European Commission supported research projects on Influenza 2008-2012
EUROPEAN COMMISSION SUPPORTED RESEARCH PROJECTS ON INFLUENZA 2008-2012
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Influenza remains a major threat to human health and a severe burden on the global economy and societies in the world. It causes every year severe illness in 3 to 5 million people and kills between 250,000 and 500,000, including 40,000 people in the European Union (EU). In addition, pandemic influenza strikes at irregular intervals, with illness spreading rapidly to billions of people across the globe. During the past 100 years, the world was hit by four influenza pandemics, of which the Spanish flu was by far the most devastating with a global death toll of between 20 and 50 million people.

In 1997, a highly pathogenic avian influenza H5N1 virus emerged in Hong Kong and started spreading westward to Europe. Its sporadic transmission to humans causing severe clinical syndromes and an extremely high mortality rate has led to fears that this virus might trigger a future disastrous global pandemic. Also of concern are influenza viruses infecting animals, especially pigs and birds, which, besides the risk of becoming potential pandemic viruses for humans, cause enormous damage to farmers and the food industry.

Preparedness to cross-border health threats is an important EU health policy, and the European Commission (EC) has significantly geared up its commitment during the last decade to support research in order to prepare for a serious influenza pandemic. The projects funded by the Sixth and Seventh Framework Programmes for Research and Technological Development (FP6: 2002-2006; FP7: 2007-2013) contribute significantly to this objective. At the same time they strengthen the European biotechnology industry and foster and maintain a strong European expertise in influenza and other infectious diseases. As the single largest funder of influenza research in Europe, the EC is putting in place crucial elements necessary for a rapid and integrated approach for the prevention and control of any future serious infectious outbreak.

EU-funded projects aim at developing new tools and products for the efficient prevention, treatment, and control of influenza. Since 2002, FP6 and FP7 have launched more than 80 influenza projects. Supported by EU funding worth some EUR 150 million, these projects involve multidisciplinary teams from over 300 institutions in around 60 countries. They address various complementary scientific aspects such as basic virology, diagnostics, epidemiology, pathogenesis, surveillance, immune responses, animal viruses, novel drugs and vaccines. The 2009 influenza H1N1 pandemic taught us the importance of communication during emergencies, so additional projects on behavioural aspects and optimized communication strategies were also initiated. Training, especially in low-income countries, is also part of FP influenza research. More recently, the EU has funded several large-scale projects that have a sufficiently broad expertise in infectious diseases to tackle, in a flexible way, any unexpected new outbreak.
A few non-exhaustive examples of contributions by FP7 projects include the development of rapid and fully automated molecular diagnostic systems for different strains of influenza that are currently pending market authorisation. Several projects have contributed significantly to various scientific and public health aspects of the 2009 influenza H1N1 pandemic that provided valuable information for the development of risk assessment and containment strategies. Some FP7 projects build on the success of previous FP6 projects that identified new drug candidates that inhibit the viral RNA polymerase. These projects are expected to bring closer to the market new drugs with a reduced risk of developing resistance aimed to treat both seasonal and pandemic influenza.

The strong commitment to influenza research continues in the last FP7 funding round, with emphasis on the development of a universal vaccine protecting against seasonal and pandemic influenza as well as clinical management of patients in serious infectious outbreaks with high health and socio-economic impacts in the EU.

This publication is a follow up to a previous catalogue of EU-funded projects covering the years 2001–2007 and containing all FP5 and FP6 funded influenza projects1. Together, these two publications demonstrate the long-term track record of FP funding in this field. This new publication includes most of the influenza projects funded so far under FP7, exceeding EUR 90 million in total, most of which have been funded through the Health theme of the Cooperation Programme.

The projects are divided into thematic chapters that cross the border between animal and human influenza, emphasizing the Commission’s strong support to the ‘One Health’ initiative, which strives to foster closer collaboration between multiple disciplines to attain optimal health for people, animals and the environment.

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In memoriam

Our dear colleague Isabel Minguez-Tudela, who sadly passed away in April 2011. Isabel was scientific officer at DG Research and Innovation and managed EU research projects on animal health including avian and swine influenza with remarkable commitment and engagement. She is deeply missed.

Infectious Diseases and Public Health
Directorate-General for Research and Innovation
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CHAPTER 1
VACCINES AND CORRELATES OF PROTECTION
**Summary**

Vaccines have so far mostly been developed using empirical approaches. To prevent and possibly cure unresolved and emerging infectious diseases and extend the benefits of vaccination to other pathologies, we need to fully exploit the potential of the human immune system. The project aims to produce the knowledge necessary to develop novel and powerful immunisation technologies for the next generation of human vaccines, including influenza vaccines. Existing and experimental vaccines, with a strong focus on influenza, will be investigated in depth (i.e. by a systems biology approach) in patient characterisation studies and in clinical trials, while animal models will be used to complement human studies. Influenza vaccines, already in common use but in need of improvement (overcoming annual variations) or adaptation (to better protect the elderly), are hence the focus of research efforts, alongside two additional model diseases.

**Problem**

Vaccines have been mostly developed empirically, by killing or attenuating pathogenic microbes without fully understanding the scientific mechanisms behind them. In modern vaccinology, we would like an answer to many scientific questions, such as the nature of immunogens, the nature of the protective immune response, how we can change the quality of an existing immune response, the development and ageing of the human immune system, and the host factors influencing susceptibility to disease and protection. The ability to study human immunology, the possibility of using systems biology to find new signatures able to explain the nature of protective immune responses and the ability to use and develop molecularly defined adjuvants offer new tools to address the above questions and to develop advanced immunisation technologies that can be applied to the development of next generation vaccines against influenza and other diseases.

**Aim**

To produce the knowledge necessary to develop novel and powerful immunisation technologies for the next generation of human vaccines.

**Expected results**

The project is structured around two major interlinked components: i) human immune response to vaccination studied through latest generation methodologies and ii) development of advanced immunisation technologies.

A systems biology approach is used to study existing and experimental vaccines, with a focus on influenza vaccines, in patient characterisation studies and in clinical trials, to investigate the effect of adjuvants, vectors, formulations, delivery devices, routes of immunisation, homologous and heterologous prime-boost schedules, as well as the impact of host factors, such as age, gender, genetics and pathologies. Animal models are used to complement human studies, and to select novel immunisation technologies to be advanced to the clinic. A broad panel of adjuvants, live vaccine vectors, formulations and delivery devices will be tested, compared, selected and optimised using three common prototype antigens including influenza haemagglutinin. New concepts and tools will be generated from the preclinical studies. The new tools will generate new vaccine candidates that will be advanced to phase I clinical trials. These trials will be focused on a cutting-edge application of novel technology developed within the project that is a genuine advance or paradigm change. Through this comprehensive and unprecedented effort, ADITEC offers the unique opportunity to create synergies and cross fertilisa-
tion between different research areas and has the potential to fill the existing knowledge gaps and enable the introduction of new effective and safe immunisation technologies relevant for next generation influenza vaccines and also applicable to other target diseases.

Potential applications

The development of new technologies is expected to speed up the employment of vaccines, decrease the risk of failure of new vaccines and enable the development of those vaccines which are not yet possible.

Key words

vaccines, immunisation technologies, human immunology, adjuvants, systems biology

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Summary

FLUPLAN is a research project, co-ordinated by Professor A.D.M.E. Osterhaus, DVM that aims to mitigate the next influenza pandemic by the development of novel intervention strategies against potential pandemic influenza viruses. More specifically, FLUPLAN aims to identify novel reassortant viruses and to make an inventory of possible reassortant viruses of potentially pandemic nature that can be used for the preparation of vaccine seed viruses for pandemic vaccines, based on the modified vaccinia virus Ankara, that are ‘ready to go’. These studies will provide fundamental insights into the mechanisms that govern reassortment phenomena and will be of great value for more adequate risk assessments concerning the pandemic potential of circulating avian and mammalian influenza A viruses.

Problem

Pandemic influenza is a major threat because there is no adequate response to such an event. Measures mitigating the effects of this infectious threat, focusing on non-medical interventions, such as social distancing, improved surveillance and diagnostic capabili-
ties are crucial, but are only effective if supported by equally adequate medical intervention strategies. Currently, the use of antivirals and vaccines are the first and last line of defence against emerging influenza outbreaks. Neither, however, provides us with sufficient pandemic preparedness. The available antivirals, at best, enable us to ‘buy time’ to develop and test novel prophylactic vaccines, but by no means offer us the needed long term defence against influenza pandemics. Moreover, influenza vaccines usually take up to 8 months to be ready for induction of protection. Hence, it is necessary to be able to develop and produce novel vaccines within a shorter timeframe and with increased efficacy.

Aim

To expand our ability to develop and produce novel vaccines within a shorter timeframe and with increased efficacy to mitigate the next influenza pandemic.

Main objectives:

- To unravel the poorly understood packaging signals that govern reassortment events between influenza A viruses in general, and between the Mexican influenza A virus (H1N1) and circulating human, porcine and highly pathogenic avian influenza A viruses in particular. This will provide us with an inventory of possible reassortant viruses of potentially pandemic nature that can be used for the preparation of vaccine seed viruses for pandemic vaccines.

- To develop novel vaccine strategies by using the modified vaccinia virus Ankara (MVA) as a vaccine vector. The MVA vaccine vector system, that proved to be highly effective in inducing protective immunity against HPAI-H5N1 viruses of different viral clades, will be used together with the continuously updated repository of avian influenza viruses that can be used for the preparation of vaccine seed viruses for pandemic vaccines that are ‘ready to go’.

- To obtain proof-of-principle that MVA-based influenza vaccines are safe and evoke broadly reactive and protective antibody titers by performing a phase I clinical trial with the MVA-H5 vaccine.
The results will not only improve understanding of the development of influenza vaccines but will also enlarge our knowledge of the emergence of influenza reassortants and will provide insights to improve and focus future prevention and intervention strategies against influenza pandemics.

Potential applications

Once FLUPLAN has established that the MVA-H5 vaccine is safe and effective in a phase I trial, this vaccine can be tested in subsequent trials and ultimately be added to prevention strategies against influenza pandemics. The studies performed within FLUPLAN will identify which reassortants are likely to emerge and in addition will reveal which reassortants will pose the greatest threats to the community. This information is invaluable and should be implemented in future prevention and intervention strategies against influenza pandemics. In addition, FLUPLAN will generate novel insights into the development of novel intervention strategies against influenza which may also be applicable to the development of novel intervention strategies for other infectious diseases.

FLUPLAN will develop novel vaccine strategies by the identification of possible reassortant influenza viruses of potentially pandemic nature and including these in the preparation of vaccine seed viruses for pandemic vaccines. To further study these new reassortants, novel animal models will be established to monitor morbidity, mortality and pathology of the reassortants. In addition, the development of in vivo reassortants will be monitored. FLUPLAN will generate a continuously updated repository of avian influenza viruses of, in principle, all HA subtypes (n=16) as well as the avian/swine Mexican influenza A virus (H1N1) to be used for the preparation of vaccine seed viruses that are ‘ready to go’. By performing a phase I clinical trial, FLUPLAN is expected to deliver a safe and effective MVA-H5 vaccine which will pave the way for future MVA-based influenza vaccines.

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Summary

The FastVac consortium brings together public health institutes and academia from eight EU Member States with established expertise in all disciplines associated with vaccine development and production. The project aims to provide the intellectual rule book to enable candidate emergency vaccines to be rapidly taken forward through preclinical testing and process development to clinical testing, production and licensure. Influenza vaccines have been chosen as a model product to illustrate the necessary ingredients of such a rule book. It is expected that the outputs from FastVac will underpin vaccine development by public health agencies to enhance the development of ‘niche market’ vaccines that could be transferred to vaccine manufacturers.

Problem

Vaccines are a key defence against infectious diseases. However, the design and production of safe and successful vaccines remains largely serendipitous and is often not economically attractive for vaccine manufacturers.

Aim

The general objective of FastVac is to produce a comprehensive set of predictive rules that will enable accelerated development, evaluation, production and release of emergency vaccines. The ‘blueprints’ produced by FastVac will inform the parallel processes of vaccine development and process design, through to phase 1 clinical testing and support for GMP production. By providing evidence-based rules to aid the production of contingency emergency vaccines, this project ultimately aims to have a significant effect on the long-term health of the human population, both in the EU and internationally.

Expected results

The project will include a systematic literature review of the scientific record to identify predictors of vaccine success or failure. From this, a set of evidence-based rules will be developed: (a) for the rational scale up of production processes; and (b) for the control of production runs and release of intermediate vaccine product by use of process analytical technology. The final principles for process scale up and production control through in-process monitoring, will undergo proof-of-principle testing at different organisations and for different vaccine products. A new and faster approach to vaccine development will have profound regulatory effects. Dialogue will be maintained with EU regulatory structures (the European Medicines Agency (EMA) and the European Centre for Disease Prevention and Control (ECDC)), public health policymakers and industry, through annual meetings and a workshop at the end of the project.

Potential applications

It is expected that the outputs from FastVac will underpin vaccine development and production by public health agencies to enhance development of ‘niche market’ vaccines that could be transferred to vaccine manufacturers.

