outcome data, particularly hospitalisation and death.
- These data need to be organised into clinically relevant and validated phenotypes.
- Data should be available to experts external to UKHSA for analysis, but without leaving its secure environment.

Section 5: Uptake, effectiveness and safety of vaccines or other therapeutic interventions:

There is a need to link vaccination (and other therapeutic) data to clinical records, ideally on a whole country scale. This might benefit from more data directly collected from the public and patient, planning to support the collection of data about adverse events of interest and developing genomic and sero-surveillance.

- Alongside computerised medical record (CMR) data more direct access to patient provided data might offer advantages. For example, symptoms might include novel associations (e.g., loss of taste and smell) on their duration and health economic impact. Additionally, worn devices (such as smart watches) might provide direct physical observations, such as pulse rate, body temperature and oximetry data.
- Adverse events of interest following therapeutic interventions including non-pharmaceutical interventions (NPIs).
- Genomic surveillance, and sero-surveillance of population immunity will become increasingly important.

In summary, whilst recognising that it would take time and resources, improved data quality particularly in primary care, along with linkage, and rapid access are prerequisites for an effective pandemic response. There may be opportunities for the existing surveillance resources including the RSC to become part of a more dynamic and responsive system; including how testing is scaled when there is a requirement for surge testing. We then provide frameworks for the analysis of risk stratification and assessment of vaccine or other therapeutic intervention's safety and

effectiveness. These frameworks set out to provide a playbook that can be then adapted, as needed, depending on the characteristics of Pathogen X. We suggest there is a need to extend capabilities beyond maintaining hibernating data infrastructures proposed following the 2009 swine flu pandemic, to framework protocols that can be applied to teams and their supporting datasets that are routinely deployed and can be urgently pivoted as needed to undertake pre-determined analyses specified in our frameworks.

1. Introduction

There is a need for pre-developed plans, we describe them in this report as 'frameworks,' to support the public health response to the risks posed by any new Pathogen X with epidemic or pandemic potential [1].

This urgent report was commissioned by the UK Health Security Agency (UKHSA) to identify and develop framework protocols that could be deployed to cover three main considerations in any future potential epidemic/pandemic in the United Kingdom (UK), namely: (1) surge surveillance, (2) risk stratification, and (3) the uptake, effectiveness, safety of vaccines and other pharmacological interventions. Data-related issues, especially data quality, linkage and access, underpin all actions proposed in the three framework protocols and are therefore also highlighted in Section 2. The three framework protocols, along with the data quality, linkage and access assurance plan, can be adapted and applied to data curated on existing UKHSA platforms and those in development, to facilitate a rapid response to Pathogen X. These existing data platforms include: The Respiratory DataMart sentinel system, which was initially set up in 2009 to automate the collection of all pandemic influenza laboratory data and has been further developed since; the UKHSA Enterprise Data Analytics Platform (EDAP) which is a key part of its data strategy; UKHSA's Syndromic Surveillance team; and the Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) in England. [2]

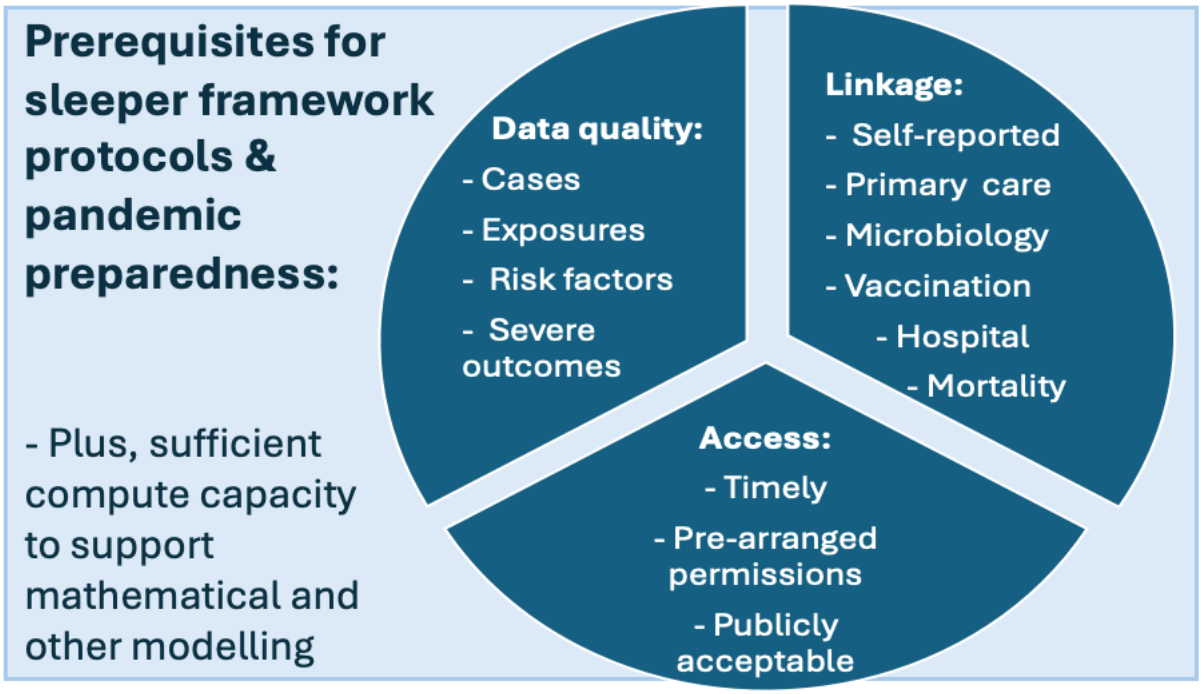
The UK's experiences in the influenza (H1N1) and COVID-19 pandemics have provided invaluable lessons for responding to Pathogen X. In developing these frameworks for Pathogen X, we have sought to summarise the resources/platforms developed during recent pandemics. UKHSA's protocols and studies were reviewed and are referenced in this report (Appendix A). Resources developed and deployed using national platforms were also included – in particular, the RSC[2], UKHSA's DataMart, and the Early Pandemic Evaluation and Enhanced Surveillance of COVID-19 (EAVE II) in Scotland [3]. RSC and EAVE II were led by members of the project team, and learning from these platforms were therefore in particular drawn upon. Utilisation of these existing primary care based infrastructures presents both a rapid option to leverage their capabilities and suggests ways to strengthen existing partnerships and collaborations across the UK and its public health agencies. Additionally, we reviewed other resources/approaches, including databases, protocols, and documents at the national, regional, and global levels, to identify and incorporate best practices into our frameworks (Appendix A). Finally, there have been many calls internationally for changes to improve preparedness, but also recognition of the time and resources for implementing such an approach [4–6].

2. Data Quality, Linkage and Access

Introduction

High quality routine data, with linkage of primary care with community vaccination and outcome data often collected in secondary care are important (Figure 2). Additionally, there needs to be a ready route to access these near real-time data in a timely way. We consider these a prerequisite for effective epidemic and pandemic management. This section describes how data quality, linkage and access are key underpinnings of all three framework protocols discussed in Sections 3-5.

Figure 2: Data quality, linkage and access are a prerequisite for the implementation of our frameworks



Data quality

Data quality is commonly defined as a mathematically calculated measure of completeness, accuracy, and timeliness, as well as fitness for purpose [7,8]. Accurate and complete data are crucial across all three framework protocols developed in this report. High data quality, particularly within CMRs, can facilitate precise analysis and timely decision-making in response to Pathogen X.

The main challenges in CMR data quality likely to arise in Pathogen X include:

- Delayed creation of new clinical terms at the Pathogen X onset may delay its recording
    - For example, clinical terms for COVID-19 and COVID-19 test results; rare adverse events such as thrombosis with thrombocytopenia syndrome (TTS), and long COVID were generally slow to have clinical terms created with no single clinical term ever created for TTS [9].
- Phenotypes created that reliably identify risk groups, which may change over the course of an epidemic or pandemic.
    - For example, four different versions of QCovid risk groups as COVID-19 evolved [10–13].
- Data gaps and inconsistencies, for example incomplete socioeconomic data (e.g., ethnicity) and inconsistencies in recording habits across CMR systems and UK nations.
- There can be tensions between collecting additional data and patients or engaging with an intervention; similarly, between focussing on testing of the causative organism in a pandemic and comprehensive testing.

Clinical data that is recorded as narrative in CMRs, so called “free text”, is much harder to identify and analyse than coded data. There is potential to enhance collaboration between UKHSA’s surveillance infrastructure and the routine primary care surveillance datasets, including RSC, to improve data quality. The emphasis should be on coding diagnoses of interest, symptoms, signs, outcome and prescriptions that may give an indication of severity.

Additionally, data quality could be improved for microbiological data (including bacteriology and virology results) within the national laboratory system, where again key data may be recorded using free text. Many microbiology test results posted into general practice CMR systems use a specimen received code rather than a clinical term for the name of the infecting organism or if no infection was found.

Whist the electronic “Lablinks” system performed well with COVID-19 laboratory test results, posting them reliably into GP computer records, data quality gaps exist in many microbiological results. Microbiological results and sensitivities and resistance to relevant therapies are often recorded in free text. Improvement here could also be beneficial.

Data collected directly from patients can also be important, and a wide range of symptoms and signs can be collected directly. For example, in the COVID-19 pandemic the Zoe app picked up information about the loss of taste and smell [14]. However, currently such data cannot be systematically linked at an individual patient level, though for clinical care the NHS App is improving its capability. Many people’s digital devices now collect oxygen saturation, pulse rate, and body temperature which are easily collected and shared.

Finally, genomic surveillance is becoming increasingly important and high-quality records should flag whether there a positive virology test has associated viral sequenced data available. For COVID-19 the COVID-19 Genomics UK Consortium (COG-UK) held these data [15], for other viruses (influenza, respiratory syncytial virus (RSV) and human metapneumovirus (hMPV)) UKHSA is increasingly storing sequence data in the Global Initiative on Sharing All Influenza Data

(GISAID) repository [16]. A Wellcome grant is facilitating recording of GISAID numbers in RSC clinical data from 1993, to facilitate genomic surveillance [17].

Regular cohort profiles could be reported (maybe annually or biannually) including any differences between the surveillance asset and national population of or inclusion of key data [18]. These findings could be used to suggest changes that might be adopted to improve surveillance assets data quality during non-epidemic or pandemic periods:

- Routinely assess the representativeness of the databases used to support epidemic or pandemic management against the national census or relevant national data. This would include national datasets, where there might be denominator inflation.
- Enhance the ability to rapidly specify UK SNOMED clinical terms for new diagnoses, signs, and symptoms, potentially exercising this capability regularly.
- Create clinical phenotypes, sets of rules enabling the identification of cases from CMR data, and disseminate them (in the public domain). This is to facilitate the development of tools such as QCovid risk scores [10–13], the Remote COVID-19 Assessment in Primary Care (RECAP) risk prediction tool [10], and the OpenSAFELY platform [19].
- Make sampling and test results reliably available within CMRs and directly accessible to patients via the NHS App.
- Promote data completeness in clinical risk factors, sociodemographic data, therapeutic interventions including vaccination, household-related information, and outcomes within CMRs.
- Standardise and maximise the use of clinical terminologies across UK healthcare settings and within CMRs.
- Facilitate genomic surveillance through the linkage of clinical and sequenced data.

