Platform foR European Preparedness Against (Re-)emerging Epidemics

Rendicontazione

Informazioni relative al progetto

PREPARE

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Final Report Summary - PREPARE (Platform foR European Preparedness Against (Re-)emerging Epidemics)

Executive Summary:
The PREPARE project (Platform foR European Preparedness Against (Re-)emerging Epidemics) has been funded by the European Union (2014 – 2021), to establish a European clinical research network covering primary care and hospital care in all EU Member States. Comprising of over 600 primary care sites and over 600 hospital sites in 27 European countries and harbouring EU's leading academic research groups on infectious diseases, PREPARE had its roots in the International Severe Acute Respiratory Infection Consortium (ISARIC), and built on established clinical research networks (GRACE, TRACE, COMBACTE, CAPNETZ, PENTA and SERGAS) and pre-clinical FP7 funded research networks

(EMPERIE, ANTIGONE, PREDEMICS, RAPP-ID).

Europe's response to severe outbreaks of infectious diseases has often been delayed, isolated, and fragmented. PREPARE implemented three observational studies in primary care, hospital care and paediatric settings as well as two adaptive platform design studies to build a European infrastructure for rapid clinical research responses in the face of new infectious disease threats. These clinical studies in inter-epidemic periods have trained PREPARE in mounting a rapid, coordinated deployment of Europe's clinical investigators. In addition to the inter-epidemic 'peace-time' activities, PREPARE initiated ad-hoc activities in response to ID outbreaks of concern. To that end, PREPARE's Outbreak Mode Committee monitored unfolding events in relation to emerging infectious diseases, notably the outbreak of a novel coronavirus in January 2020. The outbreak of SARS-CoV-2 has indeed demonstrated PREPARE's exceptional value to Europe's preparedness response, as our trained and collaborative network allowed us to respond very fast, benefiting from a set of pre-arranged protocols and CRFs and one of the largest multi-country patient cohorts on acute respiratory infections and arboviral-like illness in Europe. Our perpetual observational and intervention studies on acute respiratory infections allowed us to enrol COVID-19 patients right from the start of the pandemic.

Seven years of ground-breaking research in PREPARE have paved the way for many new promising research projects and initiatives. One such initiative is the launch of the ECRAID foundation (European Clinical Research Alliance for Infectious Diseases) which will advance clinical research in the field of infectious diseases by establishing a long-term, self-sustainable, clinical research network in Europe. As such, ECRAID is the urgently needed long-term successor of PREPARE.

Project Context and Objectives:
While the epidemiological, microbiological, immunological and genetic research responses to emerging infectious disease (ID) outbreaks are generally fit-for-purpose, the same is not true of clinical research. ID epidemics, including those with pandemic potential, are usually unexpected and characterised by a rapid spread between counties and continents. In contrast, clinical trials that produce evidence crucial for underpinning improved patient care take months or even years to plan and implement. By the time prospective clinical studies are set up, the initial stages of an outbreak are usually missed, or the outbreak has passed its peak with the loss of the unique opportunity for research to inform improved care for the citizens of Europe and world-wide. Medical and public health agencies therefore have to produce policies and guidelines, and clinicians have to manage their patients on the basis of best-guess evidence. Designing and implementing rapid, rigorous clinical research during emerging ID outbreaks is essential to produce findings that are useful to improved care immediately during the outbreak.

A key lesson from a series of recent epidemics of emerging pathogens of global public health importance (e.g. the 2009 H1N1 influenza pandemic) was that implementing clinical research in response to a rapidly emerging ID is extremely challenging and often delayed. One of the reasons for this is the lack of a European framework for ensuring that clinical research is built into epidemic responses. Because of this, clinical research studies generally miss the initial waves of an epidemic or pandemic, and in many cases fail to enroll significant numbers of patients across the clinical spectrum of disease, even during subsequent waves. This in turn means the opportunity is missed to improve patient outcomes and develop high-quality evidence to inform future clinical management strategies. Indeed, in almost all epidemics over

the last decades very little research directly aimed at improving clinical management or understanding pathogenesis has been able to be conducted. PREPARE is a unique European initiative, with strong links to the global ISARIC network, aiming to facilitate a rapid response to emerging diseases. PREPARE has been designed to change the approach to clinical research.

PREPARE (Platform for European Preparedness Against (Re-)emerging Epidemics) was created to address this shortcoming by establishing a European clinical research framework for harmonised large-scale clinical research studies on infectious diseases, prepared to rapidly respond to any severe ID outbreak, providing real-time evidence for clinical management of patients and for informing public health responses. It aims to establish a pan-European clinical research network and infrastructure for immediate 'on-demand' implementation of harmonised, large-scale clinical research studies in the context of emerging infectious outbreaks with pandemic or epidemic potential and provide the necessary evidence base for an optimal clinical management response. At the core of PREPARE are European-wide primary care and hospital networks, providing access to patients spanning the full clinical spectrum of infectious disease (ID) syndromes. Moreover, through these networks PREPARE reaches 23 primary care settings with more than 600 GPs in 17 EU countries, 121 hospitals in 10 EU countries and 426 intensive care units in 17 countries. The objectives of PREPARE were:

1. To identify and overcome the ethical, administrative, regulatory and logistical hurdles towards the immediate 'on-demand' implementation of such studies and to provide for a common network governance structure in case of emerging epidemics that warrant a response from PREPARE;
2. To build and implement a robust, reliable and secure IT-platform enabling the rapid collection, controlling and reporting of clinical research data and facilitating exchange of information within the clinical network;
3. To design and implement European wide harmonised 'inter-epidemic' patient oriented research and clinical trials, (i) testing and validating the operational readiness of the network, (ii) gaining insights into current impact, aetiologies and management of relevant ID syndromes in Europe, (iii) serving as the platform for perpetual adaptive clinical trials that enable future rapid deployment of relevant additional intervention arms in response to emerging outbreaks and (iv) providing evidence based guidance for the clinical management of ID with clinical relevance to Europe and beyond;
4. To implement European-wide harmonised, multidisciplinary, large scale, patient-oriented 'inter-epidemic' pathogenesis studies, (i) testing and validating the operational readiness of the network, (ii) serving as a flexible multidisciplinary platform for the rapid deployment of large scale patient-oriented research studies in response to emerging ID outbreaks using a systems medicine approach (iii) providing pathophysiological insights to guide development of personalized clinical management strategies of ID;
5. To establish and maintain a European diagnostic and typing platform, (i) capable of providing harmonised, timely, high quality, validated diagnostic support, (ii) preparing diagnostic algorithms, and (iii) developing whole genome mapping and sequencing outbreak tools, and (iv) developing and validating innovative point-of-care diagnostics;
6. To develop a unique on-line open access education and training curriculum that comprehensively addresses the issues relevant to empower or ensure the incorporation of clinical research and the results thereof, in the response to emerging epidemics.

These six scientific and technological objectives were supported by two supporting objectives:

1. To disseminate the results achieved to the external stakeholders of the network, including the international (clinical) research community, healthcare practitioners, national-, European and international public health authorities, other relevant EU funded research networks, and the general public;
2. To monitor the progress of work towards the milestones and objectives of the work plan and to ensure a maximum of inter-work package interaction in a general spirit of trust and collaboration.