Key words

emergency vaccine development, systematic literature review
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Summary

The European Medicines Agency (EMA) hosts an electronic database (Eudravigilance) for the reporting of adverse reactions during the development and following the marketing authorisation of medicinal products, including vaccines. The reporting obligations of the various stakeholders are defined. Guidelines for the use of statistical signal detection methods in the Eudravigilance data analysis system are available but industry-independent infrastructure to investigate a potential vaccine safety signal identified in immunisation programmes in formalised pharmaco-epidemiological studies is not available within the EU. The project, funded by the European Centre for Disease Prevention and Control (ECDC), aims to explore the potential for vaccine safety studies involving healthcare databases from different European countries to detect true associations through the use of common protocols and sharing of results.

Problem

While EU regulations on reporting and investigation of adverse events following immunisation (AEFI) are in place, the level of compliance with these and the capacity to investigate vaccine safety signals in EU/EEA Member States varies significantly. The assessment of rare AEFI may not be possible within a single country due to an insufficiently large denominator population. For new vaccines, systematic and transparent monitoring and assessment are needed to maintain public confidence in the often nationally organised immunisation programmes where a high vaccination coverage is aimed for.

Aim

The ECDC aims to establish a network of researchers in EU Member States with access to and capacity to readily perform vaccine safety studies in support of the large immunisation programmes running in all EU Member States, and in medical databases in national/regional healthcare systems complemented by formalised pharmaco-epidemiological studies should vaccine safety signals arise.

Expected results

In 2009, after the initial spread of the pandemic influenza A (H1N1) virus, the VAESCO II project was significantly expanded. Background incidence rates for medical events of interest defined by the EMA as possible AEFI were estimated. These results were used by the EMA for observed versus expected analysis of reported AEFI in Eudravigilance following pandemic vaccination campaigns.

Pharmaco-epidemiological studies were initiated in 2009 to evaluate the risk of Guillain-Barré syndrome in relation to the use of adjuvanted pandemic vaccines (mostly Pandemrix and Focetria) in the EU. Denmark, France, the Netherlands, Sweden and the UK participated in the study, with a total source population of 50 million. After adjustment for influenza-like illness/upper respiratory tract infection and seasonal influenza vaccination, receipt of pandemic influenza vaccine was not associated with an increased risk of Guillain-Barré syndrome. The 95 % confidence interval shows that the absolute effect of vaccination could range from one avoided case of Guillain-Barré syndrome up to three excess cases within 6 weeks after vaccination in 1 million people.

In conclusion, the risk of occurrence of Guillain-Barré syndrome is not increased after pandemic influenza vaccine, although the upper limit does...
Key words
vaccine safety, background incidence rates, data linkage, pharmaco-epidemiology

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not exclude a potential increase in risk up to 2.7-fold or three excess cases per 1 million vaccinated people.

In 2010, a vaccine safety signal of narcolepsy/cataplexy from routine reporting systems following pandemic vaccination campaigns was reported in Finland and Sweden. Children and adolescents vaccinated with Pandemrix developed narcolepsy and often cataplexy, within 3–6 months following vaccination. The VAESCO II project conducted a case-control study to evaluate the association between infections, vaccinations and narcolepsy.

Potential applications
Providing the safest vaccines in national immunisation programmes is the goal of all EU Member States. Introduction of new vaccines into the immunisation programmes always needs to be followed by close monitoring since only the most common adverse events will have been identified in the clinical trials before authorisation. The newly developed increased capacity in the VAESCO II network will facilitate this monitoring and assessment.
PLANT PRODUCTION OF VACCINES

Summary

PLAPROVA was a highly innovative project which exploited recent developments in plant expression systems to produce both simple and complex virus-like particles (VLPs) in plants for vaccination purposes. It had two essential components: (1) the use and refinement of plant expression systems capable of expressing high levels of candidate immunogens within a short time frame; (2) the identification of candidate immunogens and the immunological characterisation of the plant-expressed proteins. The project demonstrated that it was possible to produce VLPs from a number of viral pathogens in plants and demonstrated that the plant-produced VLPs were immunologically active.

Problem

At the beginning of the project, the use of plants as bioreactors for the production of pharmaceutical proteins was at a cross-roads. The previous five years had seen considerable advances in the technologies for expressing proteins and extracting them in an active form from plants. However, most of the successes concerned the production of well-characterised antigens and antibodies which had already been produced using previously established methods such as mammalian cell culture. This approach made sense as it was important to establish the principal that plant-produced pharmaceuticals were comparable in safety and efficacy to their conventionally-produced counterparts. Given the time lags associated with the production of lines of stably transformed plants, it was essential that proteins with previously characterised pharmacological properties were expressed as only a few candidates could be examined. The downside was that the plant-expressed proteins which were most highly developed and, in some cases, undergoing clinical testing were in direct competition with existing products. The time-consuming nature of stable genetic transformation meant that this approach could not be used in rapid-reaction situations, such as the creation of vaccines to combat newly emerging diseases.

Aim

The project aimed to develop transient expression technologies for producing sufficient material in a short time frame to enable pharmacological studies of a large number of vaccine candidate variants to be undertaken. This would permit optimisation of the methods of antigen presentation of a variety of different potential immunogens. An advantage of the transient approach is that yields can easily reach 10–30 % of total soluble protein, about 10–1 000 times higher than usually obtained through nuclear transformation. These high levels of expression can be achieved in a few days, potentially enabling high-throughput analysis. It would also allow rapid production of vaccines to combat emerging diseases. The project concentrated on the expression of proteins which form polypeptide complexes or VLPs since, due to their immunological properties, these are particularly suitable as candidate vaccines.

Expected results

Three categories of vaccine candidates were successfully expressed:

- Simple VLPs which spontaneously form when a single polypeptide is expressed. Human (HPV) and bovine papillomavirus (BPV) were expressed in plants using transient methods. VLPs from BPV have been shown to be immunogenic in rabbits.
The project demonstrated that VLPs can be efficiently produced in plants and that they have an appropriate antigenic structure. The transient expression technology has already been licensed to several companies and one of them, Medicago Inc., has used the technology to express candidate vaccines of several influenza virus strains. One such candidate, based on the haemagglutinin of AIV, has recently completed phase II clinical trials in North America.

**Key words**

transient expression, virus-like particles, vaccine production in plants

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**Complex VLPs which only form when several polypeptides are co-expressed.** All four structural proteins of Bluetongue virus serotype 8 (BTV-8) were transiently co-expressed in plants and shown to assemble into VLPs. The plant-produced VLPs conferred protective immunity in sheep, thereby constituting an experimental vaccine. Plants were also used to express proteins from Foot-and-mouth disease virus and Porcine respiratory and reproductive syndrome virus.

**Antigenic sequences which are fused to a carrier polypeptide which forms VLPs.** Avian influenza virus (AIV) was targeted. In an attempt to produce a vaccine which was protective against multiple serotypes, the M2e epitope was fused to a number of self-assembling polypeptides. Fusion of the M2e epitope to either the Hepatitis B core antigen or particles of Tobacco mosaic virus resulted in chimaeric VLPs which protected mice against AIV challenge.

**Potential applications**

The major application is rapid production of novel vaccines in plants.
Chapter 1 - Vaccines and Correlates of Protection

INTERASAL PANDEMIC INFLUENZA VACCINE

www.naspanvac.com

Summary

A highly pathogenic form of avian influenza (AI) virus (H5 subtype) is panzootic in poultry, can transmit from poultry to humans and has the potential to cause another global influenza pandemic. This project is a response to the need to develop an effective, user friendly, thermally stable influenza vaccine.

The overall objective of this programme is to develop a nasal AI vaccine using ChiSys® (chitosan), which is an enabling chitosan-based vaccine-delivery technology of Archimedes Development Ltd. Chitosan has already been tested with several nasally delivered antigens in preclinical models and in the clinic, with excellent results. The most effective way of controlling a pandemic flu would be by vaccination via the nasal route. The nasal route has the advantage of generating both systemic and mucosal immunity; the latter allowing control of the virus at its point of entry. In contrast, the currently used injectable vaccine does not generate a mucosal immune response. Intranasal vaccination also has the advantages of: 1) avoiding the need for injection, thereby not requiring disposal of syringes and eliminating the risk of HIV transmission through re-use or accidental contact with body fluids; 2) having greater public compliance; and 3) being well-suited to rapid mass global vaccination programmes.

This project will evaluate the efficacy and toxicity in preclinical studies and will evaluate efficacy and safety in humans, with the scientific objective of inducing both systemic and mucosal immunity, while providing a substantial level of cross-immunity against drifted strains of H5 or H7. The approach will be effective at low dose to meet the global demands from limited vaccine stockpiles, will have thermal stability to avoid the requirement for refrigerated storage and transportation, and will employ a user friendly vaccine applicator.

The extensive experience of all members of the consortium in their specialist fields, including basic immunology, development, vaccine trials, and the virology and immunology of the influenza virus provides optimal conditions for the success of this project. ChiSys® is an excellent candidate delivery system for developing an intranasal pandemic influenza vaccine to provide a quantum leap in successfully combating pandemic influenza globally.

Problem

The highly pathogenic form of AI virus (H5N1) has the potential to cause another global influenza pandemic. A major problem confronting pandemic planners is ensuring adequate global vaccine supplies. Manufacturing capacity for influenza vaccines is limited and clinical trials to date with non-adjuvanted split-product or subunit inactivated vaccines have found these to be poorly immunogenic, needing increased dosages of antigen content. Furthermore, AI strains are continuously drifting antigenically. Therefore, dose-sparing strategies and the development of a vaccine providing long-lasting, cross-subtype protection is required.

Aim

The aim is to develop a nasal AI vaccine, which induces durable, broad, mucosal and systemic immune responses, is easily administered by needle-free delivery using technology that could be used for any potential antigen, is thermally stable and cost effective.

Expected results

- Stable solution and/or powder formulations;

www.naspanvac.com
Chapter 1 - Vaccines and Correlates of Protection

- establishes an effective nasal dose;
- induction of influenza-specific serum (IgG) and mucosal (IgA) antibodies;
- evaluation of haemagglutinin inhibition and single radial haemolysis tests;
- assesses cell-mediated immune responses;
- evaluates kinetics of systemic and local antibody response;
- assesses the ability of the vaccine to induce cross reactive immunity.

Potential applications

A successful outcome of this project would lead to further clinical data generating a robust data package that demonstrates that the intranasal vaccine provides safe and effective immunisation against AI. These data will be suitable for regulatory filing in order to obtain a product licence, scale up manufacture and commercialise a nasal vaccine for pandemic influenza.

Key words

nasal, avian influenza, pandemic, vaccine, ChiSys®

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User friendly delivery device specific for a solution formulation or a powder formulation;

Murine studies:
- show induction of both mucosal and systemic immune responses;
- assess cell-mediated immunity;
- establish a dose response;
- determine the optimum immunisation schedule;
- evaluate the influence of parenteral priming on response to nasal boosting;
- evaluate the influence of previous infection of immunisation with H3 influenza strains on response to nasal priming with H5 strains.

Ferret studies:
- show induction of immune responses;
- show cross-reactivity to diverse H5N1 influenza strains;
- show protection against homologous or heterologous influenza strains.

Toxicology study of selected formulation(s):
- shows none or minimal (acceptable) toxic effects.

Proof-of-principle clinical study:
- shows that chitosan-adjuvanted intranasal vaccine is safe;
IDENTIFICATION OF MECHANISMS CORRELATING WITH SUSCEPTIBILITY FOR AVIAN INFLUENZA

www.imecs-flu.eu

Summary

IMECS is a proposal of the FLUSE-CURE network aimed at combating the threat of new and re-emerging forms of highly pathogenic influenza in its first stages of a disease, by identifying mechanisms of protection that are essential for a solid immune response to avian influenza (AI). The mechanisms of immunity to AI are essentially different from those for human/seasonal influenza. IMECS is unique by correlating research in humans directly to protection from influenza and aims to elucidate these mechanisms. The initiative comprises a research programme for the development of AI-specific correlates of protection, the screening of vaccine candidates in vitro, the understanding of the origin of subclinical AI infection in humans and the clinical screening of vaccine candidates in healthy adults and in different target groups.

Expected results

Identification of factors that contribute to effective pandemic vaccine production:

- identification of critical mechanisms of humoral protection in humans;
- identification of critical mechanisms of cellular protection in humans;
- in vitro model for determining vaccine efficacy;
- identification of mechanisms of protection in target groups for vaccinations.

Problem

The IMECS initiative was introduced since the recent H5N1 AI vaccine trials, results of which were published in international scientific journals, showed limited success in inducing a protective immune response as compared to the standard human influenza vaccines, despite large investments and multiple vaccine formulations having been tested. These results make clear that the mechanisms of immunity to AI are essentially different from those for human/seasonal influenza.

Aim

The consortium aims to:

- identify the basis of protection from infection with AI by investigating homologous and non-homologous mechanisms of protection in individuals who were infected with AI;
- study these mechanisms in target groups for infection;
- correlate these mechanisms to the immune responses induced by AI vaccination, applying an in vitro model and in clinical trial studies.
Potential applications

The consortium aims to identify the mechanisms of protection from AI in humans and, thus, enable the development of an effective vaccination strategy to protect the people of the EU in response to a pandemic influenza outbreak.