Data linkage

Data linkage refers to the process of connecting or combining data from multiple sources to create a more comprehensive dataset. The CMRs and other health-relevant data that are needed to empower life-saving research and treatments in the UK are mostly held by individual institutions or databases (Table 1). Therefore, cross-database linkage is necessary to enable essential data analyses in response to an epidemic or pandemic. Due to the confidential nature of individual-level CMRs, the sharing of CMRs is protected under the General Data Protection Regulation (GDPR). The strict limitations imposed by GDPR have made data linkage challenging and time-consuming, whilst on the positive side they provide a framework for epidemic/pandemic data sharing. Alongside compliance with GDPR, provision for access to medical record data for health protection, by UKHSA, is also provided by the Health Service (Control of Patient Information (COPI)) Regulations 2002, which enables urgent access to medical data in specific circumstances such as health protection [20,21]. Within the National Data Guardian 2021-2022 report, the citizens'

juries concluded that the government was right to use emergency measures to ensure that data was used to manage the pandemic, but greater transparency is needed [22,23].

During the COVID-19 pandemic, the UK Secretary of State for Health and Social Care issued NHS Digital (now part of NHS England) with a COPI notice to require NHS Digital to share confidential patient information with organisations entitled to process this for COVID-19 purposes. In the latter stages of the COVID-19 pandemic, the UK government initiated a Data Saves Lives policy [24] that limits the utilisation of English national health datasets to regional secure data environments (SDE) [25], which allows CMRs to be accessed securely in a virtual setting and analysis takes place within an SDE [26].

Table 1. UK health record databases that are capable of linkage

Type of database	**UK Examples**
Data directly collected from patients	The Zoe app collected data could not be linked at individual level. Direct to patient surveillance samples included requests for additional information such as whether a healthcare worker, willing to provide extra information etc.
Primary care data	Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC), Clinical Practice Research Datalink (CPRD), QResearch, General Practice Data for Planning and Research (GPDPR), Secure Anonymised Information Linkage (SAIL) Databank (Wales), Early estimation of pandemic influenza Antiviral and Vaccine Effectiveness (EAVE) (Scotland)
Secondary care data	Emergency Care Dataset (ECDS) Secondary Uses Service (SUS) Hospital Episodes Statistics (HES)
Surveillance data	Second Generation Surveillance System (SGSS)
Vaccination data	National Immunisation Management System (NIMS)
Prescribing and dispensing data	OpenPrescribing, NHS Business Services Authority data
Pregnancy data	Maternity Services Data Set (MSDS)
Cancer registries	NHS England National Disease Registration Service (NDRS)
Mortality statistics	Office for National Statistics (ONS) death registry

Moving health data from their original settings to SDE is a foundational step in preparing for Pathogen X. In Scotland, EAVE and subsequently, EAVE II anticipated this data sharing limitation by consolidating data within Public Health Scotland's secure national environment. The UKHSA is currently developing its own SDE, named the Enterprise Data Analytics Platform (EDAP) [27], where RSC is planning to integrate its primary care data. The freshest primary care data can be processed in CMR-based primary care databases within 48 hours. It is possible, in association with particular hospital technology providers (e.g., Cerner and Epic) or with the Hospital-Based Acute Respiratory Infection Sentinel Surveillance (HARISS) system, to accelerate the linkage between primary care and secondary care data.

The NHS number in England and Wales, and the Community Health Index in Scotland allows data linkage between primary care, surveillance, secondary care and other care data at individual level (Table 1). Much about the process of care is recorded in primary care, surveillance and vaccination data, and some secondary care data. Many of the important outcomes of disease are recorded in secondary care and in mortality statistics.

Data access

Data access:

Near real-time access to data is vitally important in any epidemic or pandemic. There is a need to consider developing data timeliness indicators that not only reflect the timing from recording to availability, but also the approval, dataset preparation and supply delays. These timeliness indicators also need to consider the lead times of data availability.

The different datasets available (Table 1) have very different processing times. Most primary care data are rapidly available, for example RSC data within 3 days, whilst the General Practice Data for Planning and Research (GPDPR) data are refreshed fortnightly potentially moving to monthly. Secondary care data national collections are slower. Hospital Episode Statistics (HES) are three months in arrears before its final curation, other secondary care national data sets do not have this lead time but they are not readily available for access in less than four to six weeks. Faster direct access to data from hospital CMR vendors might usefully be explored.

Meanwhile, ethical governance (i.e. approval as "Health protection" by the UKHSA Caldicott Guardian, or research ethics approval from the Health Research Authority (HRA)) should be in place.

Secure data environment (SDE):

Establishing an SDE for analysis and research purposes is another crucial step in facilitating rapid and secure data linkage during an epidemic or pandemic. The SDE enables the linking of multiple datasets, ensuring access to a diverse range of data while upholding individual privacy [24]. The secure data platform can also enable large-scale computation of health data. Establishing an SDE is part of UKHSA's data strategy, its new SDE, EDAP, is designed to also support enhanced mathematical modelling [27].

OpenSAFELY provides another model for an accessible analytics platform. OpenSAFELY sits on top of CMR vendors data. Queries are run on the data without the researcher having any direct access to patients' data. This innovative approach was established at the beginning of the COVID-19 pandemic [28]. OpenSAFELY runs separately analysing EMIS and TPP System One data, it proved itself a scalable solution conducting pandemic research. Its limitations are the separate analysis of these systems data and no direct link to practices to enable sentinel sampling.

UKHSA's EDAP environment should be considered as a possible environment for rapid access to data, reproducing the successes of the EAVE/EAVE II programme in making data accessible for public health as well as academic contributions to the COVID-19 pandemic.

In addition to technical preparations for data sharing, creating and strengthening data linkage between databases during normal times can empower health-related research and better prepare for Pathogen X. Data governance and ethical approval for data sharing could be prepared in advance so as to be quickly implemented in response to Pathogen X. Processes for data sharing between the four UK nations could also be agreed. Actions on data transparency should be considered.

Governance:

There need to be agreements in place to meet information governance (IG) requirements, ethical approval and other governance arrangements in place to allow rapid use of these data assets.

The UK National Data Guardian in her 2021-2022 report included:

"*…legal compliance is a necessary, but not a sufficient condition for building public trust. It is essential that any organisation handling data on a large scale should "hard bake" transparency and public involvement into every relevant aspect of its work…*

…NHS Digital's Independent Group Advising on the Release of Data (IGARD) as an example of what good, independent oversight looks like."

Alongside ensuring there are permissions in place a publicly transparent data approval process is recommended as implemented by NHS Digital, prior to the amalgamation NHS England [29,30].

Conclusion

Improved data quality particularly in primary care with linkage to comprehensive virology, serology test results and other key outcome data is essential, along with the computing power to run mathematical models and other sophisticated analyses. We consider these prerequisites for improving our pandemic response. Internationally this has been recognised as important [4–6]. In addition to the technology the right governance needs to be in place and the National Data Guardian has given a strong steer as to what she feels is required to ensure here is trust and transparency.

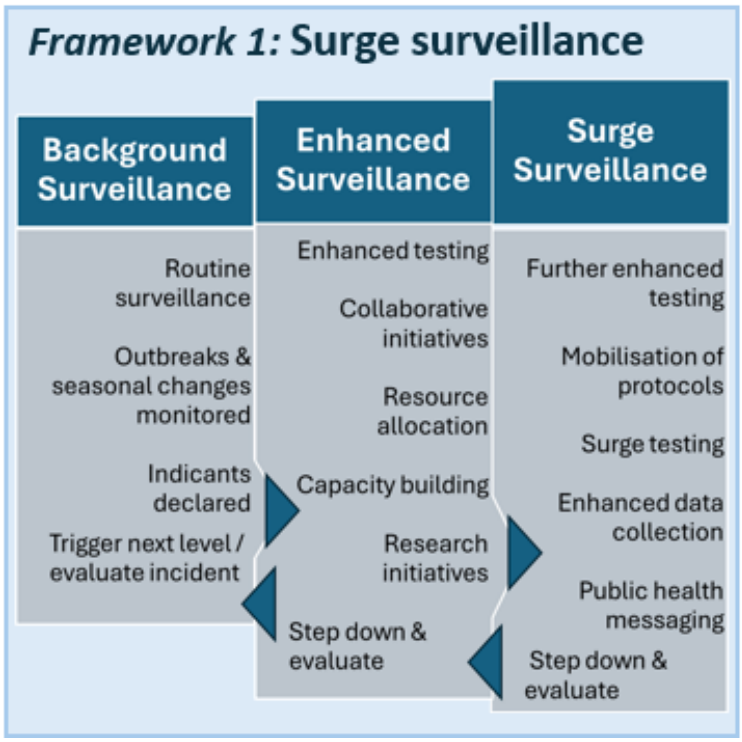
Whilst recognising that it would take time and resources, there is an opportunity post-pandemic to recognise the importance of these data, processing and governance requirements which are well aligned with UKHSA's Data Strategy.[19]

3. Surge Surveillance

Purpose

The purpose of surge surveillance is to allow public health authorities to monitor trends, identify outbreaks, and implement timely interventions to mitigate the spread of disease and protect public health in the UK when standard surveillance cannot meet this need. By definition, surge surveillance goes beyond what might be delivered by background or enhanced surveillance (Figures 1 and 3).

Figure 3: Surge surveillance is implemented when background and then enhanced surveillance cannot meet the needs for monitoring Pathogen X



Scope

We have identified and developed frameworks, tools and resources to guide decisions on when to scale up from routine ongoing background surveillance to surge surveillance, as well as to produce an *aide-mémoire* of what the implications of such transitions may entail with respect to operational, logistical, security and financial considerations. We did not include sample size recommendations and border testing due to the fact of them being out of scope of this report and it is impossible to predict them for an unknown pathogen.

Figure 4. Tiers of surveillance

Surveillance Tiers	Action Plan (Build on previous tier)
Background surveillance All-year-round surveillance of infectious diseases	• Surveillance of ILI and ARI using swabs and diagnoses in electronic medical records • Expand testing capability and scales
Steering meeting Triggers to call the meeting may include: • A new pathogen suspicious for infection detected in humans or changes in characteristics of known pathogens. • An abnormal and alarming increase in the incidence of known infectious diseases over a defined period (e.g., continuous increase for 3 weeks as evident in background surveillance). • Identification of outbreaks or clusters of cases indicating potential public health threats. • Evidence of international outbreaks or pandemics that are likely to affect the UK.	
Enhanced surveillance An observation period to assess and prepare for the risk of escalation	• Enhanced testing • Collaborative team initiative • Resource allocation • Capacity building • Research initiatives
Steering meeting Triggers to call the steering meeting and build a steering panel that oversees the surveillance process include: • Expert decisions by public health professionals • Disease modelling findings suggesting an epidemic or pandemic • Operational capacity requirements met	
Surge surveillance In response to sudden increases or surges in cases	• Surge testing • Enhanced syndromic surveillance • Enhanced data collection • Rapid response and intervention • Robust collaborative platform • Mobilisation of historical protocols • Public health messaging

Notes: Influenza-like illness (ILI), Acute Respiratory Illness (ARI)

Framework Protocol

This protocol provides a conceptual framework of stages and levels of surveillance (i.e., scale of testing) in response to a potential epidemic or pandemic in the UK. It focuses on the dynamic transition from background surveillance to surge surveillance. It does not include details on pathogen analysis or the preparation or development of tests.