Project Results:
PREPAREs observational studies (1-3) and adaptive platform design studies (4-5)
1. Acute Respiratory Infections in Adults (MERMAIDS-ARI)
2. Arboviral compatible febrile illness (MERMAIDS-ARBO)
3. Community acquired sepsis-like syndrome and paediatric acute respiratory tract infection (MERMAIDS-PED)
4. Intervention Trial on Influenza-Like-Illness (ILI) in Primary Care (ALIC4E)
5. Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP)

1. Multi-centre EuRopean study of MAjor Infectious Disease Syndromes: Acute Respiratory Infections in Adults (MERMAIDS-ARI)

Introduction

Based on historic and recent pandemics or pandemic threats, as well as on knowledge of transmissibility and epidemiology, emerging or (re-) emerging pathogens causing acute respiratory infections (ARI) are considered the most likely candidates to cause a pandemic. There is a substantial body of knowledge on clinical risk factors for disease severity and outcome of ARIs. Patient groups at risk for developing severe disease are well known, such as the elderly, patients with chronic pulmonary, cardiovascular or metabolic disease or immunocompromised patients. In national guidelines for prevention and treatment of ARI these risk groups are often combined. However, the underlying pathophysiologic processes that determine the severity of ARI across the diversity of risk groups and pathogens likely differ and are not well understood. Multi-centre EuRopean study of MAjor Infectious Disease Syndromes: Acute Respiratory Infections in Adults (MERMAIDS-ARI) is a prospective, observational study in adults with a suspected community acquired ARI across Europe to inform further research into more individualised prevention and targeted treatments to reduce risk of severe infections.

The primary objective is to identify host and pathogen related determinants of severity of community acquired ARI in adults. Secondary and tertiary objectives are to describe the aetiology, clinical management and outcomes of adult patients with community acquired ARI, in both primary and hospital care, across Europe; develop and validate complex, prognostic and diagnostic algorithms, from e.g. host gene expression profiles (classifier genes), pathogen profiles, demographics, co-morbidities, risk factors, and clinical parameters and to gain understanding into pathophysiological mechanisms contributing towards development of severe disease by conducting systems medicine analysis of pathogen- and patient characteristics (e.g. clinical data on disease progression, deep sequencing of pathogen genomes, patient associated microbiome etc.) in relation to RNA transcriptional profiles. This information can inform further research into more individualised prevention and targeted treatments to reduce risk of severe

infections.

Main S&T results/foregrounds

Healthcare Policy
In the UK, COVID-19 research is being prioritised by the Government and support is available to companies, through the NIHR, to fund, expedite, coordinate and deliver these studies.
The NIHR have streamlined the research set-up process in the UK by establishing a single, collective UK system-wide approach involving NIHR, Public Health England, UK Research & Innovation (UKRI), the Health Research Authority (HRA), Medicines and Healthcare products Regulatory Agency (MHRA) and others (SOURCE: https://www.nihr.ac.uk/). MERMAIDS-ARI has been recognised as having 'Urgent Public Health Research national priority status'. This status includes support for MERMAIDS-ARI as well as assessing NHS capacity and capability to deliver the study. As the study is UK Sponsored, this priority status has enabled rapid ethical approval of protocol changes to be implemented quicker across the European Union. Additionally, this 'priority status' is reflective of how MERMAIDS-ARI was uniquely positioned to contribute to the public health response from a research perspective and further symbolises the importance of having pre-positioned research studies in Europe, particularly for acute respiratory infections.
Regulatory Authorities
MERMAIDS-ARI has been well received by regulators throughout EUROPE. When approaching clinical institutions to join the network as a recruiting site we have emphasised the need to develop research alongside clinical and public health response preparedness. This message has resonated with local ethics committees and regulators, which has resulted in rapid approvals for the study. At some clinical institutions, turnaround from submission to approval has been as little as two weeks.

General Public
Patient retention in the study has been excellent, and this is largely due to the passion and commitment from the clinical research team at participating sites. As a non-interventional study, burden on the patient to volunteer is very low. In the most-part, patients are happy to provide additional blood samples and allow collection of nasopharyngeal swabs (which can be quite uncomfortable!). In some countries, ethics committees have allowed us to reimburse patients to account for any additional burden placed on them when taking samples. We make it clear to patients in the information we provide them about the study, that they will not benefit individually from taking part and their contribution can play a key role in informing what we know about acute respiratory infections.

Fact sheet
o Number of recruited patients: 1742
Primary Care patients (Group 1): n = 566
Hospitalised Patients (Group 2): n = 1,176
o Study duration: January 2016 – February 2021
o Recruited from 42 hospital sites, 18 primary care sites across 8 countries in Ireland, the UK, the Netherlands, Spain, Poland, Romania, Croatia and Germany

2. Multi-centre EuRopean study of MAjor Infectious Disease Syndromes: Arboviral compatible febrile

illness (MERMAIDS-ARBO)

Introduction
Multi-centre EuRopean study of MAjor Infectious Disease Syndromes: Arboviral compatible febrile illness (MERMAIDS-ARBO) is a prospective, observational study on arbovirus infections. The study looks at adults admitted to hospital with a febrile illness compatible with an arbovirus infection in regions of South East Europe, where four arboviruses are endemic and where surveillance data shows patchy reporting. Children are not included in the study, since evidence shows that adults have the highest risk of developing more severe disease requiring health care. The study is designed to capture the symptoms commonly described in (re-) emerging infectious disease outbreaks as first symptoms on clinical presentation in primary and secondary care.

The syndromes included in the study are CNS infections, haemorrhagic symptoms, undifferentiated fever and myalgia/arthralgia. For these syndromes, where diagnostics often rely on antibody testing, follow-up sampling will be done to allow studies of the kinetics of antibody decline, which will provide essential information to interpret results of future population serosurveys, thus providing important baseline information for possible future outbreaks. Moreover, we will analyse health outcomes and burden of disease in relation to severity and demographics. This information will inform early identification and diagnostics of infectious disease outbreaks with epidemic potential and strengthen networks for diagnostics and research in Europe.

Primary objective of the study is to estimate the proportion of adult hospital admissions with a febrile illness in South East Europe that are attributable to four arbovirus infections: West Nile Virus (WNV), Toscana virus (TOSV), Tick borne encephalitis virus (TBEV) and Crimean Congo haemorrhagic fever virus (CCHFV).

The secondary objectives are:
• To document treatment, clinical management and outcomes of TOSV, WNV, TBEV and CCHFV infections (in adults ≥ 18 years old) requiring admission to hospital by region;
• To analyse severity of disease in relation to demographics;
• To characterise antibody levels;
• To analyze health outcomes and burden of disease in relation to severity of disease and demographics.

Main S&T results/foregrounds

Healthcare Policy
European health systems are increasingly confronted with the challenges of arbovirus infections, with an increase in notifications and geographical distribution of vectors and viruses in recent decades. In fact, Italy recently saw its first autochthonous dengue outbreak (https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.36.2001606). A rise in global travel and trade poses a risk of introduction of arboviruses into new geographical areas. The identification of emerging outbreaks of arboviruses in Europe, and globally, is challenging. A large proportion of infections are asymptomatic, subclinical or present with non-specific symptoms. Together with variations in access to diagnostic testing this indicates that many cases are undiagnosed and the true

burden of arbovirus infections is largely unknown. The gaps and heterogeneity in surveillance reporting is another cause of concern indicating risk of delayed detection of (re-)emerging outbreaks. The risk of localized outbreaks of travel-imported arboviruses and of non-vector transmission highlights the importance of early identification of cases. Access to up-to-date information together with detailed travel and vaccination history and exposure to ticks or insects, can aid identification of cases and diagnostics. There is a need to strengthen integrated surveillance through awareness raising and access to diagnostics and harmonized case definitions. Furthermore, there is a need for research into neglected arboviruses, non-vector transmission routes, as well as effective therapeutics and vaccinations. In short, studies like MERMAIDS-ARBO highlight the need for preparedness activities in arboviruses to enable research into treatments for diseases that we still don't have a vaccine for.

Regulatory Authorities
All of the research sites for MERMAIDS-ARBO were located in South Eastern and Southern Europe. Largely obtaining local and national regulatory approval for the study was reasonable. However, there is still a big difference in some countries. For example in Greece, some locations we were unable to get the study underway due to difficulties with navigating the regulatory landscape, whereas in Romania some sites were able to be set up within two weeks. More work is needed in Europe to harmonise the regulatory landscape, if we are to better prepared for a research response in (re-)emerging infectious diseases.

