Project proposal form

Project proposal for EUPHEM fellows

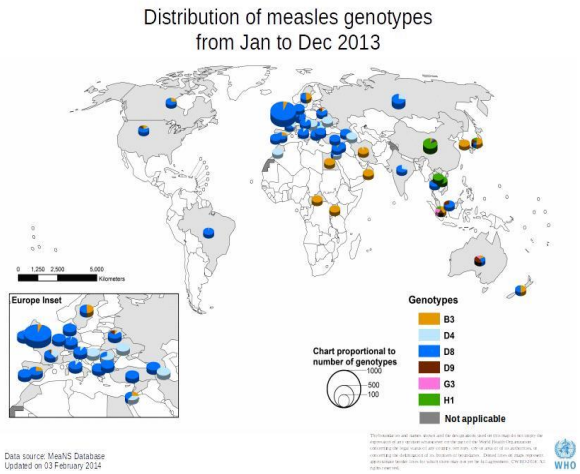
Project title	**Please indicate if the project is an ECDC network contract**
Project (local) supervisor(s)	
Department where the project will take place and other key stakeholders **Please indicate if project is ECDC contract or is part of ECDC network activities!**	
Aim and objectives of Project Background and rational Methodology (very short) Expected results Public health importance including national, EU added value and evidence for policy making/decision making	
Start date *(indicate if any flexibility)*	
Duration of project	
Time/sessions per week	
If data required, when will this be available?	
Location of project *(entirely at host site or will travel to other locations be required – if so please describe)*	
Which of the following learning objectives will the project meet? **Public health microbiology management and communication (aware/skilled)** • Design/organise/manage a public health microbiology laboratory • Asses risks to respond to a potential health threat • Apply the roles and responsibilities of local, national and international organisations involved in infectious disease control • Coordinate response using communication mechanisms and other tools • Communicate effectively with persons from a multidisciplinary	

background, authorities, the public and the media in the form of publications, reports, interviews, and oral presentations. **Applied microbiology and laboratory investigations (competent)** • Apply concepts of virology, bacteriology, parasitology/mycology and immunology to the public health disciplines • Identify the use and limitation of diagnostic and typing methods and their interpretation in patient diagnosis, outbreak investigations, surveillance and epidemiological studies • Recognise the specific issues with the use of laboratory and epidemiological methods in investigations of rare and emerging diseases • Design and apply safe specimen sampling strategies for disease surveillance and for outbreak detection and control, both in humans and animals **Epidemiological investigations, including surveillance and outbreak investigation (skilled)** • Set up surveillance systems (combined syndromic and laboratory based or only laboratory-based) • Analyse combined syndromic and laboratory or laboratory surveillance data • Evaluate an existing surveillance system • Operate microbiological support on surveillance systems • Apply combined microbiological and epidemiological knowledge in outbreaks, surveillance, or unusual events • Participate in an outbreak investigation with having one or more PH microbiology tasks. **Applied public health microbiology research (competent)** • Conduct all stages of a PHM research project, from planning to writing a scientific paper. **Quality management (skilled/competent)** • Describe quality assurance • Assess and experience different standards	

• Apply the concepts of external quality assurance (EQA) • Perform, evaluate or analyze results of an EQA. **Biorisk management (skilled)** • Apply national, European and World Health Organization (WHO) rules and regulations regarding biosafety and biosecurity and understand how these may influence response to an outbreak • Use appropriate decontamination strategies/personal protection and their applicability in field situations • Determine the need for quality management, biosecurity management, and crisis response as core elements of management of a public health microbiological laboratory. **Teaching (skilled/competent)** • Identify training needs, planning and organising courses • Moderate case studies, give lectures and perform pedagogical teaching • Design/create a case study.	
Briefly outline the work and responsibility that the fellow will be expected to take on *e.g. produce background papers, organise meetings, supervise staff and any other activities not mentioned under learning opportunities*	
Project outcomes *i.e.: publication, meeting presentation etc. background papers, and any other activities not mentioned under learning opportunities*	

Annex 10B Project proposal form (example)