In this framework protocol, we present three tiers of surveillance in response to insights gained from previous pandemics to enhance preparedness for Pathogen X, namely:

(1) background surveillance,
(2) enhanced surveillance, and
(3) surge surveillance, incorporating surge testing (Figure 4).

We describe the timing for transitioning between surveillance tiers and the actions to be taken at each tier. These surveillance tiers are determined by operational resources to deliver the outcome, not the threshold for action.

UKHSA runs a system of responding to health-related incidents. These can be categorised as either local or national. Our proposal is for there to be dynamic transitioning from background to enhanced to surge sentinel surveillance. This responsive model could potentially be integrated into UKHSA's incident management processes. For example, the director of a national incident (e.g., recent measles outbreak) could have the option of requesting enhanced surveillance should that be considered necessary.

The RSC's initial finding of and subsequent support of the UKHSA response to a case of swine influenza A (H1N2)v in England in November 2023 could also be considered as an example of responsive surveillance [31].

The step on to surge surveillance would be needed where testing was needed for health protection to inform whether a containment or other strategy had been successful.

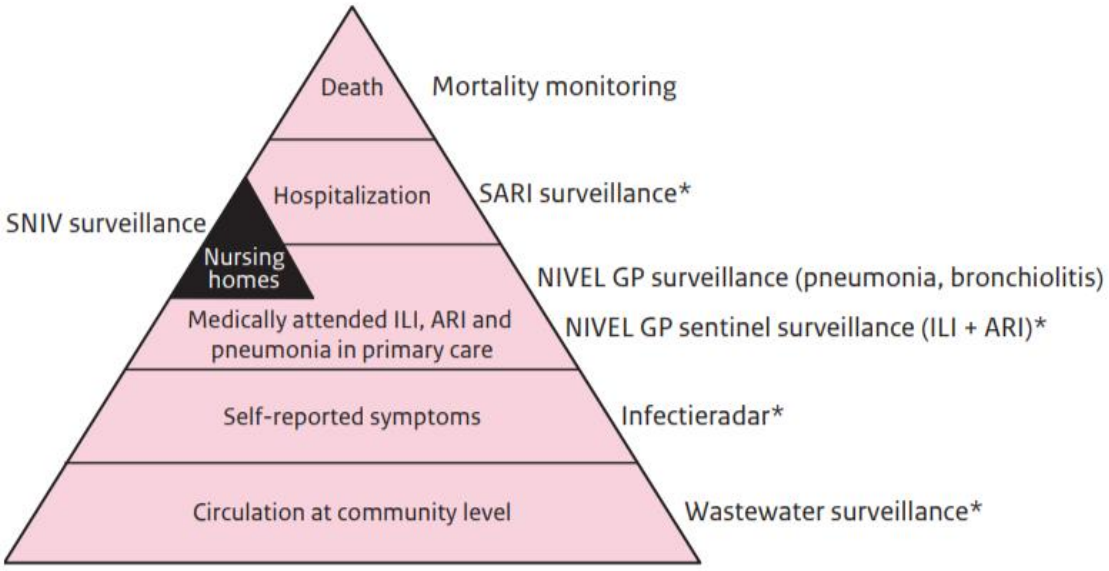
The Netherlands Institute for Health Services Research divided surveillance of respiratory infections by the severity of outcomes into a pyramid in its winter 2022/2023 annual report for Surveillance of acute respiratory infections (Figure 5) [32], which can be used as a reference for Pathogen X. Each level in this pyramid is monitored through different surveillance methods in different healthcare settings. All the outcomes and healthcare settings in this pyramid are monitored within the three surveillance tiers we proposed in this framework protocol but with varying degrees of surveillance intensity.

Background surveillance

Background surveillance is an essential precursor for surge surveillance because it holds baseline data against which any change in disease incidence might be measured and facilitates a rapid scale-up of surveillance tiers by providing a well-established infrastructure. Background surveillance should cover any pathogens that have epidemic or pandemic potential, not limited to respiratory infectious diseases and anthroponoses. Therefore, background surveillance requires

an integrated approach involving a variety of institutions such as the UKHSA and the Pirbright Institute (National Virology Centre), as suggested by the WHO One Health Initiative [33]. In addition to the routine monitoring of infectious diseases, the system can be periodically stress-tested to identify potential weaknesses in the surveillance system.

Figure 5 Respiratory infectious surveillance pyramid (source: NIVEL – Netherlands)



Footnote: *Systems with * (also) include virological surveillance. Wastewater surveillance currently only detects SARS-CoV-2.*

NIVEL= Netherlands Institute for Health Services Research, SARI= Severe Acute Respiratory Infection, SNIV= Surveillance Network Infectious Diseases Nursing Homes, GP=General Practice, ILI=Influenza-Like Illness, ARI=Acute Respiratory Infection, SARS-CoV-2=Severe Acute Respiratory Syndrome Coronavirus 2.

In England, the RSC provides year-round surveillance of respiratory viruses as presenting to general practices and serves as an example of a well-established background surveillance network. Its routine surveillance includes in-practice swabs in patients presenting with influenza-like illness (ILI) and monitoring diagnoses of respiratory infections recorded in CMRs. The five-year rolling averages of disease incidence for the over 30 monitored conditions provide a baseline against which any changes can be monitored.

Alongside the RSC, UKHSA has established a system of syndromic surveillance, a DataMart and other sources of surveillance data [34]. The Oxford-RCGP-UKHSA collaboration includes the provision of primary care data by the RSC to syndromic surveillance from EMIS, the largest supplier of primary care CMR systems in England. UKHSA and RSC also work together on project-based in-depth explorations [35,36]. Common working in the EDAP environment could enhance this collaboration, by facilitating in-depth exploration of possible signals being seen in syndromic surveillance data. A recent innovation in UKHSA is the creation of HARISS. This group

of hospitals, planned to be one or two per region, includes those that house UKHSA reference laboratories.

Enhanced surveillance

Enhanced surveillance is introduced to bridge the transition between background surveillance and surge surveillance. Following the detection of an outbreak of infection, it is necessary to observe for a period of time to assess the potential risk of escalation into an epidemic or pandemic. This intensified observation period is an appropriate time to conduct enhanced surveillance, which involves focused additional data collection in response to an outbreak or unexpected pathogen result. The UKHSA and RSC's response to the detection of a case of swine influenza A (H1N2)v [31], or concern about population immunity to diphtheria provides examples of enhanced surveillance [37].

Enhanced surveillance could be initiated by a “steering meeting” (as suggested in Figure 4), or other response process, based on the risks identified in background surveillance. Stakeholders in this meeting might include any UKHSA incident director, surveillance networks, National Health Service (NHS) parties, and other relevant government agencies (e.g., Foods Standard Agency, Agriculture, or others). Triggers to call the meeting may include:

- A new pathogen suspicious for infection detected in humans or changes in characteristics of known pathogens.
- An abnormal and alarming increase in the incidence of known infectious diseases over a defined period (e.g., incidence rate continuous increase for over 3 weeks outside of seasonal patterns as evident in background surveillance).
- Identification of outbreaks or clusters of cases indicating potential public health threats.
- Evidence of international outbreaks, epidemics or pandemics that are likely to affect the UK.
- Background surveillance suggests potential bioterrorism or deliberate release of pathogens.

The goals of enhanced surveillance should include:

- Provide enhanced surveillance and use the learning from this to update epidemic/pandemic preparedness protocols to keep them readily deployable.
- Create capacity and capability drawn from routine surveillance systems that could be mobilised and scaled for surge testing.
- Testing enhanced surveillance across a range of possible pathogens (e.g. enterovirus, mycoplasma, pertussis), testing techniques and processes, and providing contemporaneous data access to domain experts (both mathematical and risk group modellers, as well as disease experts) as well as policymakers, such as Joint Committee on Vaccination and Immunisation (JCVI) and SAGE.
- Participate in regular epidemic/pandemic preparedness exercises that mobilise different aspects of epidemic/pandemic preparedness over a three-year cycle.

During the enhanced surveillance, a number of activities may be conducted:

1. Enhanced testing: In comparison to the regular sampling (i.e., randomly testing patients presenting ILI in practices) conducted in background surveillance, a higher proportion of patients presenting with suspected infection and patients who may have asymptomatic infection will be tested to inform subsequent decisions regarding the transition to surge surveillance. Enhanced testing strategies might include sampling for reference laboratory testing (likely to be polymerase chain reaction (PCR) tests) and point of care tests (POCT) conducted by health care professionals. Home self-tests may be used depending on the availability of tests as new pathogens may not have readymade home tests at the enhanced surveillance stage. Samples to be tested may include a range of different body fluids, though nose and throat swabs are the most likely. Wastewater surveillance may be deployed.
2. Collaborative initiative: An enhanced surveillance capability is formed to build up and strengthen collaboration among relevant stakeholders, for example, RSC, UKHSA's syndromic surveillance and HARISS teams. We could work with existing infrastructure, e.g., the RSC, and possibly EAVE II, to create "enhanced" capacity and capability to work on responsive/enhanced topics. Current asks of the system suggest this may be utilised around 4 times per year. The RSC does respond to additional requests but lacks the capacity to respond with sufficient agility. Such a capability would build on existing UKHSA collaboration by developing stronger links with syndromic surveillance and new HARISS network.
3. Resource allocation: As an outbreak emerges and indicates a potential escalation, consideration may need to be given to allocate personnel, diagnostic resources, and medical supplies, including personal protective equipment (PPE), to areas at increased risk of disease transmission.
4. Capacity building: Capacity building includes training personnel, refining surveillance protocols and releasing financial support for surge surveillance. Additionally, for pathogens lacking available tests, a core aspect of capacity building involves the development, manufacturing and distribution of tests.
5. Research initiatives: At this stage, increasing sampling in high-risk populations and geographical areas would provide data for risk stratification, as detailed in the subsequent section of this report. Investigating the duration of infectiousness in symptomatic and asymptomatic individuals could offer insights into the secondary attack rate and estimating disease spread. We would also investigate viral kinetics (viral concentration over time and its relationship to infectiousness).

Surge surveillance

Surge surveillance should commence in response to sudden increases or surges in cases, particularly when there is a significant outbreak or signs of an emerging epidemic or pandemic. This decision may rely on the expertise of public health professionals, the findings of disease

modelling [38], and the capacity of operational requirements. Since the decision to initiate surge surveillance would involve numerous stakeholders and require immediate direction, a steering panel consisting of representatives from each stakeholder, including those involved in the steering meeting to initiate enhanced surveillance, should be formed and tasked with overseeing the surge surveillance process.