Patient inclusion
Inclusion into the study was well received by participants. It was noticed by many of the investigators that many participants were reluctant to return for the 60 day follow up. This should be considered when designing similar studies and the potential burden on patients to return for multiple follow ups on a research study. However, feedback from staff indicates that many patients appreciated the additional follow up as it made them feel better about their illness.

Fact sheet
o Number of recruited patients: 930 adults
o Start and end of the trial (month/year): Spring 2016 to Autumn 2019
o Countries across Europe: Albania, Bosnia and Herzegovina, Croatia, Greece, Kosovo, Romania and Serbia

3. Multi-centre EuRopean study of MAjor Infectious Disease Syndromes – Community acquired sepsis-like syndrome and paediatric acute respiratory tract infection in childhood (MERMAIDS-PED)

Introduction
Multi-centre EuRopean study of MAjor Infectious Disease Syndromes – Community acquired sepsis-like syndrome and paediatric acute respiratory tract infection in childhood (MERMAIDS-PED) is a large scale observational study of community-acquired sepsis-like syndrome (SLS) in infants and acute respiratory infections (ARI) in children across Europe. This study includes 850 children admitted to hospital care with a new episode of community-acquired SLS or ARI and afebrile controls attending the same centre for elective surgery or as an outpatient.

The primary objectives are to estimate the proportion of children under the age of 6 months with SLS

which is attributable to enterovirus or human parechovirus infection and the proportions of cases of ARI in children aged 0 to 5 years old attributable to respiratory syncytial virus (RSV), influenza virus, human rhinovirus infection or S. pneumonia. Secondary objectives of the study are:
1) To assess association between viral load (and bacterial [ARI]) and disease severity;
2) To assess association between viral-viral and viral-bacterial co-detection and disease severity in children;
3) Document the proportion of SLS associated with detection of specific subtypes of virus in blood of children;
4) Describe the clinical management of infants and children across Europe;
5) To describe the medium-term health outcome of certain viruses [only SLS];
6) To establish whether common pathways exist in development of illness between adults and young children [only ARI].

The gene expression results from the ARI group will be compared with the adult study to establish whether common pathways exist that may explain the development of severe ARI in both adults and young children.

MERMAIDS-PED enrolled participants throughout the year at 16 centres in 7 EU countries. Participants in the case groups were selected based on clinical case definitions (without consideration of imaging or laboratory testing results) to ensure that findings are easily transferable to routine settings.

Main S&T results/foregrounds

Healthcare Policy
In various non-European settings, recent studies have shown that – in the age of widespread use of conjugate vaccines – viral pathogens are dominant in causing hospitalisations for major paediatric infective syndromes. Concordantly, MERMAIDS-PED demonstrates the predominance of viruses in Europe, namely RSV and influenza for ARI and enteroviruses for SLS. These findings can translate into more restrictive guidelines for antibiotic use, helping to combat antimicrobial resistance. With limited therapeutic options available, prevention is paramount to avert hospitalisations and development and widespread implementation of an RSV vaccine is a priority in child health.

MERMAIDS-PED demonstrates that, while details of patient management differ between European countries, overall aetiologies and the usefulness of diagnostic tests are comparable. These findings can promote the development of common clinical guidelines for all of Europe.

Building the clinical research network focusing on acute respiratory infections in children has been a major success of the project. The network includes many of the largest children’s hospitals across Europe, working together to focus on the optimal management of children admitted to hospital with severe infections. This network has been very helpful in developing responses to COVID-19 in European children, harmonising clinical guidance and the research agenda. Future trials are shortly starting focusing on rapid diagnostics to improve clinical management of children with respiratory infections.

Regulatory Authorities

MERMAIDS-PED required invasive biological sampling, both for pathogen testing and to obtain blood for gene expression analysis and serology. In half of the participating countries, regulatory authorities approved the option of deferred consent. This meant that due to the necessity of obtaining samples prior to therapeutic interventions with high urgency, biological samples could be obtained before informed consent was given. Parents or guardians were then approached for consent as soon as time allowed, and samples were only used in case consent was given. The experience from MERMAIDS-PED showed that investigators were cautious to use this option, but where it was applied it tended to be well accepted by clinical teams and patients. We can cautiously conclude that deferred consent is an acceptable option in paediatric observational studies and the risk that it would be a “slippery slope”, i.e. that it would be used uncritically where not strictly necessary, is low.

Patient inclusion
Obtaining samples for pathogen detection involves invasive procedures in young children. The results from MERMAIDS-PED help to decide in which situations which pathogen detection tests are likely to provide helpful information, and where they may be of little consequence. Thus, MERMAIDS-PED helps to limit sampling to situations where the results will likely impact patient management. Likewise, the improved understanding of aetiology of infectious disease syndromes can help avoid unnecessary antibiotic treatments and hospital stays.

Fact sheet
o Number of recruited patients: 848 in total: 128 SLS, 381 ARI, Controls 339, 1000 children admitted to hospital comprised of 3 groups
o Start and end of the trial (month/year): 09/2016 – 03/2019
o Countries across Europe: 7 countries, 16 hospital sites in the UK, Spain, Italy, Belgium, Greece, Germany and Lithuania

Pathogen	Detected in cases (%)	Detected in controls (%)	Only pathogen detected in ARI (%)
S. pneumoniae	182 (51.4)	128 (41.6)	20 (5.6)
RSV	124 (35.0)	7 (2.3)	33 (9.3)
Rhinovirus	105 (29.7)	63 (20.5)	20 (5.6)
S. aureus	73 (20.6)	84 (27.3)	8 (2.3)
Bocavirus	46 (13.0)	23 (7.5)	4 (1.1)
Influenzavirus	34 (9.6)	6 (1.9)	14 (4.0)
all others	<10%		

Fig1: swabs have been analysed from 354 hospitalised ARI children and 308 asymptomatic controls included in 7 countries from September 2016 until March 2019.

Conclusion
MERMAIDS-PED was a timely and important study in building clinical networks of research across Europe focusing on the optimal management of severe infections in children. The study has provided important insights into both the causes of the infection and how both prevention and management could be improved. During the COVID-19 pandemic, the clinical infection network provided an excellent platform for educational initiatives harmonising the response across countries, optimising clinical management and

building the research agenda. The Penta Foundation and PREPARE have led the European wide paediatric response to COVID-19 and the MERMAIDS-PED study has played an important role in these important initiatives.

4. Intervention Trial on Influenza-Like-Illness (ILI) in Primary Care: ALIC4E

Introduction
ALIC4E was a first publicly funded, multi-country randomised controlled trial of antiviral treatment in primary care. The aim of the trial was to determine whether adding oseltamivir (Tamiflu®) to best usual primary care is effective in reducing time to return to usual daily activity for people suffering from influenza-like illness (ILI). The study aims to go beyond determining the average treatment effect in a population, to determining effects in patients with combinations of pre-specified characteristics (age, symptom duration, illness severity, and co-morbidities). The platform design allows the study to remain relevant to evolving circumstances, with the ability to add treatments arms. Response adaptation allows the proportion of participants with key characteristics allocated to study arms to be altered during the course of the trial according to emerging outcome data. This is done in order to make the participants' information most useful, and increase their chances of receiving the intervention that will be most effective for them. Because the possibility of taking a placebo influences participant expectations about their treatment and influences their future help-seeking behaviour, and determining effects of the interventions on patient behaviour in real-world care is critical to estimates of cost effectiveness, ALIC4E is an open-label trial.