Key words

homologous and non-homologous mechanisms of protection, influenza, avian influenza, target groups, correlates of protection, pandemic influenza
Summary

Monitoring influenza vaccine effectiveness (VE) at European level is a major challenge. The project was established to monitor influenza VE within and across the seasons in the EU and the European Economic Area. The project is a joint venture between 20 institutes from 17 EU Member States and the European Centre for Disease Prevention and Control (ECDC), which funds 11 studies. In 2008 and 2009, a multi-centre case control study was conducted among study sites in five EU Member States, to provide a pooled estimate of influenza VE against medically attended influenza-like illness (ILI) confirmed in the laboratory as influenza among the elderly (age ≥65 years) across Europe. During the pandemic season in 2009 and 2010, the multi-centre case control study was expanded to study sites in seven countries and the study population to all age groups. In the 2010 and 2011 season, study sites from eight EU Member States participated in the I-MOVE multi-centre case control study. All studies are conducted in the framework of primary care sentinel surveillance systems. The results are discussed annually in the EU and beyond, and are communicated directly to the World Health Organization (WHO), the European Medicines Agency (EMA) and the European Commission’s Directorate-General for Health and Consumers, well before publication.

Problem

- Routine annual monitoring of influenza VE needs to be established in Europe because:
  - the influenza vaccine is the only vaccine that is reformulated each year;
  - influenza is the only vaccine-preventable virus that undergoes frequent genetic and antigenic changes including major changes due to reassortment and/or genetic mutations;
  - immunologic correlates of protection are not well defined;
  - observed VE varies from year to year;
  - observed VE varies between subgroups (age groups and risk groups);
  - influenza is the only vaccine-preventable disease for which yearly monitoring of VE is performed in Australia, Canada, Europe, the United States and some countries in Asia;
  - VE is only partially correlated to the virological degree of match between the virus strains included in the vaccine and the circulating strains;
  - available vaccines are not very effective;
  - vaccine-induced immunity is not known to last beyond 6 to 12 months, and therefore annual revaccination is needed even if no major changes in the influenza virus occur;
  - with the exception of some of the 2009 pandemic vaccines and of some new vaccine formulations (live attenuated influenza vaccines (LAIVs)), all of the seasonal trivalent influenza vaccines are authorised nationally and therefore do not follow the centralised EMA procedure;
  - new vaccines are being developed for which no effectiveness data are available;
  - a system is ready to measure VE during pandemics.

https://sites.google.com/site/epiflu/
VE was 56 % (95 % CI 34–71) overall, 59 % (95 % CI 32–75) against A(H1N1) and 63 % (95 % CI 31–81) against influenza B.

Potential applications

The project’s application lies in basing EU and national decisions concerning influenza vaccination strategy on epidemiological evidence. It will also aid in providing early estimates of VE in the season, and measuring VE in an emergency pandemic situation. It can be used to advise on alternative measures if VE is low or missing.

Key words

influenza vaccine, vaccine effectiveness, pandemic, EU network, surveillance, post-marketing evaluation

Aim

The project aims to monitor seasonal influenza VE annually in a timely, robust and independent way that can be activated rapidly during an influenza pandemic.

Expected results

In the 2009 and 2010 pandemic season, the adjusted pandemic VE was 71.9 % (95 % confidence interval (CI) 45.6–85.5) overall, 78.4 % (95 % CI 54.4–89.8) in those aged <65 years, and 72.9 (95 % CI 39.8–87.8) in those without chronic disease. We measured the effectiveness of the 2010 and 2011 trivalent seasonal influenza vaccine, by influenza virus type, among all the population and among the target population for the influenza vaccine. The adjusted VE was 52 % (95 % CI 30–67) overall (N=4410), 55 % (95 % CI 29–72) against influenza A virus subtype H1N1 (A(H1N1)) and 50 % (95 % CI 14–71) against influenza B. Adjusted VE against all influenza subtypes was 66 % (95 % CI 15–86), 41 % (95 % CI 3–66) and 60 % (95 % CI 17–81) among those aged 0-14, 15-59 and ≥60, respectively. Among target groups for vaccination (N=1004),
CHAPTER 2
DETECTION, DIAGNOSTICS AND SURVEILLANCE
Concurrently, information on antigenic variation of circulating European SIVs will improve the control and prevention of infections and interspecies spread of strains.

Expected results

Through both virological and serological surveillance for influenza in pig populations, there will be a further expansion of our knowledge of the epidemiology and evolution of SIVs in Europe, and the provision of coherent data sets at EU level in relation to SIV. The rapid characterisation of contemporary viruses will contribute to better information for authorities concerned with veterinary public health, and surveillance approaches and diagnostic techniques for swine influenza will be harmonised within the network. An EU SIV bank for the scientific community will be established.

Potential applications

This project will be an invaluable resource to officials responsible for veterinary and public health alike. The co-ordination action will directly impact upon the diagnosis and control of SI in Europe and, thus, enhance the welfare of swine and the profitability of swine...
farmers. This, in turn, will increase our understanding of the public health risks of influenza in swine. The comprehensive information relating to the epidemiology and evolution of SI in pig populations across Europe will enable a robust scientific evidence base to be available when assessing public health risk from SI, directly contributing to the production of policy documents and risk assessments prepared by ECDC. Such enhanced interaction is timely following the emergence of the 2009 pandemic (H1N1) virus that has already been detected in pigs in Europe.

Key words

surveillance, European swine, swine influenza, consortium, antigenic characterisation, genetic characterisation

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NOVEL TECHNOLOGIES FOR SURVEILLANCE OF EMERGING AND RE-EMERGING INFECTIONS OF WILDLIFE

www.wildtechproject.com

Summary

The health of wildlife is of major concern throughout the world. Infectious diseases of wildlife species have significant impacts on public health and livestock health. Effective disease surveillance is essential to inform control strategies, and requires the development and application of accurate and rapid disease diagnosis methods. The project will address these problems and set up a technology centre that may be exploited in Europe and elsewhere as a basis for high-throughput disease diagnosis in wildlife.

Problem

There is an increased prevalence of new and emerging diseases arising from wildlife which has clear implications for disease spread to domestic animals and humans. WildTech is focused on wildlife as a reservoir of disease. It is reported that 61% of known pathogens infect multiple animal species and 75% of all diseases which have emerged in the last two decades have originated from wildlife. The surveillance of disease in wildlife not only impacts on communities that rely on healthy domestic animals but is also an essential tool for the protection of human health. Nevertheless, surveillance for infectious diseases in wildlife is far from satisfactory.

Aim

■ Application of microarray technology for:
  (a) the detection of known infectious agents in wildlife populations;
  (b) the detection and identification of novel and unknown infectious agents in wildlife populations;
  (c) the development of high-throughput serological screening of wildlife populations for infectious disease;

■ Using these technologies to assess the spread of selected diseases using historical and current samples;

■ Reducing the risk of further potential epidemics by producing a generic action plan in case of emerging epizootics among wildlife;

■ Development of a wildlife disease data management system with mapping capability and the establishment of a framework for pan-European surveillance of wildlife diseases.

Expected results

■ Effective and validated high-throughput microarray technology, both generic and adapted to a commercial platform, for detection of nucleic acid of a focused list of up to 20 infectious agents, including avian influenza (AI), from wild animal samples. We will, in addition, develop generic arrays for 200 infectious agents which will be incompletely validated.

■ Effective and validated high-throughput serological array technology, both generic and partially adapted to a commercial platform, for detection of specific antibodies in serum/blood against approximately 20 infectious agents, including AI, from selected wild animal hosts, in addition to incompletely validated tests for further infectious agents.

■ Information on the spatial and temporal distribution of a focused list of up to 20 infectious agents, including AI, in wild animal species in selected European countries/regions and countries outside Europe that represent potential sources of introduction into Europe.
The project results will also have indirect impact on human health as diseases coming either directly or indirectly through wildlife are likely sources of zoonotic infection. By improving our detection of these pathogens, this would enable a rapid and effective response to an emerging infection, which would minimise the impact on the human population.

Key words
wildlife disease surveillance, high-throughput array technologies, epidemiology, data management systems

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Potential applications

- Preventing major outbreaks of infectious disease in Europe.
- Reduced mortality and morbidity and associated improved welfare in domestic animals in Europe and beyond. In poorer third world countries, outbreaks of infectious disease in domestic animals can have far-reaching consequences for the well-being of entire human communities.
The project will establish a network of centres of excellence to effectively counter (re)-emerging infectious diseases. Common processes, procedures and communication channels will be established in the network linked to relevant stakeholder organisations and local ‘grass roots’ sites to contribute to a structural and systematic prediction, identification, modelling and surveillance of (re)-emerging infectious disease health threats and pathogens.

In 2009, the world was confronted with the first influenza pandemic of the 21st century, caused by the novel Influenza A/H1N1 virus. With the support of the European Commission, EMERIE responded by contributing a large share of its activities and resources to bringing this pandemic under control.

The expertise and resources necessary for adequate prediction, identification, modelling and surveillance of infectious pathogens are scattered. If a group of patients presents with a particular disease, and some infectious agent is thought to be the cause, scientists lack a functioning networked infrastructure to respond in a quick and powerful manner. Transfer of basic research results to diagnostic and clinical application is currently a bottleneck in virology research.

To effectively counter the potential public health threat caused by new and emerging infectious diseases in Europe, a powerful network capable of structural and systematic prediction, identification, modelling and surveillance of infectious diseases health threats and pathogens will be established.

Expected results

- Specimen collection
  Sufficient specimens and samples for further processing and analysis or banking will be collected. The collections will serve as an initial inventory of ‘pathogen diversity’ in humans in several parts of the world and in key risk reservoir species. Moreover, the collections will be used for the initial identification of unknown pathogens in humans and animals, especially those in key reservoir species that have previously been shown to represent an imminent health threat to humans, and of viruses already present in humans, but unrecognised.

- Isolation and identification
  An integrated set of laboratory methods will be provided to facilitate the identification of novel viruses. It will also characterise crucial traits of identified novel agents.

- Metagenomic sequencing and analysis
  Metagenomic sequencing is a novel approach for discovering emerging pathogens. Using high-throughput sequencing techniques on pooled samples from different populations, baseline databases and the bioinformatic tools to query them will be generated. In addition, novel algorithms for assessing the zoonotic potential of novel viruses by quantifying homologies with viruses in other species will be developed.

- Pathogen containment: diagnostics and intervention options
  The information from virus identification studies will be used to facilitate early intervention by diagnostics, vaccines and antiviral agents. Test formats to be developed include real-time RT-PCR, recombinant ELISA and standardised immunofluorescence assays. In addition, antiviral drug candidate libraries will be screened.
Synthesis, prediction and preparedness

New analytical tools will be built for rapid epidemiological characterisation of an emerging epidemic and optimisation of control options. Fundamental work on the evolutionary drivers for zoonotic transfer and adaptation to new host species will also be performed.

Training and capacity building

It is not unlikely that future outbreaks with novel or (re-)emerging zoonotic pathogens will originate from tropical regions in Asia, Africa or the Americas, as was the case for SARS and Influenza A/H1N1. EMPERIE will enhance the grass root laboratory and scientific capacity in these regions needed to recognise, diagnose and investigate infectious diseases outbreaks at an early stage, thereby helping to prevent global spread.

Influenza A/H1N1 2009 pandemic

EMPERIE performed several studies to understand the epidemiology of the novel 2009 pandemic Influenza A/H1N1 and its spread around the world, and to understand and predict its virulence or the spill-over between different host species. During the outbreak, EMPERIE studied the transmission over time in different age groups, which provided not only numbers of infected individuals, but also vital data on changing patterns of herd immunity. EMPERIE also studied the relation to existing protection and vaccination for vaccine strain selection and identified novel intervention strategies against novel H1N1 influenza virus.

Potential applications

- diagnostic real-time PCR and ELISA or IFA assay with validation data;
- full virus antiviral assay;
- reverse genetics system;
- replicon system;
- recombinant vaccine;
- exemplar modelling and analysis computer programs.

Key words

emerging infectious disease, virus, zoonoses, outbreak, pathogen, containment

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Chapter 2 - Detection, Diagnostics and Surveillance

Summary

The RANGER consortium brings together clinical and technical expertise to deliver a system capable of diagnosing influenza accurately and quickly, enabling healthcare professionals and outbreak specialists to make timely and informed decisions.

The system will be fully automated and capable of providing a laboratory standard result from a raw sample. Prototype instruments, cartridges and assays will be developed and validated for use as human in vitro diagnostics for influenza diagnosis and surveillance, offering:

- Rapid diagnosis of influenza (both seasonal and pandemic) in the point-of-care (POC) environment, enabling faster and better informed medical care to reduce suffering and save lives;

- Coordinated surveillance of influenza incidents and outbreaks, enabling rapid deployment of resources to control disease spread and treat patients.

Problem

Influenza is one of today’s biggest threats to the world’s socio-economic health. The global incidence of seasonal or epidemic influenza is 10–20%, is responsible for between 3 and 5 million cases of severe illness every year, and causes 500,000 deaths annually. The total direct and indirect costs of a severe epidemic are estimated at over USD 12 billion in the USA alone.