Project proposal for EUPHEM fellows

PROJECT TITLE	**Measles virus genotyping – should haemagglutin gene sequencing be part of the outbreak investigations in the measles elimination end-game?**
Project (local) supervisor(s)	Project Supervisor: Åsa Wiman, Supervisor: Mia Brytting
Department where the project will take place and other key stakeholders	Unit for Laboratory surveillance of vaccine preventable diseases, Public Health Agency of Sweden, Stockholm
Aim and objectives of Project	The main aim of this study is to re-evaluate the epidemiological links between recent measles cases occurring in Sweden (between 2013 and 2014) by sequencing the H gene to achieve higher molecular resolution. This will also support the development of molecular tools for global surveillance of measles virus as well as provide data on the evolution of neutralizing epitopes of the H protein.
Background and rational	 Measles is a highly contagious disease characterized by high fever, cough, coryza, conjunctivitis and a maculopapular rash. It is caused by the measles virus (MeV), which is a single-stranded, negative-sense RNA virus and is a member of genus *Morbillivirus* within the family *Paramyxoviridae*. The MeV genome is 15,894 nt in length, and contains six genes encoding for the nucleoprotein (N), phosphoprotein (P), matrix (M), fusion (F), hemagglutinin (H) and polymerase (P). The H protein is responsible for receptor binding (SLAM, CD46 and nectin-4) and is the major target for neutralizing antibodies. MeV can be divided into eight clades and 24 genotypes (A, B1-B3, C1-C2, D1-D11, E, F, G1-G3 and H1-H2) based on the sequence diversity within the N region (Rota et al., 2011). Since 1963 an effective and safe vaccine has been available to control measles. The WHO European Region has set the target to eliminate measles together with rubella by the end of 2015. Measles elimination is defined as the interruption of indigenous transmission of MeV for a 12-month period (Mankertz et al., 2011). To achieve

	that, a measles vaccine coverage of 95% for two doses is required and strong national surveillance systems are needed to detect all clinical cases of measles and to investigate thoroughly all single cases and outbreaks. The two dose schedule of combined measles-mumps-rubella (MMR, at 18 months and at 6-8 years) vaccine was introduced in Sweden in 1982 (Barn vaccination programmet i Sverige 2013). MMR vaccine coverage data for the second dose is collected for 12 years old (6th grade at primary school); the coverage has been over 95% since 2011. Despite this, a total of 51 measles cases (one without laboratory confirmation) were reported in Sweden in 2013 which is higher than seen since year 2000.
Methodology	The molecular epidemiology together with case classification (including case interviews and exclusive contact tracing) as well as with timely reporting is used as a sensitive way to monitor the MeV transmission. However, molecular data can only confirm independent sources of infection if different genotypes or clearly distinct lineages are detected. If viruses from the same lineages are identified as a cause of non-linked cases in a particular country, the molecular data currently used for genotyping (a 450-nucleotide long fragment of the N gene) is often not sufficient to differentiate between continuous circulation of MeV or multiple introductions from the same source (Necula et al., 2013, Carr et al., 2009). However, sequences of H (or P) gene has been used to confirm epidemiological links between measles cases in which MeV have had identical N gene sequences (WHO 1998, Rota et al., 1992 & 1996, Bankamp et al., 2008, Saitoh et al., 2012, Xu et al., 2013 & 2014). Furthermore, phylogenetic analyses based on the partial N gene and complete H gene sequence data is required for a designation of a new genotype (WHO 2012). Previously it has been shown that the H and N genes contain up to 7% variability at the nucleotide level between different genotypes, whereas nucleotide variability can approach 12% within the COOH-terminus of the N protein (WHO 1998). However, the variability is likely to be much less within the genotypes and needs to be calculated using all the existing sequence data available.
Expected results	MeV positive samples submitted to The Public Health Agency of Sweden between 2013 (n=48) and 2014 (n=20) will be used in this study. Samples obtained in 2013 originate from 5 epidemiologically confirmed outbreaks in 7 different geographical locations. Genotyping of measles virus has been performed as recommended by WHO, by sequencing a 450-nucleotide region encoding the nucleoprotein N. As a result, 82% of measles viruses were successfully typed (56/68); 28 strains were identified as genotype B3, 26 as D8 and two as genotype A (vaccine strain). However, these viruses were almost identical based on sequences from N region and thus these samples (n=56) will be sequenced in other regions (*i.e.* H gene). Epidemiological data used for analysis includes personal details (age and sex), time and place of diagnosis,