Surge surveillance requires the collection of samples from the general population or target groups within a condensed timeframe across various geographical regions. RSC's experience in conducting surge testing in collaboration with the UKHSA during COVID-19 suggests that rapidly scaling up to meet a sudden increase in testing demand is one of the primary challenges for surge surveillance. The intensified testing scale requires appropriate distribution channels capable of adequately supplying test kits and, where necessary, PPE for staff undertaking testing. Additionally, efficient and safe processing of tests, including facilities that can provide kits directly to the public, is essential.

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The activities to be added during surge surveillance may include:

1. Surge testing: Surge testing refers to an intensified and targeted approach to proactively identify individuals with clinical and asymptomatic infection who can then be isolated, treated and contact traced. In addition to enhanced testing in medical practices, implement large-scale testing that involves easily accessible tests such as lateral flow device (LFD) for the public to self-test. More tests would be targeted at high-risk populations or areas experiencing increased transmission. In a situation where tests for the specific pathogen have not yet been developed, existing tests for similar pathogens or syndromes can be repurposed or adapted for use. Mass testing data can be used in conjunction with surveillance surveys to identify gaps in the uptake of public health interventions at fine scale levels and by sociodemographic groups [39].
2. Enhanced syndromic surveillance: Enhanced syndromic surveillance is essential, especially when tests are not widely available for surge testing. Monitoring trends in symptoms and disease presentations across healthcare facilities could help assess the extent of disease outbreaks and disease activity.
3. Enhanced data collection: Collect more detailed information during testing, including demographic data, travel history, and potential contacts, to better understand transmission dynamics. Collect additional data from patients by questionnaires and direct questioning.

The results of PCR tests are easy to track as they are conducted in central laboratories. In comparison, the results of LFD tests are mostly self-reported by patients and are difficult to track. This was observed during the COVID-19 pandemic, where most people who used LFD tests did not officially register their test results [40]. Therefore, easier access to the self-reporting platform and advocacy for registering test results are needed to enable better surveillance coverage (e.g., ZOE health study [41]).

4. Rapid response and intervention: Implement response measures, such as contact tracing, isolation of cases, and deployment of resources to mitigate the spread of disease and prevent further escalation.
5. Robust collaborative platform: Facilitate collaboration between public health agencies, healthcare providers, laboratories, and other stakeholders to ensure a coordinated and effective response to surge transmission.
6. Mobilisation of historical protocols: Review and adapt protocols from previous epidemics/pandemics or health emergencies to help rapidly respond to the Pathogen X epidemic or pandemic.
7. Public health messaging: Develop and disseminate clear and timely public health messages to raise awareness about surveillance efforts, encourage testing and vaccination participation, and promote health-protective behaviours. Good use of social media could significantly enhance the effectiveness of public messaging and provide real-time updates on information.

Test results from the surge surveillance can support further studies (see *Appendix A*) such as the risk of household transmission, community prevalence, severity assessment of the infection and comorbidities and uptake and effectiveness of vaccine interventions. In England, for instance, the RSC holds both test results and CMR of patients, which could support these studies and provide rich information for policymakers. In Scotland, the EAVE/EAVE II platforms include surveillance results that could support research studies.

Conclusion

What we describe as “Foundational surveillance preparedness,” the ability to move dynamically between background, enhanced and surge, would provide the framework to deliver surge testing when needed. The key components that might be considered are:

- Regular mobilisation to ensure operational readiness with all elements tested over a three-year cycle with frameworks updated.
- Ethical approval of this process.
- Strong direct links with patient participation groups at health care providers who were part of any enhanced or surge testing exercise. Greater public consultation, possibly strengthened by qualitative research into the acceptability of NPI and therapies, including their use in specific risk groups.

- Surveillance assets might be more integrated and work more closely together, initially with an English focus, but potentially UK-wide. The RSC data infrastructure and other data assets might be housed in a single SDE, possibly EDAP, to enable the mirroring of data access and analysis achieved by EAVE II.
- Part of the preparation process might be the inclusion of disease or methodological expertise from outside the immediate team.
- The system would helpfully enhance the two-way flow and integration of data. Data should be capable of being returned to health care providers' CMR and directly to their patients through routes like the NHS App.

4. Risk Stratification

Purpose

Risk stratification during an epidemic or pandemic aims to identify individuals or populations based on their vulnerability to the effects of the circulating infectious disease. This stratification allows for a targeted and efficient allocation of resources, interventions, and public health measures to protect the most vulnerable during an epidemic or pandemic.

In addition to this, there may be a continuous change in a pandemic's dynamic, which would require adaptive responses for monitoring, identification, and assessment of new risk categories. In this document, we discuss two main adaptive changes observed in the COVID-19 pandemic:

1. A change in risk as we moved from the wild pathogen type towards new variants, this adaptive change underpins the need to consider the greater integration of genomic surveillance; and
2. A parallel change in risk as the population becomes naturally immune, vaccinated, or new therapies become available.

Risk stratification requires high quality data (see Section 2 for further details). Most risk stratification will be based on routine data where high-quality recording and processing cannot be assumed. Whilst the NHS is a country-wide institution with a unique identifier – the NHS Number, with a similar approach in Scotland, where a Community Health Index (CHI) number is provided - that allows the linkage of primary and secondary care with vaccine exposure, pathogen test results and death registry data. However, this requires additional data cleaning, covariate curation, and other key processes in conducting these risk stratification studies.

Scope

In this report, we draw on the main clinically focussed risk stratification studies to date from the COVID-19 pandemic to identify the type of studies likely to be required. We also consider the data necessary for similar analyses/protocols for Pathogen X and have produced a framework protocol, which can serve to iteratively identify high risk groups.

We have restricted our scope to those studies of risk stratification with a clinical focus, whilst recognising that there will be a need to assess risk stratification in other scenarios, such as large gatherings and events [42], to assess their safety.

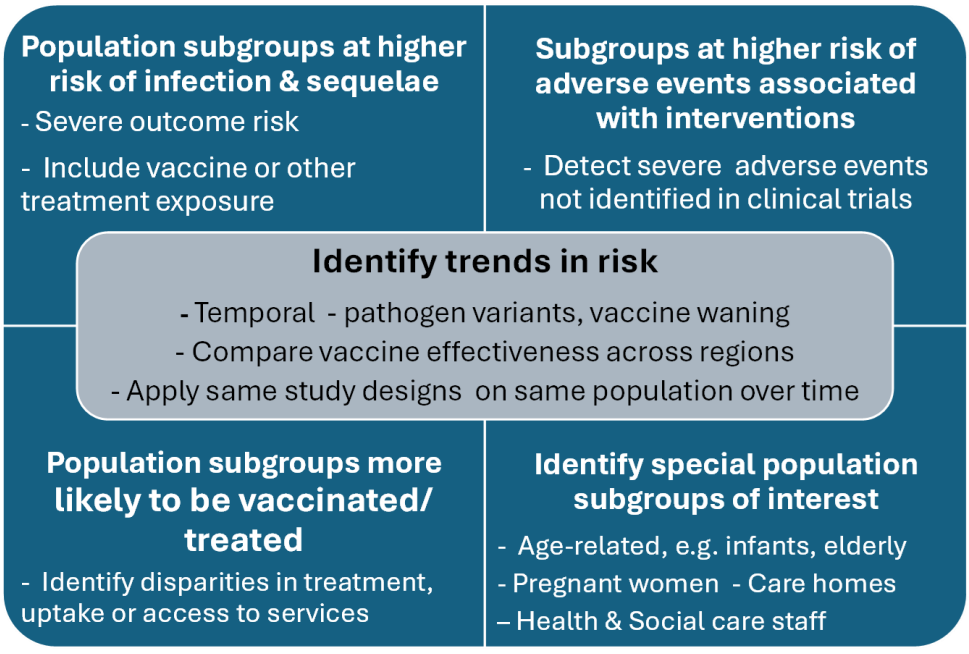
Lessons from the COVID-19 pandemic about risk groups

Overall, there exist at least four clusters of high-risk groups that were investigated (Figure 6), that may be relevant in future epidemic or pandemics:

1. Population subgroups at a higher risk of infection and its sequelae, including severe COVID-19 outcomes (e.g. hospitalisation, intensive care unit (ICU) admission and death) and long versions of the disease (e.g. long COVID), which could be coupled to previous vaccination records and vaccine effectiveness.
2. Subgroups at a higher risk of suffering adverse events associated with interventions (e.g., safety of COVID-19 vaccination using the incidence of thrombotic events as an outcome)[43,44];
3. Population subgroups more likely to be vaccinated, and if there were disparities in access to healthcare services [45–48]; and
4. Special population subgroups which were not widely investigated in the original trials or the above investigations (e.g., including pregnant women, newborns, children under 17 years old, long-term care facilities, or healthcare workers).

Together, these provide an overview of the adaptive response of our frameworks to tackle research gaps identified through the upcoming evidence (see Appendix A). Additionally, there is likely to be a need to identify trends in risk.

Figure 6: Clusters of high-risk groups identified in the COVID-19 pandemic, plus need to identify trends in risk



Changes in risk assessment

Our report found that similar study design can be deployed in the same populations at different time periods to investigate the impact from the appearance of new variants. For example, the Data and Connectivity: COVID-19 Vaccines Pharmacovigilance studies (DaC-VaP 1 and 2) investigated the temporal trends in vaccine effectiveness for the SARS-CoV-2 Delta variant in adults up to 65 years of age, [49] followed by the severity of disease and vaccine effectiveness in Omicron era.[50] The Understanding SARS-Cov-2 infection, immunity and its duration in care home residents and staff in England (VIVLALDI) study compared risk severities between the Omicron and Delta variants amongst residents of long-term care facilities [51]. Other important studies providing further insights were SARS-CoV-2 Immunity and Reinfection Evaluation (SIREN) [52,53]providing insights into healthcare workers' likely levels of infection, vaccine uptake and response; and the REal-time Assessment of Community Transmission-2 (REACT) study looking at community transmission and immunity [54].

Risk assessment can change with the appearance of new variants, and as new vaccines and therapies become available. To address this, we identified that studies:

1. Compared temporal trends across the same study population and outcomes (simultaneously addressing changes in pathogen variants and waning of vaccines) [55]];
2. Compared vaccine effectiveness across regions in the same time period but with different predominant variants (e.g., Scotland vs Brazil [56,57], four-nation comparisons[58,59]),
3. Applied similar study designs on the same populations at different time periods (e.g., effectiveness studies with 1, 2 or 3 or more vaccine doses on adults aged 18-65 years (DaC-VaP), and residents in long-term care facilities (VIVALDI).

Framework Protocol

Data requirements for risk stratification in future epidemiological emergencies

The definition of risk categories requires a multidisciplinary consensus to identify relevant target groups.

We anticipate that risk stratifications will be based on established approaches to clinical reasoning. This involves the development of a clinical consensus based on previous epidemics and pandemics, then hospital-based case series (e.g. International Severe Acute Respiratory and emerging Infection Consortium (ISARIC)) [60–62] and then population-based cohort/nested case-control studies (e.g. QCovid) [10–13] with independent validation.

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The definition of risk categories is limited by the granularity of the data available.