A global pandemic has been projected to infect 25–35% of the global population and conservative estimates from the World Health Organization (WHO) have placed the likely death toll at 2–7.4 million people and the cost at over USD 800 billion. The avian influenza (AI) strain, H5N1, has such pandemic potential. In December 2003, infections in people exposed to sick birds were identified and since then, according to the WHO, there have been 258 human cases of AI, with a mortality rate exceeding 50%. At this time, H5N1 does not easily infect or spread among humans. However, a pandemic could begin should H5N1 evolve to a form as contagious as normal influenza.

Although vaccination is effective against the spread of infection, current global vaccination coverage is less than 5% and viral mutation requires constant review of vaccine efficacy. Consequently, the most effective means of controlling the spread of influenza is early diagnosis followed by containment and antiviral therapy. However, currently available diagnostic technologies are not suitable for widespread use in developed and developing countries. Rapid antigen-based tests are insensitive and are not designed to specifically identify H5N1. Existing polymerase chain reaction (PCR)-based techniques and microarrays are slow, expensive and require specific laboratory equipment and expertise. Consequently, there is an immediate need for a rapid, robust, sensitive and cost-effective POC diagnostic tool for the identification of influenza strains and sub-types which requires minimal expertise to operate and no specialist laboratory equipment.

Aim

The RANGER consortium brings together experts in the fields of: influenza diagnosis and surveillance; sample preparation; PCR; in vitro diagnostics system development; engineering, materials science, freeze drying; and surveillance monitoring software.

www.rangerfp7.com
Together, we aim to deliver a system capable of diagnosing influenza accurately and quickly, enabling healthcare professionals and outbreak specialists to make timely and informed decisions. The system will be fully automated and capable of providing a laboratory standard result from a raw sample. It will be validated for use in both developed and developing territories, with evaluations led by the world-renowned clinical investigators in Thailand and the UK.

Expected results

Prototype instruments, cartridges and assays validated for use as human in vitro diagnostics for influenza diagnosis and surveillance.

Potential applications

- rapid diagnosis of influenza (both seasonal and pandemic) in the POC environment, enabling faster and better informed medical care to reduce suffering and save lives;
- coordinated surveillance of influenza incidents and outbreaks, enabling rapid deployment of resources to control disease spread and treat patients.

Key words

influenza, diagnostics, PCR, molecular, point of care, surveillance, rapid, automated, real-time
PORTABLE AUTOMATED TEST FOR FAST DETECTION AND SURVEILLANCE OF INFLUENZA

Summary

PORTFASTFLU’s objective is to develop and validate a rapid diagnostic test for influenza that will be used as point-of-care (POC) systems in developed and developing countries.

Problem

Experts and international bodies agree that the rapid detection of influenza is vital in combating this major threat to human health. Nucleic acid analysis is the most appropriate assay scheme for both early detection and late surveillance of influenza, and is routinely used by the World Health Organization (WHO) and the World Organisation for Animal Health (OIE) virology reference laboratories.

Aim

PORTFASTFLU’s consortium aims at developing and validating a POC instrument that will integrate sample preparation, nucleic acid amplification, microarray hybridisation and fluorescent readout in a single system. Furthermore, the project also aims at realising this goal in a format that requires little supervision and is integrated in a portable compact monolithic system for deployment in the field.

The diagnostic test will enable the rapid detection of influenza infection in a fast and specific way (typing and sub-typing) using a monolithic disposable cartridge placed in a compact, portable analytical instrument.

Influenza viruses that are adapted to humans and have caused pandemic or epidemic waves so far are characterised as H1, H2 or H3 sub-types in combination with N1 or N2 sub-types. These viruses are the major targets for the detection tool to be developed under this application. Indeed, they cause several thousands of deaths each year in Europe and there is a real need for a test providing fast identification of the causative agent and, thus, contributing to the improvement of treatment and surveillance.

However, the avian influenza (AI) virus can also be transmitted to humans and may cause severe disease. Therefore, the PORTFASTFLU consortium has decided to also include the H5, H7 and H9 avian sub-types in the new tool to be developed. For the currently circulating strain H5N1 lineages of virus, it is clear that a miniature biosensor allowing rapid detection of the virus would help contain the infection and combat the threat of disease at a very early stage. For persons having flu-like symptoms who are admitted to hospitals in regions with H5N1 case epidemics in poultry or wild birds, it is vitally important to make a rapid POC diagnosis in order to implement recommended control measures as fast as possible.

The technology that PORTFASTFLU intends to assemble in a single machine would provide essentially the same information as at WHO laboratories within 30 minutes to 1 hour after the start of sample analysis (e.g. throat or oro-nasal swabs). Furthermore, the system is designed so that it is easy to use, does not require highly qualified personnel, is robust and has an inbuilt GPS system and an online data transmission system.

Expected results

The processes of miniaturisation proposed here plus its paralleling, micro-integration and mass production have the potential of implementing major cost reductions that will broaden the use of these types of devices and the combined portable reader, and making these natural parts of the diagnostic system suitable for potential use in health care, but also in food chain control. Their main impact can be identified as cost reduction, reduced analysis time and increased throughput.
The successful development of a full diagnostic kit, component and system as described in this project will impact the low-cost diagnostic test market place and create a standard for future similar tests, imposing a major reference in the field. Several items are particularly important technologically, even if considered separately from the others: the diagnostic influenza kit (not yet demonstrated); the sample preparation, which can be applied in a number of other major needs; the compact, fast and non-supervised hybridisation and readout system with communication and GPS capacities.

Potential applications

The PORTFASTFLU proposed technology will bring about three main improvements:

- It will allow detection and identification of influenza on-site, removing the need for transportation of infected material to a reference laboratory;
- It will decrease the time required to detect and identify influenza viruses on-site from three to five days to within a few hours, nominally less than an hour;
- It will decrease the time required to implement disease control procedures, saving money and lives.

Key words

infectious diseases, viruses, diagnosis, diagnostic tests, emerging technologies, biochips, microarrays, lab on chip

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DEVELOPMENT AND VALIDATION OF A MICROARRAY BASED AUTOMATED DIAGNOSTIC SYSTEM FOR THE DETECTION OF INFLUENZA VIRUS TYPES AND SUB-TYPES AT POINT-OF-CARE

www.fluarray.eu

Summary

Influenza is an extremely contagious infection that is caused by distinct virus types and sub-types. Early diagnosis is crucial for disease treatment and control as it reduces the inappropriate use of antibiotics and provides the indication for antiviral therapy. Rapid diagnosis is also a key component of surveillance activity. This requires the ability to detect and accurately diagnose infection at or close to the source/outbreak with minimum delay, a tactic consistent with the global experience during the SARS epidemic in 2003. This experience underlines the need for specific, sensitive point-of-care (POC) testing capable of discriminating between influenza sub-types. None of the available influenza diagnostic assays combines a POC format with the multiplex capability to identify a large repertoire of human and animal viruses. This project exploits the knowledge and expertise of the partners to convert microarray assays, which have a powerful multiplex capability but are laborious, complex and expensive to perform, into a simple, robust and affordable, automated POC system for the diagnosis of influenza. This project will provide small laboratories, health offices, veterinary clinics and outposts (airports) with the diagnostic capability of major research institutions and reference centres, thus providing better care for patients and, most importantly, facilitating the implementation of surveillance activities and guiding response measures that are being built to face a possible influenza pandemic caused by a highly virulent virus.

Problem

Early diagnosis of influenza is increasingly recognised as a crucial instrument for disease treatment and control of transmission. Correct diagnosis can reduce the inappropriate use of antibiotics and provide the indication for using antiviral therapy that, if given within the first days of infection, can significantly reduce both morbidity and mortality, particularly in susceptible individuals. Rapid diagnosis is also a key component of disease surveillance activity carried out by health authorities to monitor the presence of influenza viruses in the community. Diagnosis based on clinical examination is neither obvious nor rapid because the initial symptoms of influenza, such as high fever, headache, generalised malaise and respiratory symptoms, are similar to those caused by other infectious agents. Furthermore, clinical diagnosis is also inadequate to implement surveillance measures as these require the identification of the predominant circulating virus types, sub-types and possibly strains. There is an urgent need to develop technically innovative solutions for portable, robust, discriminatory devices which allow type and sub-type influenza virus detection in low-skill settings with little or no laboratory infrastructure.

Aim

The aim is to develop an automated portable microarray assay system to distinguish influenza virus sub-types at POC.

Expected results

Define immunoassay, device and instrument specification

The objective is to set the specifications of a rapid POC influenza multiparametric diagnostic system. International experts, veterinarians and clinicians as well as representatives of international agencies will be consulted and asked to provide feedback on the different components of the diagnostic system, the assay, the device and the instrument.
POC system performance

We have planned to carry out a clinical validation of the integrated POC system utilising both reference and clinical samples in comparison with available diagnostic procedures.

Potential applications

The commercial opportunities arising from the exploitation of the technology are potentially very large with the current acute respiratory diagnostics market standing at USD 400 million per annum and exhibiting 10–20% annual growth. How the market will respond to the proposed POC system can only be gauged when such products are launched; however, several critical issues can be identified, such as the impact of multiplex testing on other diagnostic markets as well as political, economic and regulatory pressures to control spending in the current healthcare industry.

Instrument development and optimisation

The aim is to develop, from the stage of proof-of-principle/prototype, a small, simple, robust and easy to operate microarray reading/processing instrument that can be utilised in small laboratories (POC) and, if necessary, in non-medical environments such as airports.
CHAPTER 3
PATHOGENESIS, BIOLOGY AND DRUG DISCOVERY
ANTICIPATING THE GLOBAL ONSET OF NOVEL EPIDEMICS

www.antigonefp7.eu

Summary

The project aims to identify the key factors that render zoonotic pathogens prone to cross the species barrier and gain efficient transmissibility among humans. ANTIGONE will use a series of primary ‘factor finding’ research studies and interlinked Dahlem studies, using a selected set of model pathogens such as Influenza virus A. This will feed into translational risk assessment and modelling studies to improve risk assessment, prevention and intervention of human pandemics emerging from zoonotic pathogens. There will also be a web-based pathogen information sharing platform.

Problem

In recent years, an increased number of zoonotic viruses and bacteria have crossed the species barrier to humans and caused or threatened to cause human epidemics or pandemics. Due to our inability to predict the emergence of these pathogens, it is difficult to take appropriate and timely preventive measures. It is known that zoonotic pathogens need to cross barriers at the animal–human interface, at the pathogen–host interface within humans, and at the human–human interface before they can cause a human pandemic. However, it is poorly understood which pathogen, host, arthropod vector and environmental factors allow zoonotic pathogens to successfully cross these barriers.

Aim

- to identify and understand the key factors that render zoonotic viruses and bacteria with human pandemic potential prone to cross the species barriers, adapt to the human host and further gain human-to-human transmissibility;
- to translate our increased understanding of key factors in the chain of emergence to risk assessment, and options for prevention and intervention of human pandemics emerging from zoonotic pathogens;
- to develop and implement a One Health training programme, combining human and veterinary medical expertise with that from other relevant disciplines, in order to equip the future generation of scientists with the necessary knowledge to deal with emerging zoonotic infectious diseases.

Expected results

ANTIGONE will fill in critical gaps in our knowledge of the process of pathogen emergence. These studies will focus on a selected set of model pathogens. In the Dahlem studies, the key factors that render zoonotic pathogens prone to crossing the species barrier will be identified. This combination of studies provides the necessary breadth and depth for an optimal improvement of our understanding of zoonotic pathogen emergence. For Influenza A viruses, the project will identify the key factors at the interspecies barrier determining exposure to humans through poultry and pigs. At the intrahuman barrier, key processes of adaptation of zoonotic influenza viruses to replication in humans will be identified. In addition, changes in receptor tropism of zoonotic influenza viruses, caused as a side effect of naturally-driven antigenic evolution, or antigenic evolution caused by vaccination of the animal reservoir, will be identified. Whether the escape of high pathogenic avian influenza virus H5N1 (and other zoonotic influenza viruses) from specific herd immunity can change host specificity will also be determined. At the interhuman barrier, the potential of aerosol transmission of zoonotic influenza viruses will be evaluated. Furthermore, results of the experimental work to be
performed on influenza viruses will be used to improve and refine the cross-scale mathematical model of influenza virus infection in humans.

The results of the project will not only improve our understanding of the successive steps that a viral or bacterial pathogen needs to take to cross from its animal reservoir to humans and ultimately to become pandemic, but they will also lead the way to improve our ability to model and predict potential human pandemics of zoonotic origin and to develop effective and timely preventive measures.