Patients were recruited in 21 primary care networks in 15 European countries (Poland, Lithuania, Greece, Denmark, UK, Belgium, the Netherlands, France, Spain, Czech Republic, Sweden, Norway, Hungary, Switzerland, Ireland), and each network co-ordinated the recruiting sites within their network. A number of the primary care research networks had already established collaborations through the GRACE (Genomics to combat Resistance against Antibiotics in Community-acquired LRTI in Europe) Network of Excellence and were complemented in PREPARE with six additional, strategically located primary care research networks. The trial design allowed for adding in (and dropping) interventions (trial arms) in subsequent influenza seasons, however, no other suitable antivirals were available for evaluation during the trial recruitment period.

Primary goal of ALIC4E was to determine whether adding antiviral treatment to best usual primary care is effective in reducing time to return to usual daily activity. Secondary goals are to determine whether adding antiviral treatment to best usual primary care:
• Is cost effective;
• Decreases the incidence of hospital admissions;
• Decreases complications related to ILI, especially pneumonia;
• Decreases repeat attendance in primary care;
• Decreases time to alleviation of ILI symptoms;
• Decreases the incidence of new or worsening symptoms;
• Decreases time to initial reduction in severity of symptoms;
• Decreases duration of symptoms that are moderately severe or worse; reduces the use of additional symptomatic and prescribed medication, including antibiotics;
• Reduces the transmission of infection within household;

• Affects the self-management of ILI symptoms;
• Benefits certain subgroups of patients more than others.

Main S&T results/foregrounds

Healthcare Policy
Since 1999, oseltamivir has generated sales in excess of US$18bn (£11bn; €13bn). The USA stockpiled 65 million treatments at a cost of US$1.3bn. The UK spent £424m on a stockpile of 40 million doses. By 2009, 96 countries possessed enough oseltamivir for 350 million people. In 2017, WHO downgraded oseltamivir in the list of essential medicines from a 'core' drug to one that is 'complimentary'—a category of drugs considered less cost-effective. However, prior to ALIC4E, there had never been a large-scale, international, publicly funded, pragmatic randomised controlled trial of its cost-effectiveness in primary care, and so the evidence base either to support or not support the routine use of this agent in primary care is inadequate and raises the question: does the effect found in previous efficacy studies translate into a meaningful benefit in every day primary care? Specifically, what are the overall costs of the shortened symptom duration from the perspective of the individual sufferer, the health services and for society? Do patients considered to be at higher risk for complications of influenza (for example, due to age, duration and severity of symptoms or relevant comorbidity) benefit more from antiviral treatment in primary care? Meanwhile, with ALIC4E, PREPARE had established an infrastructure capable of a rapid research response in primary care in case of a (re-)emerging epidemic.

Regulatory Authorities
Although being recommended by public health agencies worldwide for treating and preventing severe outbreaks of seasonal and pandemic influenza, the use of oseltamivir was controversial due to a lack of evidence from independent clinical trials to demonstrate its effectiveness in everyday care overall, and whether it benefits key groups of patients.

ALIC4E found that, contrary to many clinical guidelines, beginning treatment with oseltamivir 48 hours after symptoms first appear results in similar benefits as taking it within 48 hours of symptoms first appearing. In addition, starting the therapy more than 48h after symptoms first appear has a similar effect. Although the average benefit for many patients is modest, it should be considered for patients who are older, seriously ill, suffering from co-morbidities, and who have been sick for longer, because they may benefit from 2-3 days decrease in recovery time. Advocation of widespread use of oseltamivir is difficult owing to concerns about possible side effects and the medicalisation of a largely self-limiting illness, clinicians and patients might wish to consider adding oseltamivir to routine treatment where a day less of illness is particularly important for patients.

Oseltamivir was the only Investigational Medicinal Product evaluated as part of the ALIC4E trial. The US Food and Drug Administration approved oseltamivir in 1999 and in 2002 the European Union issued marketing authorisation. It has a well-documented safety profile and is a commonly used medication in a secondary care setting. We did not identify meaningful differences in patient-reported repeat visits with health care services, hospitalisations, or serious adverse events, but found evidence for increased burden of vomiting or nausea in patients using oseltamivir, which is a known common side-effect of oseltamivir.

General Public
ALIC4E found that oseltamivir helps people recover from flu-like illness one day sooner, on average, than would be the case without it. Older, sicker, patients with comorbidities and a longer duration of previous illness showed greater overall benefit, and could expect to see their symptoms clear up two-to-three days sooner than those who had not received the drug. However, we also found that people who took oseltamivir experienced more vomiting and nausea. Primary care patients with influenza-like illness treated with oseltamivir recovered one day sooner on average than those managed by usual care alone. Older, sicker patients with comorbidities and longer previous symptom duration recovered 2–3 days sooner.

Adding oseltamivir to usual primary care for patients with ILI accelerates recovery by a mean of about one day, and slightly longer in individuals with risk factors, irrespective of influenza status. Initiating oseltamivir 48–72 h after illness onset appears to give similar benefit to earlier initiation. Clinicians might consider treatment in patients who are sicker or older, who have comorbidities, and who have been unwell for longer, because oseltamivir might reduce their illness by as much as 2–3 days.

Aetiology fact sheet
• Influenza Like Illness (ILI):
• Is caused by influenza viruses in 52% of all cases
• Coronaviruses (10%) and rhinoviruses (7%) are also important causes of ILI
• Differences in influenza virus strain (A versus B) were observed in the different seasons.
• Modest geographical differences in aetiology were observed as well.
• Co-infections were limited in adults: in 72% of the positive samples only 1 pathogen was detected. This is a different story in children, where significantly more co-infections were observed, mainly due to the high amount of colonizing flora in children.

Conclusion

The ALIC4E Trial is one of the largest influenza treatment trial in primary care (when reviewing against the Cochrane systematic review: Jefferson T, Jones MA, Doshi P, DelMar CB, Hama R, Thompson MJ, Spencer EA, Onakpoya IJ,Mahtani KR, Nunan D, Howick J, Heneghan CJ. Neuraminidase inhibitors for preventing and treating influenza in adults and children. Cochrane Database of Systematic Reviews 2014, Issue 4.). The trial included 21 primary care networks in 15 countries and we were able to get a primary endpoint from 96% of the participants randomised.

Through ALIC4E, PREPARE has established an infrastructure capable of a rapid research response in primary care in case of a (re-)emerging epidemics. Subsequent projects including VALUE-Dx and RECOVER have used the primary care trial management team and primary care networks from ALIC4E to deliver these new projects.

5. A Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP)

Introduction
REMAP-CAP is an Adaptive Platform Trial: A modern, innovative, smarter and more flexible type of

randomized controlled trial (RCT). The main advantages are the ability to evaluate multiple treatment options simultaneously to enhance trial efficiency and the addition of novel interventions during the lifetime of the trial.

Why an adaptive platform trial?
In RCTs there is downtime between testing sequential interventions, loss of efficiency, extra costs for setting up a complete new RCT infrastructure each time; and a lack of understanding of interactions between treatments or across subgroups of patients. In contrast, APTs incorporate knowledge accrued in the trial (adaptive design) and have 5 key features:
- Randomization, allowing robust causal inference;
- Embedding of study procedures into routine care processes, facilitating enrollment, trial efficiency, and generalizability;
- a Multifactorial statistical model comparing multiple interventions across multiple patient subgroups;
- Adaptive design including response adaptive randomization (RAR) with preferential assignment to those interventions that appear most favorable, and
- a Platform structured to permit continuous, potentially perpetual enrollment beyond the evaluation of the initial treatments.
The design has allowed REMAP-CAP to adapt to the current COVID-19 pandemic. Globally, over 1200 CAP patients including over 660 COVID-19 patients have been included to date.