Timely investigations of risk stratification require that datasets pertaining to clinical risk, occupation and residence be available. If possible, these should be dynamic so that at specified times, membership of a clinical risk, occupation or residence group can be established. This may be unlikely achieved with national data, but quarterly updates should be sufficient and yearly acceptable.

It is preferable to have clinical risk based upon access to population-based GP data as that is most likely to give the most complete picture of clinical risk in the community. It would be acceptable to have binary variables denoting membership of pre-specified clinical risk groups at fixed time points but would be much more flexible if there was the opportunity to access data with SNOMED CT/Read codes so that modifications to the clinical risk groups can be made in a timely fashion, as necessary. There is also an internal service used within NHS England 'Cohorting as a Service (Caas)' which securely identifies groups of people (known as cohorts), using national health data [63].

The choice of study design is influenced by the risk group definitions and the data availability.

The above considerations suggest that risk stratification is likely to be best investigated with large population or community-based cohorts of individuals, with baseline identification of clinical, occupational, and location-based risk groups. For identification of the risks of severe outcomes of Pathogen X, the cohorts are required to link, on an individual basis, to hospitalisations, ICU admissions and deaths in real time – at least weekly.

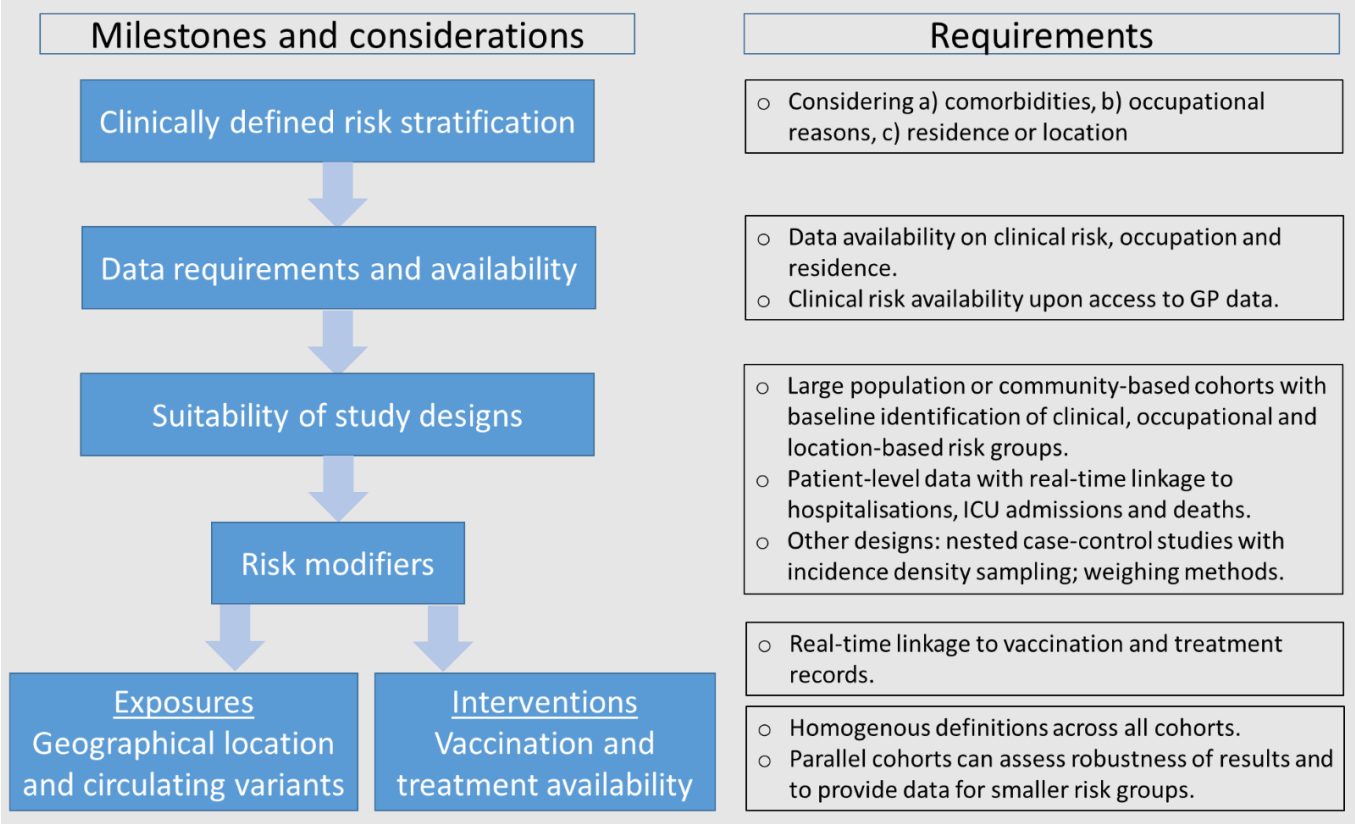
Previous studies were largely based upon cohorts, often followed up for a relatively short period of time, though nested case control studies with incidence density sampling could also have been used. The timeliest results will be through cohorts where the data are all held centrally. For extremely large datasets, efficient statistical analysis methods based upon weighting or nested case control studies should be considered.

Continuous changes in exposures and availability of new interventions should be iteratively investigated.

For the investigation of how risk might be modified by vaccination or treatment, links to vaccination and treatment records in real time are required. Consideration should also be given to using cohorts located in different geographical regions. To be timely detailed planning should take place

to ensure that the same definitions are used in all cohorts. The main reason for the parallel cohorts is to check on the robustness of the results and to provide precise information for relatively small risk groups.

Figure 7. Flow diagram for risk stratification assessment



Conclusion

We have set out implementation steps for the existing frameworks that could be applied to Pathogen X. These steps would contribute to the iterative process of identifying high-risk groups.

1. Firstly, expert opinion is used to create consensus on known existing risk categories that will be prioritised. This stage should consider the wider literature, the devolved nations' suggestions, as well as UKHSA's own learning.

2. Secondly, frameworks are activated, providing initial guidance on risk categories based on previous experiences. This initial risk stratification approach will have an unknown suitability for Pathogen X. For example, the ISARIC protocol [60–62] was activated early in the COVID-19 pandemic.

3. Thirdly, population-based risk stratification tools specific for Pathogen X are produced. This is based on the newly generated empirical evidence, to develop stratification tools that are better suited to the peculiarities of Pathogen X. For example, QCovid was developed in response to the risk group identification in the COVID-19 pandemic, replacing the influenza categories initially used as indicated in the frameworks (e.g., ISARIC).

QCovid [64], EAVE II [65] and Rapid Epidemiological Analysis of Comorbidities and Treatments as risk factors for COVID-19 in Scotland (REACT-SCOT) [66] may be suitable as an implementation template for future epidemics and pandemics, they include methods of risk stratification for severe outcomes in the general population.

5. Uptake, Effectiveness, and Safety of Vaccines and other Pharmacological Interventions

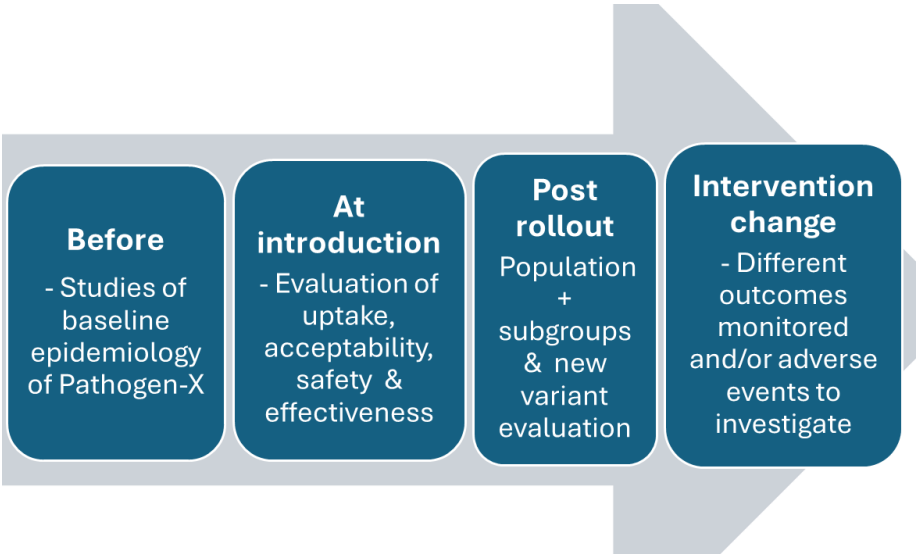
Purpose

Investigating the uptake, effectiveness, and safety of vaccines and other pharmacological interventions for Pathogen X will provide support for vaccination programs, help identify factors influencing vaccine acceptance and safety, provide evidence for clinical treatments and support evidence-based policy decisions to safeguard population health.

Scope

The scope of this framework includes the need to study the baseline epidemiology of Pathogen X, through the introduction of any intervention, post rollout and when there is any change in the intervention (Figure 8):

Figure 8: The scope of the framework to measure the uptake and safety of vaccines and other pharmacological interventions



In this framework, "vaccine" refers to developed or available vaccines that have been proven to be effective against Pathogen X. Pharmacological interventions refer to medicines that are proven or likely to be effective against Pathogen X.

Under normal circumstances, we expect that clinical trials will be performed first to establish baseline effectiveness and safety, coupled with an accelerated approval process. This will be followed by the population-wide rollout of the pharmaceutical intervention where real-world evidence (RWE) derived from population-based routine databases would provide evidence on uptake, effectiveness and safety with a focus on assessing public health impacts. This framework focuses on this second stage based on the consideration of benefit-risk (challenge about assessing longer-term efficacy versus getting to roll out rapidly), providing guidance on the requirements needed for the evaluation, in the epidemic or pandemic context. Emergency licencing may allow earlier rollout than would take place under normal circumstances, outside an epidemic or pandemic. In these circumstances much more reliance will be placed on RWE studies.

We are limiting our definition of “other pharmacological interventions” to antimicrobials, generally antivirals, monoclonal and long-acting antibodies.

Framework Protocol

The conceptual framework for this protocol is described in the following four stages:

- Preparation at the early stage of Pathogen X epidemic/pandemic as well as compute capabilities consideration
- Rapid assessment of the initial uptake, effectiveness and safety of the vaccines and interventions
- Full assessment of the interventions, particularly in high-risk groups, as the epidemic or pandemic progresses
- Reacting promptly to any changes in pathogen variants (See Section 3, the Surge testing protocol) and their impact on the effectiveness of vaccines or treatments, and safety as well as the effects of natural immunity.

Rapid assessment

A rapid assessment is needed to generate the initial evidence, particularly if there exists a scarcity of evidence on novel pathogen variants.

Study protocols with developed data analysis plans and code lists for different research questions can significantly accelerate the rapid assessment process. However, as described in section 2, this requires readiness of the data at baseline, as well as the readily available interventions shortly after the onset of the emergency. Additionally, there may be considerable overlap between studies reporting surge testing and the baseline assessment included in the scope of this framework. For example, the “Protocol and Analysis” plan from EAVE II, covered study protocol, statistical analysis plan and statistical software code used in analyses covering various aspects of the uptake, effectiveness and safety of vaccines and other interventions. The protocols

developed for COVID-19 vaccines and interventions can be useful resources for Pathogen X studies (see Appendix B).