Potential applications

- Identification and understanding the principal factors that render zoonotic viruses and bacteria with human pandemic potential prone to cross the species barriers and further gain human-to-human transmissibility;

- Development of screening methods to predict the zoonotic potential and the pathogenicity of animal pathogens for humans, and for parameterization and improving modelling techniques,
Summary

Zoonotic RNA viruses, such as influenza virus, have the capacity to emerge as major agents of human disease. Although current intervention strategies have shown success, rapid and effective solutions are needed to reduce the impact of emerging strains. PREDEMICS will study selected zoonotic viruses with epidemic potential in Europe: influenza virus, hepatitis E virus, Japanese encephalitis virus and related flaviviruses, and lyssaviruses. These diverse emerging viruses arise from the main reservoir hosts and vectors, and exhibit three major routes of transmission: respiratory, faecal-oral or vector-borne. Inter-disciplinary studies on influenza viruses will generate valuable data on the factors that determine crossing the species barrier from wild bird reservoirs to domestic animals and to humans as well as the ability to spread between humans and acquire pandemic potential. PREDEMICS will unravel the biological interactions between viruses and recipient hosts that drive viral adaptation and/or pathogenicity.

Problem

Influenza viruses are the paradigm of zoonotic pathogens leading to successful host switching and potential pandemics. Thus, there is a need to understand the factors involved in influenza virus emergence from wild aquatic reservoirs through domestic poultry and pigs to introduction and subsequent adaptation to humans.

Aim

The aim of the project is, for some of the most important zoonotic RNA viruses, including influenza, to unravel the complex interactions between the processes involved in emergence: exposure and introduction into a new host species, infection causing local chains of transmission, spread in human populations, and post-transfer adaptation leading to widespread transmission and pandemics.

Expected results

Ecological and environmental studies will provide an estimation of the biodiversity of influenza viruses and hosts and insights into environmental disturbances that affect virus dynamics. PREDEMICS will analyse the genetic diversity and evolutionary dynamics of influenza viruses within its various hosts. It will also identify viral genetic determinants involved in cross-species transmission and adaptation to humans from the wild bird reservoir to domestic poultry or pigs. Furthermore, the influence of viral and cellular factors on innate and adaptive immune responses and how these responses drive virus evolution will also be explored. Incorporation of the results into a data-sharing platform, such as GISAID, will provide a framework and new modelling tools for predicting, intervening in influenza epidemics and augmenting contingency planning. PREDEMICS will promote dissemination of knowledge through the Isabel Minguez-Tudela training programme, development of e-learning devices and workshops and symposia targeting scientists and other stakeholders involved in public health issues.

Potential applications

PREDEMICS will provide a platform for global analysis of the factors involved in crossing the species barrier and of the causal mechanisms leading to the emergence, maintenance, epidemic and potentially pandemic expansion of influenza viruses in humans. Advanced knowledge of the viral reproductive and dissemination processes and vice versa and of virus-host interactions will provide new potential approaches for antiviral interventions and vaccine
emerging disease, influenza, epidemics, pandemics, zoonotic virus, cross-species transmission, evolution, modelling, one health, information-sharing platform, training, preparedness, control measures.
Summary

The ANTIFLU project aims towards the development of innovative drugs against influenza virus infections based on a novel concept that precludes the development of viral resistance and ensures efficacy against upcoming pandemic influenza strains. While traditional anti-influenza treatments generally target viral factors, ANTIFLU aims to develop drugs that interfere with host cell factors. This approach is thought to be advantageous regarding: (i) avoidance of viral escape mutants and (ii) broad coverage against unprecedented viral variants.

Problem

Despite vaccination and currently available antiviral drugs, influenza virus infections still have a huge impact on human health worldwide. In light of the risk posed by seasonal infections and also the recurring threat of influenza virus pandemics, there is an acute need to develop effective and lasting drugs.

The current panel of preventive and therapeutic measures against influenza virus infections rests on: (i) active vaccination and (ii) the use of conventional antiviral drugs. Both strategies have their intrinsic limitations owing to the high variability of influenza viruses.

Aim

Viral replication uses the machinery and metabolism of host cells and, thus, depends on multiple host cell factors. While traditional anti-influenza treatments generally target viral components, ANTIFLU focuses on host cell factors to interfere with virus replication.

The concept of drugs targeting human factors, established in the treatment of other diseases, has not yet been fully explored for treatment of viral infections, despite bearing compelling advantages over conventional antiviral therapies: (i) avoidance of viral escape mutants and (ii) broad coverage against unprecedented viral variants. This promising, novel approach, which inhibits factors temporarily dispensable for the host but essential for virus replication, will open the route to alternative treatment options for combating influenza with the potential to complement currently available strategies and overcome their limitations, such as resistance and viral variability.

ANTIFLU will build upon an existing repertoire of indirect antiviral targets resulting from previous research work carried out by members of the consortium. The interdisciplinary consortium will identify and select validated host cell targets, druggable lead compounds (kinase and non-kinase inhibitors) against them, refine them into clinically applicable drugs, and perform preclinical assessments. In addition, crucial host cell functions not targeted by conventional drugs will be explored using therapeutic RNAi. As an extension of the EU-funded studies, the consortium will subsequently pursue, using private funds, the implementation of phase I and II clinical trials.

Expected results

After five years, ANTIFLU aims to deliver the following main results:

- proof-of-principle that influenza infection can be efficiently treated by targeting human determinants at either protein or RNA level using small molecule or siRNA inhibitors, respectively;
- a novel therapeutic strategy to combat influenza virus infections by more reliable (avoidance of resistance) and more versatile (broad intra-species spectrum) means;
Key words

influenza, virus infection, host-targeted therapy, small molecule inhibitor, drug design, therapeutic RNAi

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Potential applications

The innovative drugs developed by ANTIFLU will have great therapeutic potential against influenza virus infections. This novel generation of drugs promises to preclude the development of viral resistance and to ensure efficacy against upcoming pandemic influenza strains. Moreover, this novel antiviral therapeutic strategy also generates ample new perspectives for the treatment of acute viral infections other than influenza.
Summary

The 2009 H1N1 pandemic and the ongoing threat of highly pathogenic H5N1 influenza strains have focused attention worldwide on the urgent need for new, effective anti-influenza drug options, particularly when the public is not protected by natural immunity or vaccination. The need is pressing since several recent circulating strains have been resistant to currently available anti-influenza drugs. In the FLUPHARM project, we will exploit recent advances in the detailed mechanistic understanding of the structure and function of the viral polymerase and the replication machine of the virus to develop new drug candidates that inhibit viral replication in infected cells. The polymerase is an excellent drug target as it is highly conserved in all influenza A strains, whether of avian, swine or human origin. The project consortium includes 14 academic and SME partners from seven European countries chosen for their expertise and complementarity. The focused drug design programme will start with already existing patented small molecule hits against two different polymerase active site targets and use structure-based medicinal chemistry expertise to arrive at optimised leads to enter preclinical studies. In parallel, a world-leading network of European academic laboratories will continue fundamental research on influenza polymerase atomic structure, cellular function and role in inter-species transmission. This is not only valuable in its own right, to improve understanding of influenza biology, but will also feed back into the drug design programme with novel assays for polymerase inhibitors, improved understanding of how the inhibitors work in the cellular context and potential resistance mechanisms, as well as providing new targets for future anti-influenza drug design. If successful, the FLUPHARM project will provide new therapeutic opportunities to treat both seasonal and pandemic flu, and, thus, could have an enormous impact on public health as well as on the competitiveness of the European pharmaceutical sector.

Problem

In recent years, the serious threat posed by the influenza virus to worldwide public health has been highlighted by, firstly, the ongoing low level transmission to humans of the highly pathogenic avian H5N1 strain (63 % mortality in infected humans) and secondly, of the unexpected emergence in 2009 of a novel pandemic strain A/H1N1 that rapidly spread around the entire world. While the impact of the 2009 pandemic was fortunately milder than foreseen, under less fortunate circumstances (e.g. mutation to a more virulent form, resistance to Tamiflu), the delay in generating and deploying a vaccine could have been catastrophically costly in terms of human lives and societal disruption. It is now widely acknowledged that to bridge the period before a new vaccine becomes available and to treat severe cases, as well as to counter the problem of viral resistance, a wider choice of anti-influenza drugs is required.

Aim

The primary aim of FLUPHARM is to develop novel inhibitors targeting the influenza viral polymerase and advance a lead candidate into clinical development. In particular, we will target the unique cap-snatching mechanism of transcription of the polymerase, for which two specific active sites in two discrete domains exist, the cap-binding domain and the endonuclease domain. To this end, we have created a Europe-wide consortium, with both academic and SME partners, combining all the expertise required for bringing
Potential applications

New anti-influenza drug options for advanced clinical development and new tools, assays and diagnostics for influenza academic and medical research.

Key words
influenza virus, polymerase, structure-based drug design

this challenging project to fruition. To achieve the objective, three integrated RTD programmes will be pursued:

- a comprehensive medicinal chem- istry programme;

- a programme to determine the in vitro and in vivo efficacy of a selected set of promising compounds;

- a programme to pursue preclinical and clinical development of a selected drug candidate.

Expected results

FLUPHARM aims to complete a phase 1a clinical trial for at least one lead anti-polymerase compound. Since neither a pandemic nor seasonal influenza adhere to national borders and readily spread to the most remote human habitats, the envisaged novel therapeutics will, without doubt, significantly contribute to the ability of mankind to combat the unpredictability of influenza viruses and their mutations, and benefit universal health and well-being.
DEVELOPMENT OF NOVEL ANTIVIRAL DRUGS AGAINST INFLUENZA

www.flucure.se

Summary

The FLUCURE project aims to develop an innovative, first-in-class therapeutic against influenza targeting the replication core of the virion which is a major contributor to viral virulence. The high level of conservation combined with slow mutation rates of the target region should result in therapeutics with broad viral strain specificity associated with a reduced risk for developing resistance. FLUCURE builds on two successful EU-FP7 drug discovery projects, FLUINHIBIT and FLUDRUGSTRATEGY, both targeting specific but different protein-protein interactions with small molecule inhibitors. A consortium of nine partners with the required complementary skills will develop the lead candidates from these two projects synergistically through lead optimization and preclinical development phases, with the final objective of delivering one or more drug candidates suitable for entering clinical development.

Problem

Influenza viruses cause a highly contagious respiratory disease in both humans and animals. Typically, influenza spreads worldwide in seasonal epidemics, resulting in an estimated 3 to 5 million cases of severe illness and 250 000 to 500 000 deaths annually. In addition to these seasonal epidemics, there have been several pandemics since the early 1900s, where highly virulent strains emerged, the most devastating being the ‘Spanish Flu’ of 1918, which caused 20–40 million deaths globally. Vaccination is currently the primary means of controlling the spread of influenza virus infections but due to the virus’s notorious ability to mutate, new vaccines must be developed each year. There are a few antiviral drugs that are currently on the market; however, their therapeutic potential is restricted through the rapid appearance of drug-resistant viruses during treatment. Thus, the need for novel effective drugs against influenza is evident.
**Acronym:** FLUCURE  
**Grant agreement number:** HEALTH-F3-2010-259972  
**EC contribution:** EUR 5 982 600  
**Duration:** 48 months  
**Starting date:** 1 October 2010  
**Funding scheme:** Collaborative Project  

**Aim**

We aim to develop a novel broad-spectrum antiviral therapeutic against the influenza virus that is less prone to development of resistance.

**Expected results**

We aim to develop an antiviral drug candidate with proven efficacy against the influenza virus that has successfully undergone preclinical testing phases, and is ready to enter a phase 1 clinical trial.

**Potential applications**

Treatment of influenza virus infection

**Key word**

influenza
Chapter 3 - Pathogenesis, Biology and Drug Discovery

**Aim**

We aim at gaining new insights into the role of pigs in overall influenza ecology, with particular reference to the generation of human pandemic viruses. In order to allow us to more accurately predict, respond to and control such events, in depth research on the pathogenesis and the transmission of influenza viruses between pigs and from pigs to other relevant species is essential; in particular, improving our knowledge on the gene constellation and genetic interactions that are necessary to generate pandemic viruses in combination with an improved understanding of host-dependent variables such as receptor distribution and immune response. Gaining insight into the characteristics of the pathogen and combining this with the host component will be the main goal of our consortium. Combined with improved surveillance for influenza in animals, effective vaccines and antiviral drugs, this knowledge will be critical to the control of future influenza pandemics.

**Expected results**

The use of state-of-the-art technologies will allow us to develop advanced and innovative knowledge on (i) virus-
Chapter 3 - Pathogenesis, Biology and Drug Discovery

The primary goal of the FLUPIG project is to study the effect of certain mutations on pathogenesis and transmission of influenza virus. However, certain mutants may turn out to be potential vaccine candidates, which could, after further study, be exploited by the commercial sector as swine or human vaccine strains.