Before the COVID-19 pandemic, REMAP-CAP investigated the best treatment for Community Acquired Pneumonia (CAP) in the ICU. The study has adapted to the pandemic by including moderately ill patients (hospitalized on the ward) as well as severely ill ICU patients with COVID-19; and adding COVID-19 specific domains. In REMAP-CAP, the pre-pandemic interventions are grouped under four domains:
- Antibiotic Domain with five alternative antibiotic strategies;
- Nested in that the Macrolide Domain evaluating extended macrolide therapy (versus short course);
- Corticosteroid Domain with three alternative hydrocortisone dosing regimens;
- Influenza Antiviral Domain with three alternative oseltamivir strategies.
Each qualifying patient is randomly assigned a one specific intervention within each domain. The set of interventions across the domains assigned to a specific patient defines the treatment regimen.

COVID-19 specific domains that are currently active are:
- COVID-19 Antiviral therapy (no antiviral, lopinavir/ritonavir, hydroxychloroquine, lopinavir/ritonavir + hydroxychloroquine)
- COVID-19 Immune modulation (no modulator, interferon-beta, anakinra, tocilizumab, sarilumab)
- COVID-19 Immunoglobulin (no immunoglobulin, convalescent plasma)
- COVID-19 Anti-coagulation (standard thrombosis prophylaxis, therapeutic anticoagulation)
- COVID-19 Vitamin C (no intervention, high dose vitamin C iv)
- COVID-19 Kinin-kallikrein blockade (no ACE2 blocker, icatibant + lanadelumab)
- COVID-19 RAS domain (no angiotensin receptor blocker (ARB), ARB, ACE-inhibitor)

REMAP-CAP sites can choose from the “menu” of classic (pre-pandemic) and COVID-19 domains to allow a tailor-made trial at each institution.
Main S&T results/foregrounds

Healthcare Policy

REMAP-CAP can be a true learning healthcare system. During the pandemic, it can incorporate knowledge acquired inside and outside of the trial to adapt the available domains and interventions. This allows the trial to continue in the evolving situation of a pandemic; and avoids downtime between different studies making sure we can learn from every COVID-19 patient. It can inform policy quickly, as interim analyses can be performed regularly and important conclusions or safety concerns can be shared with policy makers and public health institutions. REMAP-CAP is able to incorporate changing treatment policy across the globe into the design of the study. It merges the strengths of a global research consortium with flexibility to adapt locally.

Regulatory Authorities

We realize there are many COVID-19 studies ongoing at this time. However, centrally coordinated and large-scale projects with innovative study designs such as REMAP-CAP offer the best chance to rapidly find effective treatment(s) for COVID-19. The global collaboration and high number of participating sites ensures the highest chance of recruiting sufficient patients to draw conclusions on the effectiveness (or not) of the interventions in REMAP-CAP. The flexibility ensures the study is feasible at the local level, and can align with a variety of regional and national rules and regulations. The multifactorial design allows patients to contribute to answering multiple important scientific questions at the same time, ultimately leading to improved patient care. REMAP-CAP is open to collaboration and aims to be inclusive; co-enrolment with other clinical trials is possible.

Patient inclusion

For patients, participating in REMAP-CAP ensures that their contribution is not wasted, as may happen in smaller local studies that are unable to meet their recruitment target.

The response adaptive randomization used in REMAP-CAP means patients have a higher chance of being randomized to more favorable interventions, if compared to traditional clinical trials. The multifactorial design allows them to contribute to multiple relevant questions about effective therapies. It also results in very few patients randomized to a treatment regimen without any active component. As REMAP-CAP learns from data accrued in the trial, we learn about the effectiveness of interventions as soon as possible. If an intervention is found to be effective, this can be implemented into the trial immediately. Inferior interventions are removed from the trial as early as possible, while in a conventional RCT this can only be done after the trial is concluded.

Conclusion

Despite a global pandemic, we were able to deliver the start-up of 170 sites (including training, contracting, pharmacy setup, site initiations and more) and get approval for nine new domains in 14 countries in less than a year. Second, the conceptual framework of REMAP-CAP works as intended. We have seamlessly integrated the investigation of over 20 new interventions, and have platform conclusions for several of these within a year of starting them. This level of efficiency and speed could never be delivered without the seed funding of PREPARE, and the work done in the previous years. Lastly, we have delivered results that have immediately led to practice change in the treatment of patients with COVID-19 across the globe.

There were several important results from the trial:
1. Glucocorticoids improve outcomes for hospitalized patients with COVID-19. We've added to the global knowledge on this by publishing our results and providing our data for the WHO meta-analysis, published on the same day.
2. Hydroxychloroquine does not improve outcomes, and potentially harms patients with COVID-19. We've published our results in a collaborative meta-analysis as a preprint, the manuscript has been accepted for publication.
3. Tocilizumab and sarilumab reduce mortality and prevent progression to invasive mechanical ventilation or ECMO in critically ill patients with COVID-19. This has now been published.
4. Therapeutic anticoagulation is futile, and possibly harmful, in critically ill patients with COVID-19. This is now published as a preprint and has been submitted. This was a multi-platform collaboration (mpRCT) with the ATTACC and ACTIV-4 consortia.
5. Therapeutic anticoagulation improves outcomes in hospitalized patients with COVID-19 who are not admitted to an ICU with organ support. The manuscript is in preparation. This was a multi-platform collaboration (mpRCT) with the ATTACC and ACTIV-4 consortia.
6. Convalescent plasma does not improve outcomes for critically ill patients with COVID-19. Shortly after this REMAP-CAP platform conclusion, the RECOVERY trial announced that based on preliminary analysis of data from more than 10,000 patients, there was no significant difference in 28-day mortality. In light of these results, the REMAP-CAP ITSC decided to also pause recruitment in the Moderate State of this domain. These data will be integrated in the publication that is in preparation.
7. Lopinavir/ritonavir does not improve outcomes for critically ill patients with COVID-19. The manuscript is in preparation.

Several treatments are still under investigation for COVID-19, but also for CAP. We are still recruiting CAP patients who do not have SARS-CoV-2 as the causative agent. Currently, over 1200 randomizations have occurred globally.

In addition to the delivery of many new countries and sites, the randomization of large numbers of patients and the large list of results, we have also improved the trial governance, and the education and engagement of the scientific community. In addition, we've expanded to include Asia, Japan and Colombia to the regions of REMAP-CAP already present (Europe (incl UK), Canada, US, Australia, and New Zealand). We have adapted the governance of REMAP-CAP (in addition to the regional organization and in domain specific working groups) by creating teams. These teams work independently but in close collaboration, to make the trial more agile. The teams are: a prioritization committee, design and analysis team, CRF team, delivery team, reporting and analysis team, pharma liaison team, external communications and media team, and a new regions team.

REMAP-CAP has delivered multiple results that have led to important improvements in outcomes for patients. It has lived up to the mission of PREPARE to establish a European clinical research framework, providing real-time evidence for clinical management of patients and for informing public health responses.

Additional ground-breaking results from seven years of PREPARE

6. Ethical, Administrative, Regulatory and Logistical Solutions

Introduction

EARL (Ethical, Administrative, Regulatory and Logistical requirements) barriers and potential solutions to conducting large adequately powered multicentre clinical trials arise at multiple levels including global, country, regional, institutional, community, interpersonal and intrapersonal levels. This reflects the complexity of identifying and implementing solutions and the need for inter-sectorial and inter-disciplinary working at all levels to effectively and efficiently conduct clinical research during a pandemic. We have identified barriers and solutions that relate to the initial set-up of research, those that relate to the ongoing conduct of research and those that relate to dissemination and uptake of findings.