Table 2. Summary of the action points

Topic	Action points
Data linkage	Develop data sharing agreements and documentation during non-pandemic times Provide technical and financial support to facilitate the rapid and flexible development of a responsive data sharing platform
Rapid assessment	Prepare study protocols with developed data analysis plans for different study questions
Full assessment	Follow evolving study questions Standardised protocols
Changing pathogen variants	Standardised or automated process of the rapid and full assessment Close follow up of new technologies like artificial intelligence and implement where possible
Patient and public engagement	Vaccine hesitancy can be important in the uptake of vaccines and there can be a need to inform and test interventions to improve uptake and understanding of benefit risk This may need to also be targeted towards specific populations or risk groups

Full assessment

A full assessment provides a more detailed and in-depth understanding than a rapid assessment by focusing on special population subgroups (e.g., children, patients with comorbidities), as well as more targeted outcomes. These research questions would likely evolve over time to accommodate specific needs identified from patients, clinicians, and policymakers as the epidemic/pandemic progresses. In addition to mobilising existing protocols to expedite the study process, standardising protocols may ensure consistency and comparability across different settings and populations.

Changing pathogen variants, examples from COVID-19

The capacity for near real-time surveillance of Pathogen X is important to initiate a rapid response to new variants. Existing protocols for evaluating vaccine uptake, effectiveness and safety during

the COVID-19 pandemic were adopted taking into account the evolution of the pathogen and the pandemic:

1. Before the intervention is introduced:

The learning from previous pandemics, should be part of preparedness.

All anticipated data requirements must be in place at a baseline level (e.g., as used for routine surveillance), and at an enhanced level (e.g., in anticipation of the implementation of an intervention). For example, for EAVE II, in anticipation to the introduction of vaccinations in November 2020, covariates were curated, documentation created to keep data in place, ethical approval requested, and data cleaning tasks initiated. However, most epidemics and pandemics have also had unanticipated data requirements, which may also need to be proactively considered.

There will generally be clinical trials, which may provide insights from the reported efficacy and any adverse events that emerged in this context. However, such trials may be conducted on younger healthier people who may not be representative of the population to be vaccinated. The pharmacology of the intervention may also provide insights into the potential benefit-risk profile.

There may well be learning from an initial outbreak, epidemic or pandemic which informs the level of risk from the pathogen. This may come from the UK or internationally. This should include its likely transmissibility, if it is readily tested for, and if it is capable of asymptomatic carriage and spread. It is likely that in order for this framework to have been initiated, UKHSA's National Incident Response Plan (NIRP) will have been initiated, where the health security threat is considered to be Pathogen X. The NIRP establishes how UKHSA will respond and recover from any significant public health or business continuity incident, its scope is broader than just Pathogen X.

As with the framework protocols, there may be overlap with data requirements during surge testing, for example collection of data direct from patients and public may provide important insights (e.g., Zoe app identified loss of taste and smell as potential COVID-19 symptoms [14]). We may also be able to collect more detailed information about the course of the illness and its health economic impact. Smart watches and other devices may allow the collection of observations such as pulse, temperature, oximetry.

Serosurveillance may provide insights into population levels of immunity to the pathogen, and how it differs by age-band and in high-risk groups.

2. At the introduction of the intervention:

This stage aims at an initial evaluation of the uptake, acceptability, safety and effectiveness of an intervention (see Rapid Assessment section above).

3. Post rollout of the intervention:

This stage evaluates how the intervention behaves amongst the general population as well as the changes in population subgroups, exposures and outcomes (see *Full Assessment* section above). This stage provided the strongest body of evidence during the COVID-19 pandemic. For example, most of the DaC-VaP studies investigated the general adult population in the UK countries (England, Northern Ireland, Wales, and Scotland) [43–45,47,50,56–58,67–69;] while other studies investigated special subgroups such as healthcare workers [46,48], pregnant women [70], children under 17 years of age[71], and school staff, students and their household members. International collaborations would be useful at this stage to compare amongst different regional pathogen variants as well as pooling a larger number of individuals for analysis. This is particularly useful for the special populations (e.g., children under 17 years of age) or where a lower number of cases may translate into rare safety signals (e.g., immunocompromised people).

Genomic surveillance may provide insights into the evolution of the pathogen. The spread of speed of spread of these variants may provide additional insights. International differences in the variant circulating may help understand if vaccine effectiveness is maintained.

Serosurveillance may provide information about vaccine waning, particularly in high-risk groups.

4. When the initial intervention needs to be changed:

Pathogen variants could be a main trigger for an intervention to be modified, requiring changes in the testing strategy, new outcomes and data requirements. For example, while the most common outcomes at the start of the COVID-19 pandemic included symptomatic infection, hospitalisation, ICU admission and death, later stages included serious bleeding and clotting events, cerebral venous sinus thrombosis (CVST) events and other minor adverse events as security measures. DaC-VaP also compared temporal trends of fixed outcomes across a population, addressing pathogen variants as exposures (namely Omicron versus Delta SARS-CoV-2 variants), as well as the effect of waning of vaccines, as an example of changes in treatment effectiveness.

Conclusion

This section on the uptake, effectiveness, and safety of vaccine and other pharmacological interventions is potentially the most challenging of the three framework protocols. In this effectiveness-adverse event section, both the pathogen and therapy are uncertain. Hence our framework for our approach is broad.

Rapid then full assessment will inevitably include expert consensus. We will need to maximise our learning from previous pandemics, what we know about the pathogen and the proposed therapeutic intervention, but also to have the flexibility to recognise that we will need to respond to unforeseen circumstances and issues.

6. Conclusion

The core elements of this report are the frameworks about surge testing, risk stratification and uptake, effectiveness, and safety of vaccine and other pharmacological interventions, as set out in Sections 3 to 5. They describe how these might be developed dynamically from existing resources, promote greater collaboration, and build on the learning from the extensive research conducted in-pandemic.

Appendix A provides links to relevant protocols and studies that could be modified for use in any future pandemic. Appendix B summarises available resources.

In preparing this report the authors have suggested that if the implementation of these frameworks is to be successful, we will also need to include processes that test them in our health service as well as the wider societal context in which they will need to be implemented.

The key areas that we have flagged for ongoing activities are set out below. We believe them to be a prerequisite for the successful implementation of our frameworks:

- We need for high quality routine CMR data, that can be linked and readily accessed. This is explored in detail in Section 2.
- Linkage, access, and subsequent use of these data requires ethical arrangements need to be in place for testing and updating as well as deployment of frameworks.
- Great public and patient involvement, and as far as possible co-design of interventions are also recommended. This co-design might include plans to potentially collect more data direct from patients, but with the ability to link these data to routine data about risk, exposure to vaccination and other interventions, and outcome data.

After the 2009 pandemic a National Institute for Health Research (NIHR) Hibernated Influenza Studies Collaborative Group concluded that ongoing activities were important to maintain readiness [72]. This report endorses these findings and proposes that UKHSA's key surveillance resources along with external relevant domain experts, regularly exercise the implementation of key frameworks. A summary of this pandemic preparedness frameworks report is published in The Lancet Infectious Diseases [73].

We suggest exercising one or more components regularly, ideally in the context of an incident related need for enhanced surveillance in UKHSA. For the broader scope of our frameworks, we recommend testing over a three-year cycle.

Appendix A. Research protocols outputs and their contribution to the Pathogen X frameworks

A.1 Relevant protocols

Theme	Source	Research questions
Surge testing	EAVE II	Protocol for the linked Scottish national data (2020)
	RCGP RSC	Protocol for extending RCGP RSC background surveillance (2020)
	SHARP	Syndrome based case definition and management plan for high consequence infectious diseases (2022)
	UKHSA	sKIDs project: COVID-19 surveillance in school children (2021)
	WHO	FFX protocol: The first few X cases and contacts (FFX) investigation protocol for coronavirus disease 2019 (COVID-19) (2020)
Risk stratification	DaCVaP	Study protocol: observational study using linked UK national data (2022)
	VIVALDI	Protocol: Asymptomatic testing – cluster RCT (2023)
	EAVE II	Protocol: validation of the QCOVID algorithm across the four UK nations (2021)
	Other	ISARIC protocol (2022) ISARIC Resources (2021) QCovid project (2020) REACT-SCOT protocol (2021) SIREN protocol: Reinfection in healthcare workers (2020)
Uptake, effectiveness and safety of interventions	DaCVaP	Protocol: Investigating the uptake, effectiveness and safety of COVID-19 vaccines | The University of Edinburgh (2022)
	VIVALDI	Protocol: Asymptomatic testing – cluster RCT (2023)
	EAVE II	Statistical analysis plan (SAP) for first and second dose COVID-19 vaccine waning in adults (2021) SAP for first dose vaccine failures in adults (2021) SAP for second dose waning (2021) SAP for programmatic evaluation of COVID-19 vaccination against hospitalisations in adults (2021) SAP to investigate effectiveness of COVID-19 vaccines in children and young people aged 12 to 17 years in Scotland (2021) SAP for studying the uptake, safety, and effectiveness of monoclonal antibody therapy for COVID-19 (2022)
	UKHSA	Protocol: Safety of booster COVID-19 vaccination – cardiac arrythmia and arrest (2023) Protocol: COVID-19 CONSENSUS (2021) Impact of vaccination on virological response (2024)e

		Protocol: COVID-19 vaccine surveillance strategy (2021)

A.2 Relevant Studies

Theme	Source	Research questions
Surge testing	EAVE II	Cohort profile of EAVE II database (2021) Cohort profile for COVID-19 in pregnancy in Scotland (2022) Cohort study on SARS-CoV-2 tests in neonates (2023)
	RCGP RSC	Cohort profile for RCGP RSC during COVID-19 (2022)
	VIVALDI	Cohort study: incidence of COVID-19 in care home residents and staff (2021)
	UKHSA	FFX adaption: tests in cases and contacts (2020) Enhanced surveillance: impact of vaccination and SARS-CoV-2 variants on the virological response (2023)
	I-MOVE	Rapidly adapting primary care sentinel surveillance across seven countries in Europe for COVID-19 (2022)
	Zoe	Use of self-report test result from COVID Symptom Study app (2021)
Risk stratification	DaCVaP 1	Self-controlled risk series: Risk of thrombocytopenic, haemorrhagic and thromboembolic disorders (2022) Cohort study: Sociodemographic and Health Factors Affecting Uptake of Second Dose Covid-19 Vaccine in England (2022) Cohort study: First dose ChAdOx1 and BNT162b2 COVID-19 vaccinations and cerebral venous sinus thrombosis (2022) Self-controlled case series: Adverse events following first and second dose COVID-19 vaccination in England (2021)
	DaCVaP 2	Severe COVID-19 outcomes after full vaccination of primary schedule and initial boosters (2022) Pregnancy outcomes following Delta and Omicron SARS-CoV-2 infection in Scotland (2022) Evaluation of Risk Factors for Postbooster Omicron COVID-19 Deaths in England (2022) SARS-CoV-2 infection and COVID-19 vaccination rates in pregnant women in Scotland (2022)
	VIVALDI	Cross sectional survey: Built Environment and SARS-CoV-2 Transmission in Long-Term Care Facilities (2023) Cohort Profile: Using linked data to characterise COVID-19 infections (2023) Prospective cohort study: Antibodies in staff and residents of long-term care facilities (2021) Cross sectional survey: SARS-CoV-2 infection and outbreaks in long-term care facilities (2021)
	EAVE II	Prediction model: national derivation and validation of QCOVID risk prediction algorithm in Scotland (2020) Prediction model: external validation of QCOVID risk prediction algorithm in Scotland (2021) Statistical modelling: temporal trends and forecasting COVID-19 hospitalisations and deaths in Scotland (2021) Observational study: COVID-19 in Pregnancy in Scotland (2020) Cohort study: association between multimorbidity and mortality with COVID-19 hospitalisation (2022) Self-controlled case series study: Neurological complications after first dose of vaccines and SARS-CoV-2 infection (2021) Cohort study: Risk of COVID-19 hospital admission among children aged 5–17 years with asthma in Scotland (2022) Cohort study: Severity of omicron variant and effectiveness of vaccine boosters (2022) Cohort study: Risk of serious COVID-19 outcomes among adults with asthma (2022) Cohort study: Accelerated waning of the humoral response to COVID-19 vaccines in obesity (2023) Cohort study: Risk of COVID-19 hospitalizations among school-aged children in Scotland (2022) Cohort study: Pregnancy outcomes after SARS-CoV-2 infection (2022)