Key words
pig, influenza, pathogenesis, transmission, cross protection, pandemic, H1N1, genetic adaptation

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Potential applications
Various approaches will be used to design and test experimental live-attenuated influenza virus and/or multivalent PrV/influenza vaccines. The results of these studies will allow us to conclude on a rational vaccine design, based on identified targets for the induction of protective immunity. Furthermore, a large collection of genetically modified influenza virus mutants will be generated throughout the FLUPIG project.
Summary

Despite widespread immunisation, influenza kills thousands of people, and costs the USA, Europe and Asia enormous amounts of money in terms of healthcare expenses and productivity losses. Small-molecule antiviral agents represent a novel opportunity for effective prevention and therapy for flu. Inhibitors of neuraminidase (NA), an essential enzyme for viral replication in all three classes of influenza viruses, have recently been found. Two of these inhibitors have reached the market, namely Zanamivir and Oseltamivir phosphate. The recent health concerns related to avian flu have increased the demand for stockpiles of NA inhibitors, both as a frontline therapy against a possible flu pandemic and as a preventive agent. Natural sources of Shikimic acid are scarce and increasing demand has put pressure on developing new routes that do not involve complex natural products. There is a need to simplify the synthetic processes and make them cheaper in order to find new drug candidates, cut drug costs and improve availability as well as efficiency, and new chemical syntheses are necessary. The project proposes a new domino reaction based on an organocatalytic approach to the synthesis of new Tamiflu derivatives.

The chemistry involved in this project is easy to perform and can be well adapted to the industrial context. Moreover, new chemical structures will be prepared and evaluated as potential drugs against virulent and mutated flu viruses.

Problem

Influenza is a leading cause of morbidity, mortality and economic loss. The influenza pandemic in 1918 (the Spanish flu) is estimated to have killed more than 30 million people worldwide. The avian H5N1 influenza, which originated in Hong Kong in 1997, has already infected over 100 humans and shows a lethality of over 50%. There is concern that a mutated form of this virus may lead to a new pandemic. Prevention and treatment of influenza rely on inactivated vaccines and antiviral agents. Although vaccines are considered to be the best option for controlling influenza, at least six months are needed to produce vaccines based on the surface glycoproteins of an epidemic virus strain. The efficacy of antiviral drugs such as Amantadine and Rimantadine is limited due to their inapplicability to influenza B viruses and to the rapid emergence and transmission of drug-resistant variants. Synthesis of NA inhibitors, such as Oseltamivir, was a significant milestone in antiviral influenza therapy. The active centre among all influenza viruses makes it the potential target of Oseltamivir that would offer protection against any influenza virus that might emerge in humans. However, Oseltamivir supply is a problem. The relative production processes are expensive, complicated and not environmentally friendly. Although catalysis can sometimes solve difficult synthetic problems, Oseltamivir derivatives cannot be prepared in a single metal catalytic reaction. In the case of a pandemic episode or dangerous mutation, Europe, China and the entire World will face the problem of preparing NA inhibitors in a relatively short period of time.

Aim

The aim of CATAFLU.OR is to achieve new, innovative, simple and straightforward synthetic routes for enhancing the availability and supply of NA inhibitors. The project addresses this target through the objective of preparing difficult and highly challenging NA inhibitors. Five main tasks characterise the work plan of the CATAFLU.OR project: 1) Synthesis of modified catalysts for an organocatalytic domino reaction. Scale up of the reaction. Test of the new catalyst in the established domino
reactions aiming at the production of new cyclohexene derivatives. The manipulation of the derivatives will be used for practical and rapid access to newly designed NA drug candidates. 2) Use of the catalysts in the design of new organocatalytic domino reactions. Synthesis of cyclic compounds via domino reactions. 3) Preparation of a new NA inhibitor through the use of organocatalytic domino reactions. 4) Testing the new NA inhibitor with cell lines, animals and viruses. 5) Testing the newly prepared inhibitor against influenza viruses in silico, in vitro and in vivo.

Expected results

- propose new NA inhibitors for screening against flu viruses;
- define a new strategy for organocatalytic, highly economical domino reactions;
- decrease costs and minimise problems related to the supply of Oseltamivir and Oseltamivir derivatives;
- contribute to solving the problem of avian flu where it has developed (Hong Kong and China).

Potential applications

The action may have a profound long-term effect in contributing to solving problems related to the supply of Oseltamivir derivatives experienced by European industries and European countries during the crisis of the Asian flu.

Expected results

- propose new NA inhibitors for screening against flu viruses;
- define a new strategy for organocatalytic, highly economical domino reactions;
- decrease costs and minimise problems related to the supply of Oseltamivir and Oseltamivir derivatives;
- contribute to solving the problem of avian flu where it has developed (Hong Kong and China).

Key words

influenza, tamiflu, neuraminidase inhibitors, influenza pandemic, shikimic acid, oseltamivir phosphate, new drugs, organocatalysis
**Summary**

FLUINHIBIT aims at discovering small molecule inhibitors of the influenza virus A subunit interaction between PA and PB1, which is crucial for viral replication.

Starting from an inhibitory peptide, and supported by characterisation of the PB1-binding domain of PA, molecular modelling will be employed to rationally design and synthesise peptidomimetics via traditional medicinal chemistry and a novel fragment-based library synthesis approach. In parallel, a high-throughput assay will be developed to screen large compound collections and unique in-house small molecule libraries. The resulting hits will be profiled in cell-based assays and lead candidates with antiviral activity will be identified for preclinical development.

**Problem**

Influenza is a highly contagious, acute viral infection, which causes annual epidemics as well as recurring devastating pandemics.

Due to its ability to rapidly mutate its genome, influenza A virus is capable of causing worldwide pandemics. Over the past century, mankind has relied mainly on vaccination in the fight against viral pathogens. As a consequence, very few antiviral drugs are available to date. Of the two classes of drugs specific for influenza, the oldest and most affordable drugs face several problems, e.g. development of resistance, safety in pregnant women, reduced dose in elderly patients and the need of close clinical monitoring in certain patient groups. The second and newer class, the neuraminidase (NA) inhibitors, have a better safety profile but their price and limited supply are major constraints for worldwide use. In addition, the development of resistance to NA inhibitors has been reported. Nonetheless, antiviral drugs have important roles to play at the start and in the course of a pandemic.

In the absence of vaccines during the first wave of infections, antivirals will be the only medical intervention for providing both protection against disease and therapeutic benefit in diseased persons. Thus, the development of novel, more effective therapeutic approaches to inhibit the replication of the influenza virus is of utmost importance and urgency.

**Aim**

FLUINHIBIT’s major objective is the discovery of small molecule inhibitors of influenza polymerase subunit interactions as novel antiviral drug candidates.

**Expected results**

FLUINHIBIT will identify inhibitors of the protein-protein interaction between PB1 and PA. Since the N-terminal PA-interaction domain of PB1 is highly conserved, molecules able to block the interaction can be expected to inhibit most, if not all, Influenza A strains. The most promising hits will then be optimised and processed for preclinical development.

**Potential applications**

The viral trimeric polymerase complex is an attractive and novel target for inhibition of viral replication. Due to the high level of conservation among different virus strains, subunit inhibitor compounds will bear a lower risk of resistance development. This may be a big advantage with a rapidly mutating virus.
FLUINHIBIT aims to better prepare for emerging epidemics by providing lead candidates of a new target. This may help to protect the public’s health in the event of an influenza pandemic. Also, the provision of novel lead compounds will improve competitiveness in the European Pharmaceutical and Biotech Industry.

**Key words**

influenza virus polymerase, novel target, subunit interaction inhibitor, high-throughput screening
COMBATING INFLUENZA USING A NOVEL DRUG STRATEGY

Summary

During the last century, three influenza pandemics occurred and the threat of a new influenza pandemic has become imminent. A new pandemic would indicate that the influenza virus had undergone major changes such as antigenic reassortment. Current treatments are unlikely to be effective, and new vaccines and antiviral agents will be essential to combat such an outbreak.

The FluDrugStrategy approach is to develop a new class of antiviral drug candidates. The target protein is highly conserved among human strains of the virus as well as strains infecting other species, including birds. This would indicate that its rate of mutation is considerably lower than those of the surface proteins (i.e. haemagglutinin, neuraminidase and the M2 ion channel) upon which the currently available antiviral drugs act. Another feature of the target that makes it very interesting and promising in this context is its involvement in a variety of important viral and cellular processes. The FluDrugStrategy project will design and synthesise molecules that either inhibit or, conversely, stabilise protein-protein interactions, so that either the formation of virus particles is prevented or release of the viral genetic material does not occur.

The project combines knowledge-based design and synthesis of compounds with unique patented image analysis and mathematical algorithm software to find and develop these new types of potential antiviral molecules. The methodology allows for rapid discovery of lead molecules. Key molecules with optimal binding kinetics to the target protein will be designed and synthesised, then analysed and tested in two separate experimental systems for their effect upon the virus structure and maturation process.

Problem

Vaccination is the main clinical approach to protecting against influenza infection. However, the epitopes on the surface of the influenza virus change rapidly, which means that a new vaccine must be developed each year. Thus, we are always one year behind, employing the vaccines raised against the previous season’s prevalent viral strains and hoping that this year’s prevalent strains are not too different. This approach means that the efficacy of current vaccines fluctuates greatly. For example, in 1997, this efficacy was only 50 %, whereas in 1998 it was 86 %. There are also two classes of antiviral medication that can be effective in the prophylaxis and treatment of influenza. These are inhibitors of neuraminidase and of M2 ion channels. However, the influenza virus can develop resistance to these standard antiviral drugs, and during the 2005/06 influenza season, the USA CDC recommended against treatment with M2 ion channel inhibitors.

This project instead focuses on antivirals which inhibit virus maturation. This is a novel class of antivirals and is of interest for three important reasons: (1) The targets for this class of antivirals are mainly protein-protein contacts between the virus structural proteins, contacts that are crucial for correct assembly of the virus into infectious virions; (2) The target protein is highly conserved among different viruses within the same family which could result in broad range antivirals; and (3) Development of drug resistance to this type of antiviral is less likely since this would affect protein-protein interactions that are critical for overall virus particle integrity and survival.

Aim

The FluDrugStrategy project aims to
target protein of the Influenza A virus as well as molecular models for the protein target and in silico screening, and will determine the pharmacologically relevant properties of the lead compounds.

The work will also optimise the algorithm for detection and characterisation of influenza virions in electron micrographs.

### Potential applications

The FluDrugStrategy consortium proposes a novel class of antivirals to produce a novel class of maturation-inhibiting antiviral drug candidates against the Influenza A virus. We have chosen a systematic approach that is rapid and efficient, and offers unique opportunities to define lead compounds against novel targets for antiviral therapy. The project will bring together experts from highly diverse fields, starting from identification of small organic compounds that interact with virus proteins; to the design and synthesis of these compounds and derivatives thereof; to the observation and analysis of the effects of these compounds on particle formation; to testing of their efficacy in combating the influenza virus, employing unique patented technology; and, finally, to the production of novel antiviral drug candidates.

### Expected results

This project is expected to deliver maturation-inhibiting lead compounds against the Influenza A virus. This will include the identification of substances that inhibit maturation and/or alter the structure of the influenza virus, as well as a description of the mechanisms of action of these compounds.

The work will develop methods to screen fragments directed against the influenza virus. Upon successful completion of the project, we hope to have a broad-range antiviral lead compound that is insensitive to virus mutation. Such an antiviral would have great value considering the evolution of the influenza virus and the threat it poses for initiating a human pandemic.

### Key words

drug discovery, maturation inhibitors, influenza A virus, image analysis

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EFFECT OF NATURAL VIRAL RNA SEQUENCE VARIATION ON INFLUENZA VIRUS RNA FUNCTION

Summary

Influenza A virus has an amazing ability to rapidly change its properties. We believe that the pathogenic properties of an influenza virus could also be determined by differences in influenza virus RNA sequence that do not affect the protein sequence of the viral genome. In other words, sequences that affect structure and/or function of the viral RNA, could themselves contribute to the pathogenic properties of the influenza A virus, as well as its ability to adapt to a new host. All RNAs in a cell are associated with proteins and RNAs are dependent on these interactions to function efficiently. Interactions of RNA with proteins depend on the RNA sequence and secondary structure. The exact RNA sequence is, therefore, of paramount importance since it affects secondary structure and function and utilisation efficiencies of the viral RNAs. RNA sequence has a direct effect on mRNA splicing, mRNA stability and translation. The exact sequence of the influenza virus RNA should, therefore, affect the replication efficiency of each virus strain. It is reasonable to speculate that RNA sequence variation itself could affect virus pathogenic properties.

Problem

Can pathogenic properties of various influenza viruses be determined by differences in the influenza virus RNA genome that do not affect viral protein sequences?

Aim

The immediate goal of this short, two-year project is to investigate whether naturally-occurring RNA sequence variations in various influenza virus isolates with different pathogenic properties affect influenza virus RNA structure and function. The long-term goal of this project, which extends beyond this two-year period, is to determine whether the influenza virus RNA sequence itself, independently of effects on viral protein sequence, affects viral pathogenesis and tropism.

Expected results

Identification of naturally-occurring influenza virus sequence variations that affect processing efficiency and translation of influenza virus RNAs.

Potential applications

Novel markers of pathogenicity identified in this project may aid in early detection of emerging, highly pathogenic influenza viruses.
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Key words
influenza, Spanish flu, bird flu, pathogenic, RNA, secondary structure, microRNA, splicing, translation, NMR

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CHAPTER 4
PUBLIC HEALTH ASPECTS, COMMUNICATION AND TRAINING
EFFECTIVE COMMUNICATION IN OUTBREAK MANAGEMENT: DEVELOPMENT OF AN EVIDENCE-BASED TOOL FOR EUROPE

www.ecomeu.info

Problem

Although scientific knowledge to respond to outbreaks has increased, deficiencies remain in the ability of health authorities to communicate the need for large-scale measures, such as vaccination and antiviral therapy, and increase its acceptance. For effective behavioural and communication strategies, integration is needed of social, behavioural, communication and media sciences. We bring together these disciplines to go beyond current knowledge.