Potential solutions to study setup in the face of an emerging pandemic include the need for rapid access to funding and for the establishment of legal contracts that allow flexible and rapid movement of funds between European project partner institutions for a pandemic research response. Pre-identification of research question, study methods, standardized case definitions, participant information, consent forms in pre-approved protocols will expedite the set-up of clinical studies. Fast-track ethical and regulatory approvals specific to emerging outbreaks are now available in many countries throughout Europe. PREPARE clinical studies have the advantage of having been set up during inter-pandemic “peacetime” with capability to pivot to response mode. Pre-existing research networks were of real value in expediting recruitment of study sites and recruiters in PREPARE and are essential in forming a research ready infrastructure for pandemic clinical research across Europe. Targeted staff training and mechanisms for rapid deployment of training on emergency protocols are required to ensure research ready staff are in place.

Potential solutions related to study conduct include the need for optimising information provision to potential participants with sign posting to recruitment sites (e.g. cascade through public health information channels, families, influenza clinics, pharmacies). Simplified recruitment processes need to be considered and adopted. There is a precedent in the UK for ethics committees to agree these processes, however ethical oversight and acceptability across a range of stakeholder groups (ethics boards, potential participants, clinicians, researchers, and public health bodies) will need to be demonstrated to support implementation and across other European countries. Effective community engagement during inter-pandemic peacetime is essential and in the face of emerging challenges with misinformation frequently disseminated via social media future emphasis on providing accurate updates and forums to address concerns of the general public should be explored.

Main S&T results/foregrounds

EARL Experience in PREPARE

We have gained further insight into EARL barriers and solutions through working with the PREPARE clinical work packages. The challenges across the different work packages have varied but thus far delays related to obtaining regulatory approvals and contracting are common. Contracting in particular has given rise to delays in many sites. Experience from the set-up of ALIC4E illustrates the value of pre-existing networks and collaborations. In contrast, REMAP-CAP is laying new ground in establishing and

coordinating pan-European networks for Intensive Care studies. We have also gained insight into the recruitment experience of ALIC4E during its first winter season. These experiences highlight delays related to recruitment processes and confirm concerns that even in primary care patients may feel too ill to go through research recruitment processes. These findings inform recommendations to PREPARE regarding expedited research recruitment processes for clinical studies to be able to recruit during an infectious disease (ID) outbreak. Our ethics tracking data highlight informed consent processes as a key concern of ethics committees and any proposed adaptation to these would need pre-approval, with clear processes delineated for when emergency protocols might be used.

More recently our experience has highlighted that whilst there have been delays in receiving approvals during the initial weeks of the COVID-19 pandemic, the overall experience has been extremely positive. Much of the delays and administrative red tape disappeared. Ethic committees were willing to meet much more frequently and with improved flexibility to facilitate important studies to be reviewed. National regulators undertook to review COVID-19 related trials in days in contrast to previous experience of months. We have developed a range of tools to capture EARL experience in the PREPARE clinical work packages including data capture tools for contracting, ethics and other regulatory approvals and a 'lessons log' for capturing recruitment experience.

Recommendations made to PREPARE

The aim of PREPARE is to enable a rapid clinical research response to severe infectious disease outbreaks that present a threat to the health and security of people in Europe. Based on our work conducted thus far and, on the solutions outlined in this report, we made recommendations for enhancing the response capability of PREPARE that directly informed PREPARE's outbreak response capability. This included the development of tools and support packages to enable rapid research deployment functions. For example, we developed living maps of EU member states that had processes for fast track ethics and regulatory review, together with directories for rapid contact. To ensure capability of PREPARE clinical studies to pivot to response mode, we recommended that protocols for the clinical research work packages include an emergency response plan. Emergency response plans were to be developed during inter-pandemic periods to outline how each clinical study would rapidly upscale to respond to an ID outbreak. Plans should align with the PREPARE outbreak clinical response modes, ethical and other regulatory pre-approval for these plans was anticipated, and we recommended these plans include the following:

- Detail of mechanisms to activate and deactivate outbreak response modes;
- Operational management plans and contingency plans in the event of illness;
- Staff training in emergency protocols
- Participant recruitment processes e.g. pre-approved abbreviated information and consent forms
- Follow-up data collection process e.g. on-line follow-up data collection
- Laboratory capacity
- Media strategy and public awareness mechanisms
- Interactions with social media forums to improve the dissemination of accurate information

PREPARE's response to COVID-19

PREPARE's outbreak response process was triggered in relation to the COVID-19 pandemic: On 22 January 2020, PREPARE triggered Outbreak Mode 1 (clinical research preparation mode), on 6th

February 2020, PREPARE triggered Outbreak Mode 2 (clinical research mobilisation mode) and on 3rd March 2020 RECOVER was initiated as a means to directly tackle the COVID-19 pandemic by acting as PREPARE's Mode 3 response, the highest response Mode. These trigger points were deliberated and decided by an expert committee and informed by rapidly emerging evidence in relation to the epidemiology spread of COVID-19. Decisions were made in a context of high levels of uncertainty and guided by well-defined processes, including in relation to how these escalation points should be communicated to PREPARE stakeholders. By the time the funding decision on the RECOVER research consortium was confirmed, EU member states were in varying stages of response to COVID-19. Countries that were significantly impacted first, such as Italy and Spain, provided sobering insight into the early phases of the pandemic and the urgency for evidence to inform policy decisions and responses.

Many lessons have been learned through the rapid set up, delivery and dissemination of research through RECOVER. High-level reflections point to the rapid emergence of solutions to well defined EARL barriers. Where mechanisms did not exist, for example, in relation to rapid ethical approval at national level, bespoke solutions were established driven by the urgency of the situation. In consequence, several tools that EARL developed quickly became redundant. A lesson here was that, while these tools and mappings were necessary for preparedness – for example, to identify where capacity gaps exist – they were perhaps less useful for response where stakeholder mobilise to find solutions. Contracting with clinical sites remained a key bottleneck despite the emergence of a novel solution to speed up agreements. This solution from University Medical Center Utrecht was use of a letter of intent as sufficient to allow research activity to progress while contract negotiations were underway. Bespoke solutions to public involvement in pandemic relevant research also emerged. For example, in the UK where there is a strong policy context for patient and public involvement in research, the Health Research Authority set up a central public panel to efficiently match research teams with relevant patient and public contributors.

The framework and expertise offered by PREPARE was also hoped to offer a central reference point for researchers outside the consortium seeking to develop pandemic ready research, particularly in relation to novel trial designs. For example, the time and expertise developed through the PREPARE ALIC4E trial in primary care directly informed the rapid set up of PRINCIPLE, a platform randomised trial of treatments in the community for epidemic and pandemic illness. The REMAP-CAP trial also became a source of trial related expertise as it facilitated clinicians/researchers to communicate and exchange on scientific and pragmatic aspects of novel adaptive platform trials. This occurred on a national level as networks and individuals were observed to be keen to participate in trials and thus were immediately interested in models provided by REMAP-CAP but also on a higher level as national societies / funders all supported REMAP-CAP in their respective regions. Many of the informal communication links with research network, funders and regulatory authorities came together to expedite communication, reduce barriers and ease implementation of trials.

At the time of writing, the COVID-19 pandemic continues to shape health, social and economic realities for European citizens and the need for evidence to inform effective health and policy responses continues. COVID-19 has demonstrated how ill prepared the world was to respond to an event of this scale. Global trends such as climate change, urbanisation, deforestation, and mass displacement of populations create ideal conditions for the emergence and spread of novel pathogens and signpost the need to strengthen preparedness for response to future events. In this broader context, it is critical to take stock of the lessons

learned that can strengthen preparedness to deliver clinical research that improves rapid diagnosis, treatment, and care for those affected. To that end, PREPARE's legacy will be consolidated in the European Clinical Research Alliance for Infectious Diseases (ECRAID) that aims to establish a financially self-sustaining clinical research organisation for infectious diseases.