		Characterising adults in Scotland who are not vaccinated against COVID-19 (2022) Cohort study: Ethnic inequalities in COVID positive tests, infection prognosis, hospitalisations and deaths (2023) Cohort study: Predictors of incomplete COVID-19 vaccine (2023) Meta-analysis of cohort studies: Under-vaccination and severe COVID-19 outcomes (2024) Cohort study: Risk of winter hospitalisation and death from acute respiratory infections (2024)
	Other	Cohort study: Transmission of SARS-CoV-2 in the household setting (2021)
Uptake, effectiveness and safety of interventions	DaCVaP 1	Self-controlled risk series: Risk of thrombocytopenic, haemorrhagic and thromboembolic disorders (2022) Cohort study: Factors Affecting Uptake of Second Dose Covid-19 Vaccine (2022) Variations in COVID-19 vaccination uptake among people with mental health conditions in Northern Ireland (2022) COVID-19 vaccine uptake, effectiveness, and waning in health care workers in Wales (2022) Cohort study: First dose COVID-19 vaccinations and cerebral venous sinus thrombosis (2022) Self-controlled case series: Adverse events following first and second dose COVID-19 vaccination in England (2021)
	DaCVaP 2	Electronic cohort study: SARS-CoV-2 infection and vaccination in school staff and students (2022) COVID-19 booster vaccination uptake and infection breakthrough amongst health care workers in Wales (2023) Waning of first- and second-dose ChAdOx1 and BNT162b2 COVID-19 vaccinations across the UK (2022) Early Pregnancy Outcomes following COVID-19 Vaccination and SARS-COV-2 Infection (2022) COVID-19 vaccination uptake, safety, effectiveness and waning in children aged 12–17 years in Scotland (2022) Severity of omicron variant and effectiveness of vaccine boosters against symptomatic disease (2022) Test-Negative Case-Control Study: Waning of mRNA Boosters in Brazil and Scotland (2021) Nested test negative cohort study: Severity of Omicron variant and vaccine effectiveness (2021) Two-dose vaccine protection against COVID-19 hospital admissions and deaths in Brazil and Scotland (2021)
	VIVALDI	Effectiveness of booster vaccine doses against SARS-CoV-2 related mortality in long-term care facilities (2023) Immunogenicity and waning following third vaccine dose in older residents of care homes (2023) Prospective Cohort Study: Effectiveness of Booster Vaccine Against Omicron Infection (2022) Prospective Cohort Study: Outcomes of SARS-CoV-2 omicron infection (2022) Immune responses in vaccine-naïve residents of long-term care facilities (2022)
	EAVE II	Cohort study: Interim findings of first dose COVID-19 vaccine effectiveness against hospitalisation (2021) Cohort study: Safety of First-dose ChAdOx1 and BNT162b2 COVID-19 vaccines (2021)
	UKHSA	Self-controlled case series study: Risk of cardiac arrhythmia and cardiac arrest after COVID-19 vaccine (2023) Test-negative case-control study: Effectiveness of COVID-19 vaccines against Omicron and Delta (2022) Test-negative case-control study: Vaccine Effectiveness against Omicron (2022) Test-negative case-control study: Duration of Protection against Mild and Severe Disease by Covid-19 Vaccines (2022) Test-negative case-control study: Effectiveness of COVID-19 vaccines in older adults in England (2021)

Appendix B. Existing resources

Surge testing

Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC)

RSC's infectious disease sentinel network provided immediate community support of the initial COVID-19 surge testing [74]. It detected the first COVID-19 case in the UK, not related to foreign travel, and set out early on the epidemiology of this disease in the community [75]. Before the COVID-19 pandemic, RSC's sentinel network covered a large number of general practices in England and Wales that routinely collected virology samples for influenza surveillance. The virology samples were collected in practice among volunteer patients who presented with influenza-like illness to general practices. During the COVID-19 pandemic, RSC's well-developed in-practice virology sampling procedure was adapted for COVID-19 testing. A home COVID-19 virology swab testing procedure was also made available quickly to protect health workers.

RSC expanded its sampling scheme during the COVID-19 pandemic to help understand the evolution and transmission of the virus. In addition to virology sampling, RSC's network began collecting serology samples from volunteer patients in member practices to study various questions relevant to COVID-19, such as understanding disparities in community infection and vaccine waning in the immunocompromised population [76,77]. In the later stages of the COVID-19 pandemic, RSC initiated pilot programs for asymptomatic testing, point-of-care testing, and urinary antigen tests. The details of the sampling strategy were described in RSC's commissioning letter to member practices.[78]

UKHSA's Virology Reference laboratory conducts all the sequencing of the samples collected in RSC network. The UKHSA lab conducts sequencing for a panel of eight viruses at the moment: (1) SARS-CoV-2, (2) influenza, (3) respiratory syncytial virus (RSV) A and B, (4) Human metapneumovirus (hMPV), (5) Other seasonal coronaviruses (NL63, 229E, OC43, HKU1) in addition to SARS-CoV-2, (6) Adenovirus, (7) Human rhinovirus, and (8) Enterovirus. The test results were provided as feedback to the GP and recorded in patients' electronic health records to support research on various topics.

RSC's sentinel network identified the first case of COVID-19 and supported the initial rollout of COVID-19 tests later. The network shifted quickly from influenza surveillance to COVID-19 surveillance during the pandemic. This enabled the initial testing and evaluation of virus transmission when massive lateral flow testing was not available. The test results helped shape the public health interventions like social distancing later in the pandemic.

EAVE II and connected projects

We have identified different clusters of studies which have addressed different sampling strategies during the COVID-19 pandemic. A common theme is the linking of test results (e.g., PCR testing results, lateral flow tests) to the broader national CMR based databases, to sample individuals from a national pool for constructing study cohorts. The incorporation of real-time test results allows us to associate different interventions and outcomes to the current circulating variant of the pathogen as an exposure (e.g., SARS-CoV-2 Delta vs Omicron variants).

On the one hand, test-negative study designs have been utilised as part of the DaCVaP2 study to investigate symptomatic infection as an outcome during the COVID-19 pandemic. For example, the use of retrospective cohorts from national databases was coupled with PCR test records to provide initial estimates of Omicron severity as well as the effectiveness of vaccine boosters against symptomatic disease in Scotland. Similar results were also used to perform international comparisons between Scotland and Brazil [50,57,68].

Another set of studies coupled PCR test results to retrospective and prospective cohorts from national databases in all UK countries to investigate vaccination uptake, effectiveness and waning as outcomes [46,50,59]

EAVE II and its connected studies informed public health and health policy on the impact and severity of new pathogen variants. For example, it was reported that Omicron was associated with a two-thirds reduction in the risk of COVID-19 hospitalisation compared with Delta. Similarly, it impacted policymakers by informing on the need for booster doses. For example, it was reported that mRNA boosters after a primary vaccination schedule with either mRNA or viral-vector vaccines provided modest, short-lived protection against symptomatic infection with Omicron, but substantial and more sustained protection against severe COVID-19 outcomes for at least 13 weeks. (ref: surge testing + test negative)

Sampling and testing also allowed the measurement of outcomes based on PCR confirmation versus only clinical diagnosis. A study reported that those who were vaccinated had a reduced risk of PCR-confirmed SARS-CoV-2 infection, compared to those unvaccinated. This allows prioritising high-risk groups for additional boosters, including novel optimised versions, and the increasing array of COVID-19 therapeutics. (ref: surge testing + PCR)

WHO Mosaic Respiratory Surveillance Framework

During the COVID-19 pandemic, the World Health Organization (WHO) produced a framework to help the detection, monitoring and informing of respiratory viruses with observed epidemic or pandemic potential [79]. It consists of Domain I: detection and assessment of an emerging or re-

emerging respiratory virus; Domain II: monitor epidemiological characteristics of respiratory viruses in interpandemic periods; and Domain III: informing use of human health intervention. For each domain, the framework suggested various surveillance approaches to fit into the set-out objectives (Figure S1).