Aim

The overall aim of our project is to develop an evidence-based behavioural and communication package for health professionals and agencies throughout Europe to be used in the case of major outbreaks. This is achieved through a number of specific objectives to:

- assess the time-dependent influences of epidemiology and risk communication including media content on human behaviour during the A/H1N1 pandemic;
- analyse, using social marketing principles, vaccination behaviour, audience segmentation and vaccination service delivery;
- analyse knowledge, attitudes, risk perception, vaccination non-response and reasons for resistance during past epidemics;
- apply discrete choice experiments to determine acceptance of preventive measures in the case of epidemic outbreaks;
- integrate the key findings of the studies under the first three objectives to determine critical factors, groups and media to be addressed in the development of effective strategies;
- test behavioural interventions and communication strategies tailored to different target audiences;
- finalise and disseminate a package of evidence-based tools that can be tailored to individual European countries.

Expected results

There are four impacts that the research activities in this project aim to achieve:

- better communication preparedness for the next major epidemic outbreak;
- minimise deviations between perceived and intended messages during the full course of the pandemic;
- establish a means for dialogue between citizens, health care workers and policy makers at the national and supranational levels during future pandemics;
- provide tools to gain and strengthen citizens’ trust in national and EU institutions concerned with risk communication.
Potential applications

- guidance tool on crisis communication strategy;
- guidance tool on message strategy;
- guidance tool on online communication strategy;
- guidance tool on how to embed communication strategies in outbreak-response activities;
- guidance tool on behavioural intervention options using incentives/disincentives;
- demonstrator of the online rapid public-opinion surveillance tool;
- online report with the guidance tools in PDF format;
- demonstrator of the online personal risk assessment tool.

Key words

infectious diseases, pandemic, behavioural change, communication strategy, media, vaccination

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Funding scheme: Collaborative Project
Summary

TELL ME aims to provide evidence and to develop models for improved risk communication during infectious disease crises. TELL ME combines public health, social sciences, behavioural sciences, political sciences, law, ethics, communication and media, in order to develop original communication strategies regarding complicated messages and advice based on uncertainties, also addressing vaccine-resistant groups.

Problem

There is little knowledge about how people are likely to react to a pandemic such as influenza. Moreover, communication strategies adopted during the 2009 H1N1 pandemic were largely unsatisfactory. We also lack effective social simulation models that allow an evaluation of communication strategies in advance.

Aim

TELL ME aims to:

- carry out a horizon investigation on population behaviour during infectious outbreaks;
- construct an evidence-based and field-tested communication package that would support the communication preparedness and efficacy during major epidemic outbreaks, minimising deviations between perceived and intended messages;
- create an agent-based simulation to represent a simplified model of the processes of information exchange and action in an epidemic.

Expected results

The main outcomes of TELL ME will be an integrated communication kit for outbreak communication and a specific simulation software. Users, notably primary care staff and health professionals, will be closely involved in the design of the model from the earliest stage, using the principles of the participatory approach.

Potential applications

TELL ME will provide policymakers, public health agencies and communicators with a new model of crisis communication, on the basis of which messages can be produced for various sub-populations in different countries. The model will offer guidelines for working with different sub-populations of health professionals, in order to recruit them as local opinion leaders for the messages of the government organisations. The project will specifically develop and test strategies to support vaccine uptake with a special focus on new communication strategies for health professionals and/or agencies to engage with vaccine-resistant groups. Health professionals and agencies will have a prototype for a new warning system that can be used to alert the public about the scope and severity of disease outbreaks, as well as test results concerning new messages and new media that can be used to shape public perception. This information will increase public understanding of risk conditions and enhance effective information dissemination by public health organisations.

Key words

public health communication, public health policy, epidemics, flu pandemics, vaccination strategies, social simulation, social web, new media, participatory exercise, civil rights, ethics
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Summary

The project aims to promote immunisation among health care workers (HCWs) in Europe. To enhance knowledge on HCW immunisation, HProImmune will review, summarise and disseminate existing information and best practices, as well as explore behaviours and barriers through qualitative analysis. This knowledge will be compiled in a comprehensive communication toolkit, which will be piloted, addressing the needs and perspectives of medical personnel in primary care as well as in a hospital setting. It will enable public health authorities and hospital administrators to plan and organise successful immunisation activities, thus contributing to the achievement of national strategic goals for increasing vaccination coverage, especially in the case of seasonal influenza.

Problem

Pathogens transmitted via blood or infectious droplets are known health and occupational risks for HCWs, many of whom have died while caring for patients. A fundamental ethical rule in health care is that sick persons must receive care. A number of new vaccines and updated immunisation recommendations have also been developed in the past few years.

Despite a relevant EU directive from 2000 dictating immunisation of employees against biological threats, which has already been transposed into national legislation, no significant increase in vaccination coverage has been recorded for HCWs. No uniform recommendation exists for the particular vaccinations needed for HCWs, who in turn do not seem to comply with existing guidance and recommendations for vaccination.

Aim

- to increase awareness about the most important vaccine preventable diseases which pose a particular risk to EU HCWs;
- to increase awareness about immunisations among HCWs through a database with vaccination-specific information from across the EU;
- to provide new knowledge about vaccination behaviours and barriers among HCWs;
- to identify best practices for the immunisation of health professionals;
- to provide new knowledge on how to communicate and promote immunisations among HCWs by piloting a purpose and tailor-made immunisation promotion toolkit;
- to increase awareness and promote HCW immunisations through a widely disseminated and pilot-tested HCW Immunization Promotion Toolkit consisting of recommendations, communication guidelines, tools and fact sheets.

Expected results

A comprehensive HCW Immunization Promotion Toolkit will be created which will help achieve higher vaccine coverage rates and improve the resilience and response capacity of the European health sector. By increasing HCWs’ awareness and providing them with appropriate training and knowledge, we would enable them to protect their health and act as a role model in their work place and community. The two-tiered toolkit will provide access to a database of relevant information from across the EU, including an approach for primary care practitioner, hospital personnel (doctors, nurses, auxil-
HCWs in the hospital setting who come into contact with vulnerable populations and whose vaccination status can impact their patients' outcome will be indirectly targeted through public health professionals and health care administrators who will be able to use the HProImmune products, in order to promote and organise vaccination programmes.

The project can be used by public health professionals (working at regional or national level) and health care administrators (working in hospitals or at national level) who are responsible for organising large scale immunisation campaigns for HCWs. The HCW Immunization Promotion Toolkit will also include information and tools to assist in organising such activities, registering vaccinated personnel and monitoring adverse effects.

Key words
- immunisations, healthcare workers, vaccine preventable diseases, communication tool, vaccination coverage
-...

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Summary

The project aims to redefine the main human pandemic scenarios at European level, describe and cluster possible response strategies, and assess these response strategies in the frame of multi-criteria and cost-effectiveness analyses, taking into account lessons from the 2009 pandemic situation in Europe. The integrated approach of decision-making proposed by the FLURESP consortium would constitute a first at European and global levels, and would support countries in selecting the most appropriate and efficient public response to various scenarios of a human pandemic.

Problem

The strain of swine flu from spring 2009 and winter 2009 and 2010 has recently confirmed the pandemic threat. Due to the low immunisation rate in Europe, it is expected that potential new waves of swine flu will occur in the near future; EU Member States should be prepared to respond appropriately to any potential pandemic scenarios or alert, taking into account lessons from 2009. The threat of a human influenza pandemic has prompted urgent development of national preparedness plans. Although preparation for surveillance, planning and coordination, and communication were good, maintenance of essential services, putting plans into action, and public health interventions seemed inadequate. Substantial differences existed in countries’ plans for border control measures, and many plans converged from World Health Organization (WHO) guidelines. Likewise, EU Member States’ plans concerning antiviral drugs and vaccines varied, and operational planning remained weak. Problems remain unsolved regarding national plans’ divergence from international recommendations, persisting strategic incoherence and operational limitations in relation to potentially scarce resources. Border control plans also show gaps and inconsistencies, and these are likely to be politically volatile during a pandemic. Translation of plans to concrete actions is very difficult without specific decision-making tools. Policy decision-makers still have great difficulty in selecting the appropriate action for a given threat.

Aim

Influenza pandemic planning is a complex, multifactorial process, complicated by the unpredictability of the time of emergence, the severity of the next pandemic and the effectiveness of influenza epidemic interventions. The aim of the first phase of the FLURESP project is dedicated to describing and assessing human pandemic scenarios in Europe. The aim of the second phase is to describe response strategies according to a set of standardised criteria (epidemiological, socio-economic, ethical and legal, and intersectoral impact, etc.). The aim of the third phase is to compare response strategies using various multi-criteria modelling approaches, including cluster, outranking and multidimensional analyses in four pilot target EU countries. The aim of the fourth phase of the project is to perform cost-effectiveness simulation models, comparing a sequence of response strategies composed of various combinations of individual measures (first-line measure, second-line measure, third-line measure, etc.), related to each pandemic scenario.

Expected results

The expected results of the project will be presented as a comparative cost-effectiveness league table of various combinations of response strategies. The key lessons will be presented as guidelines and recommendations for comparative efficiency of pandemic
interventions according to different alert levels. The FLURESP project is expected to result in:

- better knowledge concerning performance and cost-effectiveness of responses;
- more efficient links between graduated national responses and pandemic scenarios;
- facilitation of comparisons of influenza human pandemic response strategies by promoting standardisation criteria and indicators;
- improvement of the capacity of European health services to monitor intervention efficiency in a standardised manner in the longer term.

Potential applications

The project should be considered a decision-making tool, which will contribute to:

- updating business continuity plans of health sector organisations and critical commercial and non-commercial service providers, by enriching the ‘solution design’ phase with the most cost-effective response strategies;
- updating international and national preparedness plans, which will optimise both effectiveness and costs.
- suggestions for more efficient cross-border coordination between European Member States towards a European pandemic plan, which

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Key words

human influenza, cost-effectiveness, pandemic, modelling
Summary

Forums, social networks and blogs mainly serve as entertainment and informal communication platforms. Can the information provided through such channels also be used in other contexts? The M-Eco project is investigating whether Web 2.0 and multimedia data can support the early detection of disease outbreaks.

Problem

Public health officials are faced with new challenges for outbreak alert and response due to the continuous emergence of infectious diseases and their contributing factors, such as demographic change or globalisation. Only the early detection of disease activity, followed by a rapid response, can reduce the impact of epidemics. Conflictingly, the time taken for information to propagate through traditional channels can undermine time-sensitive strategies. Faced with these limitations, the M-Eco project will help to complement traditional systems with additional approaches for the early detection of emerging threats. Potential information on disease outbreaks will be gathered by the M-Eco system from social sensors, i.e. social media and user-generated content. Since this helps to avoid time-consuming reporting, the spread of dangerous diseases could be detected earlier by such a system, and appropriate actions could be taken earlier.

Using the Web as a source of information for intelligence gathering clearly brings challenges with it. First, natural language is ambiguous and extracting information and events from text is still difficult. Further, given the informal nature of user-generated content, the complexity of the extraction increases. Finally, given the volume, variety, redundancy, evolution and subjectivity of user-generated content, it is important to develop approaches for appropriately finding relevant, information-bearing facts. M-Eco tries to find solutions to address these problems.

Aim

The M-Eco project aims at improving the gathering of epidemic intelligence by developing methods that complement current systems for health event detection and to allow consideration of multiple information sources, including social media and multimedia data. The main objective of this project is to increase the facilities for early event detection in surveillance systems by:

- using additional resources that are not monitored by current detection systems, including medical social media data, and multimedia content;
- offering more sophisticated event detection technologies;
- providing personalised recommendations and access to the detected events;
- developing a user-centric system which emphasises not only risk monitoring, but also provides a basis for further assessment and evaluation.

Expected results

The M-Eco portal will make detected events visible in a personalised, user friendly way — through charts, word clouds, maps and other visualisations. The results are filtered according to user interest and their presentation is adapted according to user needs. Data from existing indicator-based systems, such as SurvNet@RKI, and event-based surveillance systems, such as ProMED mail and MedISys, will be integrated into the M-Eco system. In this way, M-Eco ensures monitoring of a broad range of information sources.
Thus, the project results contribute to health organisations’ abilities to master information overload and to consider a broad range of information sources. The developed methods and technologies prepare Web and multimedia content for disease monitoring. As an impact, the M-Eco system will enable health organisations to consider other sources of information for public health event detection than they are currently monitoring. Depending on the content available in the social media, health officials can receive information about potential health threats earlier or they can receive additional information about health threats already detected by another system. This enables them to react earlier. A subset of the developed components will be made available through the MedISys system, which is hosted by the European Union’s Joint Research Centre (JRC).