Public health importance (including national and EU added value, evidence for PH decision making)	vaccination status as well as country of origin (if infection likely obtained abroad). To study MeV variability across the genome, all previously published full-length as well as complete N and H gene sequences of MeV will be downloaded from PubMed and MeaNS (http://www.hpa-bioinformatics.org.uk/Measles/Public). MeV variability at nucleotide and amino acid level across the genome or genes will be calculated between and within genotypes. Further measles virus genes can be sequenced if this analysis indicates bigger variability within them. All previously published H-gene sequences of MeV are used to support primer design and further sequence comparisons. Initially we will use two different previously published primer sets to amplify the H-gene, within normal PCR, nested PCR and one-step (nested) PCR if necessarily. Old measles virus culture isolates will be used as controls. Establishment of a method for H-gene sequencing that would give a higher molecular resolution than N-gene sequencing alone in outbreak investigations and also to study vaccine escape mutants 1. H-gene sequence obtained from at least 80% measles positive samples (45/56) 2. Phylogenetic data from H-gene keeping with the epidemiological data (*i.e.* outbreaks better defined than based on N-gene sequences) 3. Bioinformatic analysis based on published sequences might reveal another genomic region with even higher variability (this study to be extended or new study planned) 4. No vaccine-induced escape mutants suspected to be found (2/49 received 2 doses of MMR in 2013 and hence could have vaccine-induced escape mutant) Molecular epidemiological investigations are vital not only in monitoring the progress of measles elimination but also in establishing source and transmission networks of specific MeV strains. However, with the progress in the control of measles, the genetic variability of circulating MeV strains have decreased especially in the WHO European region and it has become increasingly difficult to determine the origin of a virus on the basis of the N gene alone (Rota et al., 2011). Thus the development of method for sequencing other gene regions of MeV (*i.e.* H gene) will support both the global measles elimination and local investigations

	in Sweden. Furthermore, monitoring the immunodominant epitopes within H gene and the possible emergence of escape mutants from vaccine-induced neutralizing antibodies in humans is also becoming increasingly important (Finsterbusch et al., 2009) during the end-stage of elimination process. Measles elimination relies entirely on effective vaccine, and this cannot be compromised.
Start date *(indicate if any flexibility)*	1st November 2014
Duration of project	3 months
Time/sessions per week	Approximately 3 days per week
If data required, when will this be available?	All data already available
Location of project ***(entirely at host site or will travel to other locations be required – if so please describe)***	Entirely at host site
Which of the following learning objectives will the project meet? **Public health microbiology management and communication (aware/skilled)** Design/organise/manage a public health microbiology laboratory Asses risks to respond to a potential health threat Apply the roles and responsibilities of local, national and international organisations involved in infectious disease control Coordinate response using communication mechanisms and other tools Communicate effectively with persons from a multidisciplinary background, authorities, the public and the media in the form of publications, reports, interviews, and oral presentations. **Applied microbiology and laboratory investigations (competent)** Apply concepts of virology, bacteriology, parasitology/mycology and immunology to the public health disciplines Identify the use and limitation of diagnostic and typing methods and their interpretation in patient	Applied public health microbiology research (competent) • Conduct a PHM research from data analysis to writing a scientific paper, and linked it to epidemiological data Epidemiological investigations, including surveillance and outbreak investigations (skilled) • Analyze combined epidemiological and laboratory surveillance data • Apply both microbiological and epidemiological knowledge in outbreaks and surveillance Applied microbiology and laboratory investigations (competent) • Identify the use and limitation of diagnostic and typing methods and their interpretation in outbreak investigations, surveillance and epidemiological studies • Recognize the specific issues with the use of laboratory and epidemiological methods in investigations of rare and emerging diseases • Apply both microbiological and epidemiological knowledge in outbreaks and surveillance • Apply knowledge of phylogenetics and existing measles database Quality management (skilled) • Assess and experience different standards

diagnosis, outbreak investigations, surveillance and epidemiological studies Recognise the specific issues with the use of laboratory and epidemiological methods in investigations of rare and emerging diseases Design and apply safe specimen sampling strategies for disease surveillance and for outbreak detection and control, both in humans and animals **Epidemiological investigations, including surveillance and outbreak investigation (skilled)** Set up surveillance systems (combined syndromic and laboratory based or only laboratory-based) Analyse combined syndromic and laboratory or laboratory surveillance data Evaluate an existing surveillance system Operate microbiological support on surveillance systems Apply combined microbiological and epidemiological knowledge in outbreaks, surveillance, or unusual events Participate in an outbreak investigation with having one or more PH microbiology tasks. **Applied public health microbiology research (competent)** Conduct all stages of a PHM research project, from planning to writing a scientific paper. **Quality management (skilled/competent)** Describe quality assurance Assess and experience different standards Apply the concepts of external quality assurance (EQA) Perform, evaluate or analyze results of an EQA. **Biorisk management (skilled)** Apply national, European and World Health Organization (WHO) rules and regulations regarding biosafety and biosecurity and	

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Briefly outline the work and responsibility that the fellow will be expected to take on ***e.g. produce background papers, organise meetings, supervise staff and any other activities not mentioned under learning opportunities***	- Review literature on that subject and write proposal
Project outcomes ***ie: publication, meeting presentation etc.background papers, and any other activities not mentioned under learning opportunities***	- Working experience in ISO/IEC 17025 accreditated and WHO acreditated (for measles and rubella) laboratory - ESCAIDE 2015 abstract - Publication - Recommendation (and method) for additional measles typing in Sweden