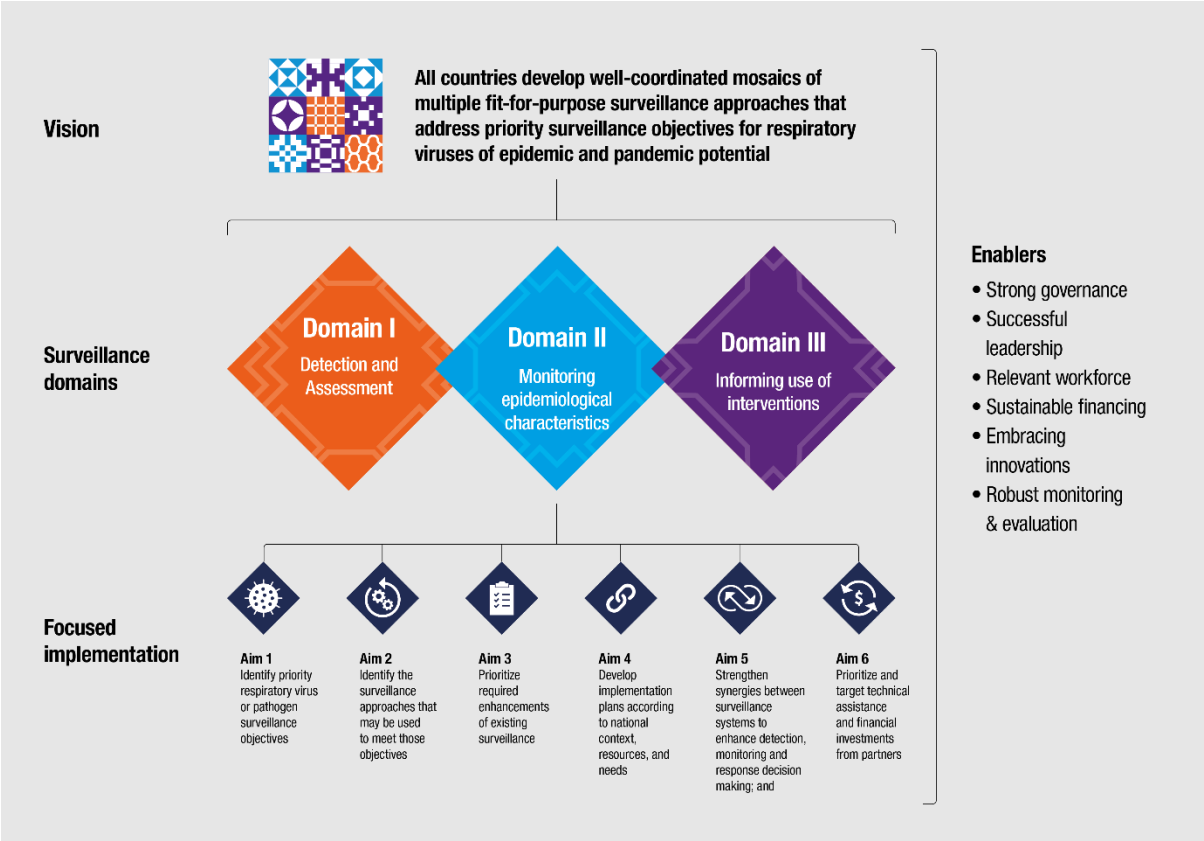


Figure S1. WHO mosaic framework

Surge testing is directly linked to the objectives in Domain I on detection and assessment. The framework suggested the strengthening of coordinated surveillance systems in health care and community settings throughout the year and at the animal-human interface (for pathogens with a zoonotic reservoir) to support the early warning, alert and response capability. It was emphasised that a pre-existing monitoring system is essential to enable a rapid transition to sustained and standardised case detection and to provide a platform for further investigations.

Enhanced surveillance approaches include targeted special population surveillance, media event-based surveillance and syndromic surveillance. Innovative approaches were also suggested for Domain I, for example, the integrated disease surveillance and response strategy and surveillance for human respiratory viruses in wastewater.

Other resources

A number of other projects were launched in response to the COVID-19 pandemic. Similarly, the VIVLADI studies coupled PCR test results to investigate confirmed infection cases amongst staff and residents of long-term care facilities in the UK. In some of these cases additionally investigating antibody and humoral response as an additional layer of testing.

The SIREN study investigated the coverage and effectiveness of the COVID-19 vaccine in UK healthcare workers [80]. VIVALDI Study investigated COVID-19 infections in care homes [81]. COVID-19 surveillance in school KIDs (sKIDs) led by Public Health England were for COVID-19 surveillance in children attending preschool, primary and secondary schools [82]. QResearch database was developed to enable rapid analysis of COVID-19 [83].

Platforms were developed or adapted in response to COVID-19. OpenSAFELY is a UK-based platform for data analysis [84], while the I-MOVE (Influenza – Monitoring Vaccine Effectiveness in Europe) network is a European platform [84] and the ISARIC (International Severe Acute Respiratory and Emerging Infection Consortium) [85] is an international platform. Protocols were developed by WHO (e.g. Unity studies [86]) and in the EU (e.g. the SHARP Joint Action [87]) and were adapted locally (e.g. UKHSA adapted the Unity Studies First Few Cases (FFX) protocol to the UK system).

An Enterprise Data and Analytics Platform (EDAP) that will consolidate and unify many data assets in a common Enterprise Data Platform was set out by UKHSA to enable standardisation of both processes and tools used to analyse data [27].

Risk Stratification

EAVE II

EAVE II project has supported multiple studies on risk stratification of COVID-19 during the pandemic. It identified people at higher risk of developing severe outcomes after COVID-19 infection and vaccine related adverse events. It also helped to inform predictors for vaccine uptake and vaccine waning.

One example is the adoption of the QCovid model [88,89], a tool developed to estimate the risk of being hospitalised or dying due to COVID-19 based on England's primary care data. QCovid was further validated in the EAVE II platform in the Scottish population.

The risk of hospitalisation and death associated with COVID-19 was evaluated in different populations, such as pregnant women [90,91] and neonates[92], children [93,94], people with multimorbidity[95], people with asthma [96]and ethnic minorities [97]. Other topics included the waning of COVID-19 vaccines in people with obesity [98] and characterising the patients who are not vaccinated against COVID-19 [99], stratifying patients based on vaccination status/dose [100].

The EAVE II database covers the primary care data for around 99% of Scotland population [101]. The primary care data are linked to data sources of out-of-hours care, emergency, and secondary care. It also links to laboratory testing data, registration and mortality data, self-reported data and enhanced surveillance data [101]. This powerful EAVE II data platform supports the risk stratification studies, which are mostly cohort studies, with some modelling.

DaCVaP1 and 2

DaCVaP1 and 2 investigated which population groups are at increased risk of COVID-19 death after receiving a booster vaccination, amongst adults in England and Wales[48,102], using retrospective cohort study designs linking data from the Office for National Statistics (ONS) Public Health Data Asset, and a population-level linked dataset combining the 2011 Census of England and Wales. Similarly, a prospective cohort study investigated risk factors for severe COVID-19 outcomes (i.e., COVID-19-related hospitalisation or death) in adults who had completed their primary COVID-19 vaccination schedule and had received the first booster vaccine across all four UK nations. This required linkages of primary care, RT-PCR testing, vaccination, hospitalisation, and mortality data on 30 million people.

In addition, studies investigated risk categories amongst pregnant women in Scotland.[70,103,104] This included describing the incidence of SARS-CoV-2 infection in pregnant women, the rates of hospital admission, critical care admission, preterm birth and extended perinatal mortality following SARS-CoV-2 infection in pregnant women, and the effect of COVID-19 vaccination status on these post-infection outcomes.

In addition to the above, the DaCVaP study investigated the uptake, effectiveness, waning, and safety of ChAdOx1 and BNT162b2 COVID-19 vaccines, where the results were stratified by population subgroups which may inform potential risk groups (see *Uptake, effectiveness and safety* section).[71] However, further research is needed to follow up on those findings signalling risk groups.

Green Book Chapter 14a

The UK Health Security Agency published since November 2020 the public guidance for health professionals on COVID-19, namely the "COVID-19: the green book, chapter 14a". This guidance indicates the priority groups for primary vaccination advised by the JCVI (see Table S1 below).

Table S1. Priority groups for primary vaccination advised by the JCVI

Priority group	Risk group
1	Residents in a care home for older adults Staff working in care homes for older adults
2	All those 80 years of age and over Frontline health and social care workers
3	All those 75 years of age and over
4	All those 70 years of age and over Individuals aged 16 to 69 in a high risk group[1]
5	All those 65 years of age and over
6	Adults aged 16 to 65 years in an at-risk group (Table 3)
7	All those 60 years of age and over
8	All those 55 years of age and over
9	All those 50 years of age and over

The guidance indicates that the risk of severe outcomes from COVID-19 increases with age in adults with or without underlying health conditions. Residents in care homes for older adults were disproportionately affected by the COVID-19 pandemic. Similarly, staff involved in direct patient care, who have frequent face-to-face clinical contact with patients, are also a priority group for vaccination.

The guidance also identifies clinical risk groups for individuals aged 16 years and over, who are associated to poorer COVID-19 outcomes and who are prioritised for vaccination. These includes individuals with any of the following conditions: chronic respiratory disease, chronic heart and vascular disease, chronic kidney disease, chronic neurological disease, diabetes mellitus or other endocrine disorders, immunosuppression, asplenia, morbid obesity, severe mental illness, younger adults in long-stay nursing and residential care settings, and pregnancy.

Examples of studies addressing changes in risk assessment

The same study design was implemented on different geographical areas in the same time periods, allowing direct comparisons between predominant circulating variants and vaccine coverage of different countries. For example, in the DaCVaP 1 and 2 project two studies conducted international comparisons on effectiveness of two vaccine doses on severe outcomes

in Scotland (Delta variant) vs Brazil (non-Delta variant). [56,57] A four-nation comparison of severe COIVD-19 outcomes in the UK investigated the effect of 1 and 2 doses of vaccination comparing regional differences, which may account for different circulating variants.[58,59]

Lastly, the effectiveness of therapies was re-evaluated on the same populations across time periods under different treatment options. The VIVALDI studies evaluated the effectiveness of different available vaccine intervention combinations on residents and staff of long-term care facilities. These included reporting the effectiveness for dual primary series[105]; for one booster vaccination [106]; for 1, 2 or 3 vaccine doses [107]; and for 3, 4, and 5 booster doses [108].

This suggests an iterative approach with follow-up studies on risk stratification following the same line of the initial successful risk stratification study designs.

Impact of risk assessment on health policy

The risk stratification during pandemic helps identify patients at risk and support both clinical and policy decisions.

Relevant studies in the DaCVaP2 study provided results for prioritising high-risk groups for additional boosters, including novel optimised versions, and the increasing array of COVID-19 therapeutics amongst adults. They also informed on high-risk groups for health policy, where age remained the factor most associated with the risk of death, and men were at higher risk than women.

We described above four clusters of studies in which risk was investigated: 1) risk of severe COVID-19 outcomes, 2) risk of adverse events associated to interventions; 3) risk of not being vaccinated, and 4) risk in special populations such as children or pregnant women. While most studies include the adult population, it is important that at least a proportion of studies assess the impact of the pandemic on specific risk groups. For example, a study[103] concluded that addressing low vaccine uptake rates in pregnant women is imperative to protect the health of women and babies in the ongoing pandemic; since vaccine coverage was substantially lower in pregnant women than in the general female population of 18-44 years. Other special risk groups separately investigated were healthcare staff, staff and people in long-term care facilities (e.g. VIVALDI), newborns, and children under 17 years of age.

We acknowledge our clinical data focus and there may need to be other studies that explore the impact of attendance at events and other gatherings [109].

Uptake, effectiveness, safety of vaccine and other interventions

The EAVE II project evaluated interventions for COVID-19, including COVID-19 vaccines and pharmaceutical interventions (e.g., dexamethasone, remdesivir, and tocilizumab). It evaluated the uptake, effectiveness and safety of COVID-19 vaccines, overall and by individual doses, in

different population groups. It studied the utilisation pattern of drugs that were used as treatment for COVID-19 (Tables 1&2).

The commonly used approach for vaccine effectiveness was test-negative design, while the common approach for vaccine safety was self-controlled case series analysis.

These studies informed public health on the vaccine effectiveness under different populations comparison groups (namely adults, pregnant women, newborns, children under 17 years, and healthcare workers); different pathogen variants as exposures (namely Omicron versus Delta SARS-CoV-2 variants); and outcomes (symptomatic infection, hospitalisation, ICU admission and death). The population subgroups studied might have been selected on the basis of the inclusion criteria of the main vaccine effectiveness studies, to cover the research gap in non-included groups.

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