Potential applications

By tackling the challenges faced in using today’s Web for medical intelligence gathering, M-Eco supports public health officials and brings them one step closer to the early detection of and rapid response to disease activity. The final outcome of the project will allow health organisations to consider social media events is also crucial. The technologies developed by M-Eco could be adapted to other domains and could open new ways of using Web content.

Key words

epidemic intelligence, surveillance, event detection

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DEVELOPING THE FRAMEWORK FOR AN EPIDEMIC FORECAST INFRASTRUCTURE

www.epiwork.eu

Summary

EPIWORK, a project sponsored by the ‘Future and emerging technologies’ programme, proposes a multidisciplinary research effort aimed at developing the appropriate framework of tools and knowledge needed for the design of epidemic forecast infrastructures.

Problem

Infectious diseases remain a serious medical burden all around the world, with 15 million deaths per year estimated to be directly related to infectious diseases. The emergence of new diseases and, most recently, the rise of the new influenza pandemic, represent a few examples of the serious problems that public health organisations and medical science research need to address. The ability to forecast how a disease might spread at local and global levels is essential for the identification and development of appropriate control strategies. Information and communication technology (ICT) advances allow us to envisage the creation of computational infrastructures to forecast global epidemic spread.

Aim

Improved ICT techniques and methodologies, supporting interlinkage and integration of data sets, can change the way epidemic processes are modelled. The project aims to provide the scientific foundations for:

- the development of the needed modelling, computational and ICT tools to predict disease spread in complex social systems;
- the development of large-scale, data-driven computational models;
- the design and implementation of original data-collection schemes;
- the setting up of a computational platform for epidemic research.

Expected results

- Identification of general principles and laws of complex epidemiological systems.
- Development of a collaborative information platform to exploit the abundance of digital data in epidemic research.
- Development of an open, data-driven, computational modelling platform to be used in epidemic research as well as in policymaking for the analysis of global epidemics.
- Development, deployment and validation of an Internet-based monitoring system (IMS) producing real-time data on disease incidence and epidemic spread.

Potential applications

The project has publicly released an interactive modelling computational platform called GLEaMviz (http://www.gleamviz.org) that simulates the spread of emerging human-to-human infectious diseases across the world, particularly influenza-like illnesses. The software is already in distribution for research purposes by public health agencies and in educational settings. The project has delivered the first version of the Epidemic Marketplace (EM 1.0), the first publicly available data repository of this type. The consortium is already working on EM 2.0 platform development, and is finalising the integration of the Marketplace with the modelling computational platform for release in 2012. The IMS system is fully functional and comprises 10 platforms in 10 coun-
tries. It has been publicly available since early 2011. The Influenzanet website (http://www.influenzanet.eu/) presents the project by federating the entire IMS platform across Europe.

The project was ongoing during the A(H1N1) 2009 pandemic emergency: it provided real-time monitoring of pandemic incidence and of the health-seeking behaviour that was then used to improve estimates of the number of symptomatic H1N1 cases and to assess the two waves experienced in some EU countries. Side by side, computational models were used to produce successful predictions of the spread of the H1N1 pandemic, anticipating the peak pandemic activity by about two months. This was a major breakthrough that, for the first time, showed the potential of computational methods to anticipate and produce forecasts in a real-world situation that can be used to support policymakers and public health decision-making processes.

Key words

epidemic forecast, integration, complex systems, ICT
Summary

The public health threat posed by novel strains of influenza A gaining transmissibility in people and causing a human pandemic has been recognised as potentially catastrophic, especially since the emergence and global spread of the highly pathogenic avian H5N1 virus. Several mathematical models have been developed to evaluate patterns of spatio-temporal spread of infection, and the effectiveness of various containment strategies. However, these require significant improvements, elaboration and application in order to better inform EU-wide policy and responses. Key to the determination of the spatio-temporal patterns of pandemic influenza are data on contact patterns, such as those that are being acquired by the EU projects INFTRANS and POLYMOD. Building on these projects, we will collect detailed data on population structure, workplace sizes and population movement, while also undertaking new surveys focused on identifying potential behavioural super-spreaders, and attitudes towards, and potential behavioural changes during, a pandemic. A suite of mathematical models, ranging from deterministic and stochastic differential equations to individual-based microsimulations, will be developed and integrated, taking into account all of the new data that are acquired above. The models will be validated against data on past pandemics and on the dynamics of seasonal and endemic infectious diseases. The effectiveness of control/treatment strategies, including measures to increase social distance (school and workplace closure, travel reductions), quarantine, antiviral prophylaxis and mass or targeted vaccination, which also consider contact-tracing protocols, will be evaluated through these models. An essential ingredient to the usefulness of detailed models is the possibility of updating them on the basis of new information or on the patterns of an emerging epidemic; hence, a specific effort will be devoted to developing modular and efficient algorithms allowing for real-time analysis.

Problem

The public health threat posed by novel strains of influenza A gaining transmissibility in people and causing a human pandemic has been recognised as potentially catastrophic, especially since the emergence and global spread of the highly pathogenic avian H5N1 virus. Several mathematical models have been developed to evaluate patterns of spatio-temporal spread of infection, and the effectiveness of various containment strategies. However, several significant improvements (in the data on contact patterns, in the methods to use them in predictive modelling, and in real-time model updating) are needed in order to better inform EU-wide policy and responses.

Aim

The main objective of the project is arriving at an accurate and data-based modelling of the expected course of an influenza pandemic, and of the impact of public health measures on its scale and severity. The aims of the project include the study of the social acceptability of public health measures during a pandemic, and of the behavioural changes that are to be expected under such circumstances. The final aim will be the development of a knowledge-based computational environment necessary for real-time analysis and modelling in the case of a pandemic.

Expected results

- improvement of the characterisation of population contact and travel patterns in epidemic models, on the basis of extended data collection, and model-driven extrapolations when data are lacking;
Key words

pandemic influenza, mathematical models, containment strategies

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Potential applications

- evaluation of the social acceptance of restriction measures in the case of a pandemic, and of the impact of behavioural changes on the expected epidemic course;

- development of a suite of models for the spatio-temporal spread of a new influenza pandemic, that integrates the dual approaches of compartmental modelling and individual-based simulations;

- extensive evaluation of the impact of intervention options for containing and mitigating a pandemic influenza outbreak;

- development of an integrated environment for the efficient and extensible simulations of individual-based models.

■ providing advice to the health authorities in the case of a pandemic;

■ development of a research team with rapid analysis capability in the case of an epidemic outbreak.
Summary

Operational planning to implement strategic pandemic influenza plans remains a major challenge. This project will help to ensure that resources are deployed effectively and efficiently in countries in Asia in the event of a pandemic. There is no universally accepted, organised method for evaluating preparedness. This proposal builds upon and extends a pilot research project between collaborators in Thailand, linking coherently quantitative analyses of resource gaps with qualitative assessments of governance constraints given different epidemiological scenarios. The goal of the project is to provide a framework to evaluate health system operational capacity in four settings (Vietnam, Indonesia, Thailand, Taiwan), and to systematically determine operational capacity gaps in order to support containment and mitigation of pandemic influenza. Operational capacity gaps will be determined under four hypothetical pandemic scenarios. Governance arrangements will be evaluated according to the same pandemic influenza scenarios. With ministerial support across sites, the results from this work will inform revisions of strategic and operational pandemic influenza plans, provide a critical resource for the ‘war room’ in the event of a pandemic and inform decisions about future resource allocation.

Problem

Although considerable progress has been made in Southeast Asia and substantial domestic and international efforts are being focused, public health system capacity to respond to pandemic influenza remains a profound challenge. Highlighting this issue, a recent report to the United Nations System Influenza Coordinator (UNSIC) captured a critical gap in preparedness planning, noting: ‘Very few countries have succeeded in transforming high-level political plans into a strategic framework and detailed annual operational plans to drive implementation. In addition little systematic research has been undertaken to determine operational capacity gaps in pandemic influenza planning.’

Aim

The goal of this project is to provide a strategic framework to evaluate operational capacity in four countries at risk of being at the epicentre of a future influenza pandemic and to systematically determine operational capacity gaps in order to support containment and mitigate the consequences of pandemic influenza in these countries and elsewhere.

This goal will be achieved through the coherent strategic linkage of several work packages. These build upon a body of research activity being undertaken in Thailand and extend this work in its geographic scope and ambition.

Expected results

- to develop a detailed methodological framework to evaluate operational capacity to respond to pandemic influenza, through countries’ resources characterisation and mapping, evaluation of operational response capacity, and assessment of gaps and governance arrangements in the response to a pandemic;

- to support evaluation research for pandemic influenza preparedness in Asia and to identify basic principles in determining capacity to ensure a coherent approach to pandemic preparedness in both Asian and European countries;
tries. It will provide, in partner countries, an identification and analysis of gaps between needed and available resources, contribute to strengthening operational capacity response for those countries, foster a better preparedness of health systems in those countries, foster generic contingency planning and support national public health functions.

The project will also support capacity building across the region, introducing evidence-based best practices originating from both Asia and Europe. The project will foster constructive cooperation within the region, promote the development of research and policy networks, and promote a high quality evidence-based response strategy to pandemic influenza in participating and neighbouring countries.

**Key words**
pandemic influenza, health systems, preparedness, capacity development, Asia

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**Potential applications**

Our project will foster an innovative and integrated research approach to support operational capacity development in a number of key countries in Asia that may, many experts believe, be the epicentre of the next influenza pandemic.

The project’s main impact will be the strengthening of institutional response capacity across a number of key countries. It will provide, in partner countries, an identification and analysis of gaps between needed and available resources, contribute to strengthening operational capacity response for those countries, foster a better preparedness of health systems in those countries, foster generic contingency planning and support national public health functions.

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Summary

The objective of EuroMOMO was to develop and operate a coordinated approach to real-time mortality monitoring across Europe. The project, which started in 2008, had 24 partners (both associate and collaborating) from 21 European countries.

The key output was a robust and simple consensus model to monitor all-cause mortality. This model has been running since mid 2009. The system is ready to be extended to a business operation system applicable across Europe. The project has demonstrated the usefulness of mortality monitoring, and has facilitated the implementation of mortality monitoring in several EU Member States.

Problem

Mortality is a basic indicator of health, and an understanding of mortality patterns is fundamental for effective public health planning, risk assessment and action. Vital statistics are accessible for all European countries, but these data are not made available in a timely manner during health crises or for imminent health threats. However, decision-makers request such data in case of epidemics or when new diseases and threats emerge.

As these threats are not restricted by borders, a European approach to detect and estimate the magnitude of deaths is required. A joint approach is critical; pooling of real-time vital statistics increases power to detect changes. Mortality monitoring should be an ongoing process, so as to allow detection when and where excess mortality occurs.

Aim

The objective of EuroMOMO was to develop and operate a coordinated approach to real-time mortality monitoring across Europe. This will enhance the European capacity to assess and manage serious public health risks: pandemic influenza and other emerging infections are examples, as are environmental conditions with an impact on public health, e.g. heat waves and cold snaps.

Results

The main actions included:

- an inventory of existing mortality monitoring systems;
- a definition of minimal requirements for a mortality monitoring system;
- a retrospective analysis of mortality data;
- identification of a uniform analytical approach;
- piloting of a consensus system for real-time mortality modelling in several European countries.

On this basis, the consortium developed a simple and robust consensus model to monitor all-cause mortality. The model was implemented gradually from 2009, and includes data from a number of EU Member States.

What is the European value of this project?

The project has increased the European capacity to monitor the spread of threats such as the 2009 influenza pandemic or other major health threats, and to measure their impact on mortality. This supports risk managers when targeting interventions and prioritising resources.

The EuroMOMO approach to mortality monitoring has a clear added European value, as explained below:

- the use of a common mathematic model ensures that figures on excess mortality are collected in a
the collection of data across several Member States supports risk assessment — to determine whether a health threat is unique for a Member State or is common to several Member States;

- discrete changes in mortality may not be visible in small countries, but when considered together, important patterns or trends may be recognised and thus allow for early countermeasures.

As a response to the 2009 H1N1 pandemic, EuroMOMO accelerated its pilot phase; in June 2009, the consortium implemented a common mortality monitoring test system in four countries. This system was conceived as a pre-pilot system. More countries joined the improved monitoring pilot system in autumn 2009 in order to track the impact of the pandemic. The outputs were validated and interpreted by an internal risk assessment forum before being made available on a restricted EuroMOMO website. Outputs include a weekly bulletin, maps and graphs of weekly total and age-specific all-cause mortality using standardised indicators (z-score), that allow impact comparison between countries. A pooled analysis, available for the public, was added from 2010.

Potential applications

The EuroMOMO project created a unique network for real-time quantification of all-cause mortality. The pilot project was successfully completed, and the model can be implemented as an operational system serving the public health of Europe.

Key words

mortality, surveillance, monitoring, influenza pandemic, public health threats, impact assessment, early warning, time-series modelling

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* refers to page number in catalogue of EU-funded projects 2001–2007
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#### PROJECTS ADDRESSING A BROADER RANGE OF VIRAL AND OTHER INFECTIOUS DISEASES BUT WITH SIGNIFICANT PART DEVOTED TO INFLUENZA

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The information presented also shows the involvement and participation of a multitude of small and medium-sized enterprises working in close collaboration with the academic institutions.