Conclusions

We aimed to identify strategies to enhance the ability to conduct harmonised research in the event of a rapidly developing Infectious Disease outbreak. It was recognised that Europe did not have the links or infrastructure necessary in 2014 to launch co-ordinated research across multiple sites and thus missed opportunities to improve outcomes and develop effective and safe treatments for novel infectious diseases in previous outbreaks. There was widespread anticipation of a further impact of a new influenza strain which could severely impact global health and security. Despite increasing attention and urgent calls for investment and action in anticipation of a respiratory pandemic, the world was unprepared to respond to an event the size and scale of the COVID-19. At the time of writing, this pandemic continues to shape health, social and economic realities for people around the world and the need for evidence to inform effective health and policy responses continues.

Many potential obstacles that we highlighted were proven pertinent but relatively easily addressed. These included anticipating and exploring relevant ethical concerns that would arise in the context of establishing research trials rapidly, developing practical solutions regarding maintaining infrastructure, staffing, local expertise and shared protocols to assist in the implementation of trials. Most importantly however we highlighted two key aspects of pandemic preparedness that were central to a successful rollout of large multisite clinical trials across Europe and beyond. Firstly, engagement with the public to explore their views on potential research and to address issues that might arise in the development of working issues of consent, education with respect to trials and preferred methods of involvement appears central in driving many aspects of the successful conduct of future trials. In the face of multiple sources of information and misinformation, this will likely be a key area to continue to explore and develop strategies to ensure that public engagement and education and concerns are identified and addressed both pre-emptively and iteratively.

Secondly, the development of strong working links across sites, between research groups, sharing knowledge and building mutual trust via collaborating on central and branching projects from this work package was key. We developed strong links with European and International partners well before the pandemic emerged, which allowed us to have confidence in our shared goals in conducting research. This in turn allowed for rapid engagement in the implementation of novel trials such as PRINCIPLE and REMAP-CAP in the face of an emerging pandemic. Some issues however proved more difficult to resolve-contractual issues remained problematic during the pandemic. However, there is now wide recognition of the problem and this will likely lead to potential solutions in the future. one such example, is the UK adopting a NHS template contract and if the sponsor does not adjust this template contract it will not require legal review just local R&D approval. This greatly increased the speed of contractual issues in the UK. Such lesson could be learned in other member states.

Thirdly, in contrast to previous pandemics COVID-19 has witnessed an unrivalled shift in funding and focus to research activity. This has led to an immense amount of research trials, often conducted within

small sample sizes, lacking appropriate control groups. In an effort to assist rapid dissemination of findings, avenues such as preprint publications and media release have had the unintended consequence of creating challenges in identifying and synthesising evidence that was useful and valid. A key challenge in the future will be making best use of funding and allocation to ensure it is allocated to large, adequately powered well conducted clinical trials.

Finally, it is important we retain the collective memory of both lessons and mistakes made so we can be better prepared for future public health emergency events. Global trends such as climate change, urbanisation, deforestation, and mass displacement of populations create ideal conditions for the emergence and spread of novel pathogens and signpost the need to continue strengthen preparedness for response to these events. In this broader context, it is critical to take stock of the lessons learned that can strengthen preparedness to deliver clinical research that improves rapid diagnosis, treatment, and care for those affected.

7. Clinical protocols and harmonised guidelines for the management of infectious diseases in Europe

As a clinical counterpart of the EARL study (see above), we also aimed to remove obstacles to the conduct of clinical trials and to map the pan-European clinical management of severe infectious diseases (IDs). Furthermore, in response to severe infectious disease outbreaks in Europe, we sought to develop harmonised clinical case definitions, guidelines, and pre-approved protocols. This work was conducted in collaboration with the International Severe Acute Respiratory and emerging Infection Consortium (ISARIC), the World Health Organisation (WHO), Cochrane response, Evidence Aid UK, the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) and the European Respiratory Society (ERS).
To harmonise timely, international, multisite clinical research responses, we produced a range of open access study protocols, including protocols implemented in response to the Covid-19 pandemic. The protocol designs were based on thorough evidence reviews. These protocols aim to characterise acute and long-term patient outcomes in response to an emerging infection of epidemic potential.

One such protocol was PREPARE (Preparing for (re) emerging infectious disease outbreaks). The PREPARE protocol considers data from patients presenting to either primary care or secondary care across Europe with symptoms of infectious diseases. Outcome measures concentrate include health-service utilisation, clinical management, risk factors for severe disease and clinical outcomes. The data explores the burden of infectious diseases on population health and health systems. It highlights variations in the clinical management of infectious disease and that a high proportion of infection remains undiagnosed. PREPARE's arbovirus study highlights the risk of prolonged hospitalisation from arthropod-borne and central nervous system (CNS) infections, affecting adults of all ages, including previous health younger adults.

Data on health utilisation, risk factors, clinical management and outcome were documented by the clinical studies of PREPARE. The study protocols were designed with a syndromic approach to facilitate a timely research response to any (re-) emerging infectious diseases of clinical importance to Europe. They were made available as open access protocols on the PREPARE virtual learning platform. By using a syndromic design, the MERMAIDS-ARBO study was able to include patients presenting with symptoms of zika virus

infection during the outbreak in 2016, and the REMAP-Cap trial has successfully responded to the Covid-19 pandemic.

The recent Covid-19 pandemic has further emphasised the importance of strategically pre-positioned and harmonised syndromic study protocols alongside standardised data collection forms, to be ready to respond at the outset of an emerging epidemic. In response to the Covid-19 pandemic, PREPARE partners have supported the global research response by disseminating open access research protocols and case report forms. It has done so in collaboration with the International Severe Acute and emerging Infection Consortium (ISARIC), the World health organisation and clinical networks across Europe and globally.

Our results demonstrate that infectious diseases are an ongoing threat to Europe. Coordinated efforts are needed to strengthen and sustain preparedness, capacity and capability for early identification, diagnostics, reporting and clinical management. The PREPARE clinical study protocols and data collection forms for adult and paediatric populations are open access, enhancing the response to (re-) emerging infections of public health importance in Europe. These protocols need to be regularly reviewed and updated as new evidence emerges and new technologies are invented.

We identified a need for an improved, harmonised framework for the clinical management of infectious diseases. Key to this framework will be mechanisms for rapid review, update, and dissemination in interepidemic times and during an epidemic. To maintain pandemic preparedness, the networks, local capacity, and capability built up over the last five years across Europe must be sustained. The PREPARE partnership have increased research capacity and capability in Europe. The Covid-19 pandemic confirmed our vulnerability to infectious diseases and the need to work together in a harmonised, coordinated manner to improve outcomes.

8. Clinical Research Information Sharing Platform

To guarantee the rapid availability of relevant clinical study data in an emerging infection outbreak it is of utmost importance that procedures are in place for both the start-up of data collection as well as the sharing of collected data after data collection has been ended. PREPARE has developed such data procedures, which are split up into two main lines that are both related to large pan-European clinical research studies after emerging infections outbreaks:

1. Procedures to enable the rapid start-up of data collection.
2. Procedures to enable the rapid sharing of data for analysis during the study conduct as well as shortly after study end.

This work is a cornerstone for future clinical research response to emerging infectious diseases.

Some lessons learned/recommendations for future EU clinical research response during pandemics
- Create structures and partnerships that allow top-down prioritisation of clinical research
- Develop digital models and procedures for data collection and sharing

- Develop a mechanism to rapidly leverage pandemic funding and to liaise EU funding with national funding
- Invest in clinical trial networks, adaptive platform trials and master protocols
- Embed EU pandemic clinical research response in global response

Potential Impact:
1. From preparedness to an actual pandemic

In addition to the inter-epidemic ‘peace-time’ activities, PREPARE could initiate ad-hoc activities in response to ID outbreaks of concern. When responding to an actual ID outbreak, the scope and scale of this response of PREPARE are customized to the specific ID outbreak, depending on the epidemic risk, particularly in Europe. Next to its default Inter-Epidemic Mode, PREPARE distinguishes between the Outbreak Modes as summarized below:

- Outbreak Research Preparation Mode (Mode 1): In this Mode, PREPARE is available to provide expert advice to health authorities and research teams involved in the clinical research response to an ID outbreak that is considered to be a limited threat to Europe.

- Outbreak Research Mobilisation Mode (Mode 2): In this Outbreak Mode, PREPARE is developing and implementing necessary preparatory activities in anticipation of the rapid initiation of a clinical research response to a specific ID outbreak that is considered to be of a potential threat to Europe.

- Outbreak Research Response Mode (Mode 3): In this Outbreak Mode, PREPARE ‘pushes the fast forward button’ by initiating and implementing clinical research studies in response to the specific ID outbreak in Europe that is an immediate threat to Europe.

Cross network activity regarding outbreak response: PREPARE and ALERRT collaborated to share experience and materials for developing operational readiness procedures for network outbreak response. Wider collaboration has continued through the ECRAID-Plan project, PREPARE’s sustainability planning mechanism. In December 2019 PREPARE participated in the GloPID-R hosted event for pandemic preparedness planning in London.

PREPARE’s Outbreak Mode Committee monitored unfolding events in relation to the novel coronavirus from early January 2020. On 19 January 2020 the OMC triggered a response assessment and moved to an Outbreak Mode 1 shortly after. On 30th January, the Director General of the World Health Organization declared a Public Health Emergency of International Concern (PHEIC).

On 30 January, the European Commission published an H2020 Public Health Emergency Call for Proposal in response to the novel coronavirus (SARS-CoV-2) epidemic in China. As this is at the heart of PREPARE’s purpose, it was decided to develop a comprehensive application called RECOVER (Rapid European SARS-CoV-2 Emergency Research response). RECOVER is positioned as PREPARE’s research response plan as part of its Mode 3 research response to the SARS-CoV-2 Epidemic. RECOVER

has indeed been selected for funding (2020 – 2022) and will address the most urgent questions for patient and public health level interventions through a set of research response activities, combining: clinical studies in primary and hospital care; epidemiological studies and modelling; and clinical biological studies. RECOVER includes essential needs for preparedness and response and will inform future research response efforts to further strengthen Europe's and global clinical research preparedness to future emerging infectious diseases. In fact, The COVID-19 pandemic has so far been the only occasion where PREPARE has decided to go into full outbreak response. Fig. 1 shows the timeline of the decisions to go into Mode 1, Mode 2 and Mode 3. The outbreak response in Mode 3 has been made possible with EUR 20 million funding from the EU's H2020 programme. On 12 February 2020, the RECOVER project was started. For more detailed information about the RECOVER project we refer to www.recover-europe.eu

2. PREPARE's heritage: towards a long-term, sustainable, clinical research network in Europe

Although PREPARE came to an end after seven years, it's work will be continued. ECRAID (European Clinical Research Alliance for Infectious Diseases) is the envisaged, long-term successor of the European funded projects COMBACTE and PREPARE. It aims to advance clinical research in the field of infectious diseases by establishing a long-term, financially self-sustainable, clinical research network in Europe.

In the last few decades, the emergence and spread of antimicrobial resistance (AMR) has further increased the mortality and morbidity of bacterial infections. Bacterial infections that could once be treated successfully with antibiotics are increasingly becoming untreatable due to antibiotic resistance. The global emergence of AMR coincides with a marked reduction in the development of new antibiotics. Few new products and drug classes are currently in development due to a lack of investment in drug discovery, constrained and costly clinical development, and limited economic return on investment (O'Neill, 2016; McDonnell et al, 2016). Unless action is taken, some estimate that by 2050, 10 million people will die each year due to antimicrobial resistance (O'Neill, 2016).

In addition to the problem of AMR, we have seen the (re)emergence of new pathogens, especially zoonotic pathogens (pathogens that have crossed the species barrier from animals to humans). The frequency and impact of these (re-) emerging infectious diseases (EID) have been amplified by global trends such as population growth, increases in trade and travel, urbanisation, deforestation, and climate change. The COVID-19 pandemic has led to unprecedented social and economic disruption across the globe, both through the rapid spread of the SARS-CoV-2 pathogen itself and through public health measures that aim to slow transmission. Meanwhile, the scientific research community is developing epidemiological and social science intelligence, diagnostics, vaccines and antiviral treatments to reduce the impact of COVID-19. Partners in ECRAID are collaborating in RECOVER.

Long-term, sustained, and coordinated efforts are needed to develop and implement a wide range of preventive and reactive interventions to limit the impact of infectious diseases. This includes both clinical interventions as well as public health interventions. Ideally, these inventions act as complementary components of a coherent, coordinated strategy against infectious diseases, developed and implemented with inputs from a wide range of academic disciplines (including sociology, anthropology, behavioural sciences), governmental organisations and industry.
ECRAID aims to provide for the platform to support such a coordinated approach in Europe, focusing on

the efficient and effective development and implementation of clinical interventions against infectious diseases. Our vision is to efficiently generate rigorous evidence to improve the diagnosis, prevention and treatment of infections and to better respond to infectious disease threats. This is facilitated by a European multidisciplinary clinical research network and innovative research approaches.

ECRAID aspires to become the first network of its kind in Europe to offer a single point of access to a pan-European clinical research network for infectious diseases. Its distinctive features in comparison to the current clinical research landscape on infectious diseases in Europe are its scale and continuity of operations, supporting the provision of clinical research studies with greater speed and efficiency, without compromising scientific quality.

The ECRAID network aims to provide an efficient European infrastructure capable of performing all aspects of clinical studies, from design to dissemination, that will function as the backbone of clinical research activities in the field of infectious diseases. Activities of the network will be coordinated by a lean organisation, with direct and a single point of access for all relevant stakeholders to the network and to world-leading infectious disease experts. Key design principles built into the network's organisation and operations will ensure the delivery of a rapid and coordinated research response to public health emergency events that represent an imminent or immediate threat to the health and security of people living in Europe.
The clinical research network of ECRAID will encompass over 2.000 sites in more than 40 European countries. It includes primary care settings (general practitioners), hospital settings (emergency rooms and intensive care units), paediatric care settings, clinical laboratories and long-term care facilities. At the heart of ECRAID-Base are six perpetual clinical studies. All will mature towards adaptive platform trials, with capability to rapidly respond to public health threats.

3. Virtual Learning Centre

The Virtual Learning Centre (or VLC) is PREPARE's educational website, which, over the course of the project, has grown into a rich archive of educational tools. The VLC is accessed directly from the PREPARE Home page (https://prepare.ersnet.org/home.aspx) and in turn allows visitors to link directly sister societies – ERS, ESCMID, WONCA, ESWI. There is the opportunity to tailor educational resources to individual requirements via 'My resources', visit domains of the PREPARE syllabus and examine the activities and goals of PREPARE work packages, use the Forum for discussion, and access current details on PREPARE trials and publications.

The domains of VLC were constructed in response to a survey of stakeholders' educational needs and comprise: Trial methodology, Biology of infectious diseases, Clinical management, Global aspects, Publications, Patient/public engagement and policy-shaping.

The VLC provides educational resources from 2020-2021 on webinars devoted clinical and research topics on covid-19, and prior to that resources from pandemic scenario training workshops, Arbovirus workshops, and joint symposia and postgraduate courses at society congresses. There is also a link to multi-language material from the GRACE project.
The content is directed towards our stakeholders: multidisciplinary clinicians, researchers, trainees,

laboratory teams, public health, epidemiologists and policy makers.

List of Websites:
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final1-prepare-logo.jpg

Documenti correlati

final1-overview-prepare-corporate-communication-tools.pdf

final1-overview-prepare-press-releases.pdf

final1-overview-prepare-video-s.pdf

Ultimo aggiornamento: 7 Maggio 2020

Permalink: https://cordis.europa.eu/project/id/602525/reporting/it